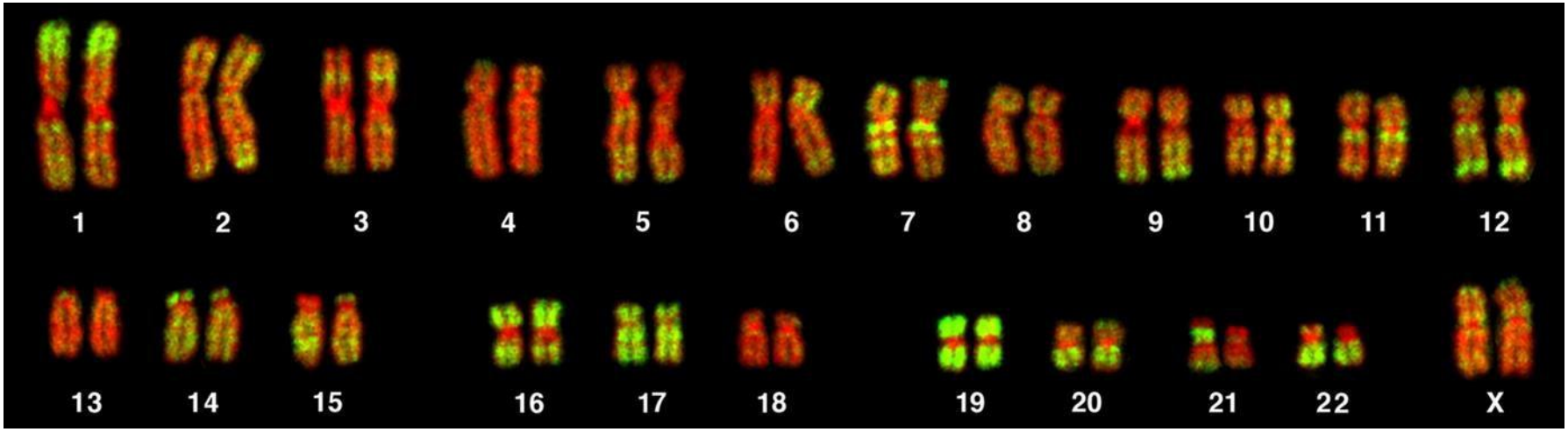
Chromosomal Disorders



Prof. Nilmini Silva Gunawardene
Molecular Medicine Unit
Faculty of Medicine
Ragama
25th May 2018

Overview

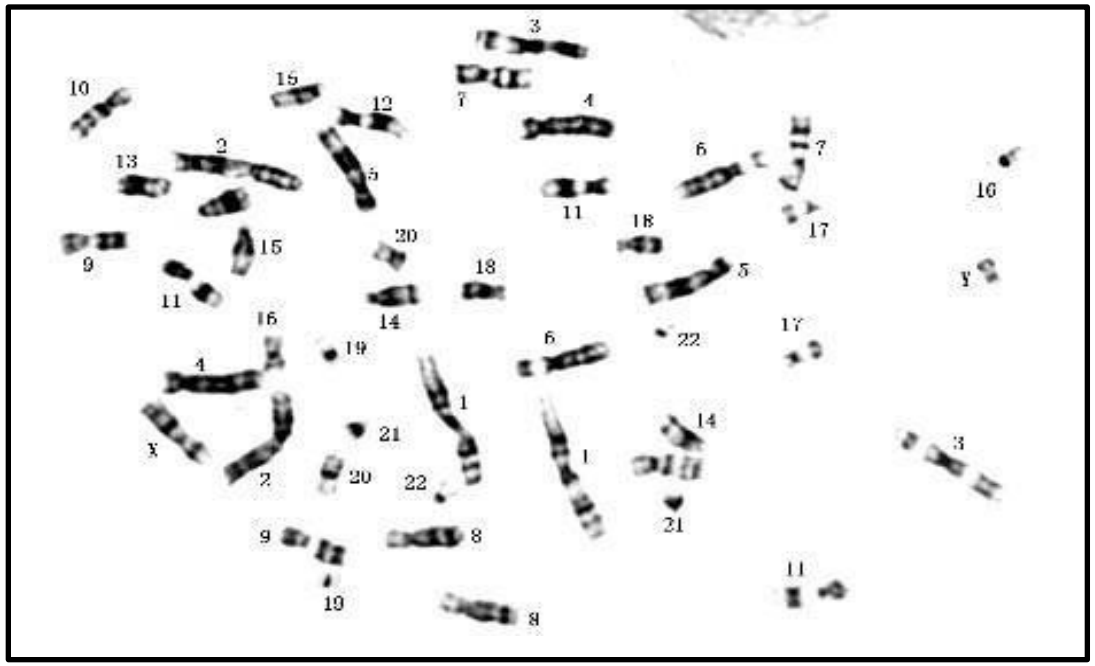
- Chromosomes numbers, identification and nomenclature
- Consequence of chromosome aberration
- Maternal age and its relevance
- The types and mechanism of chromosome aberration
    1. Numerical abnormalities
    2. Structural abnormalities
- Chromosome number abnormalities

1. Chromosome Non-Disjunction in Meiosis and Aneuploidy
2. Mitotic Non-Disjunction and Chromosome Mosaicism

- Chromosome Structural Rearrangements
- Sex chromosome diseases

Chromosomes

The structure and number of chromosomes in various species are constant. Thus those within the same species are the same, and those in different species are different.



Chromosome Numbers

- **Somatic cells contain 46 chromosomes (23 pairs) and are termed diploid.**

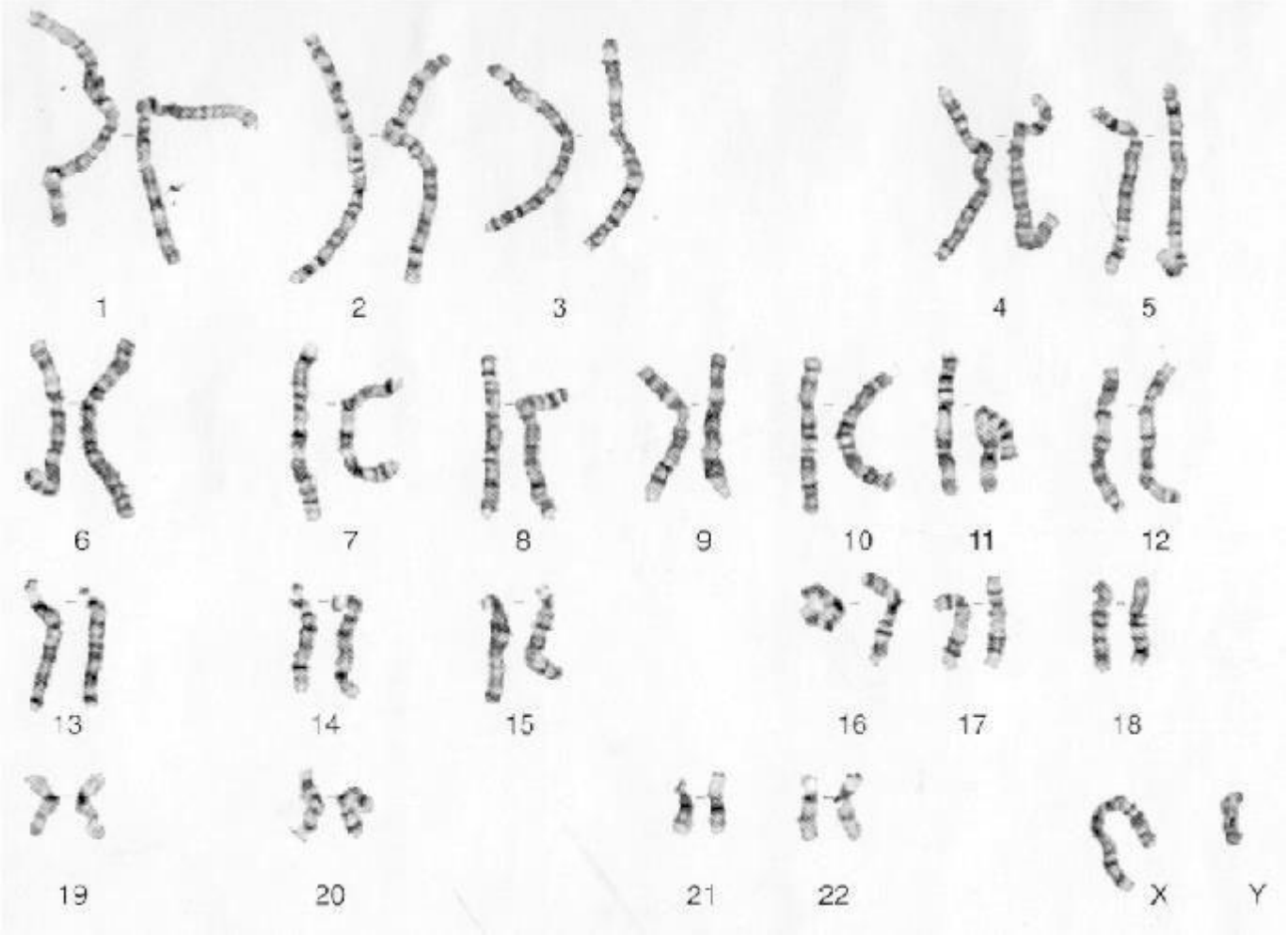
- **The haploid number of 23 are found in gametes.**

- **22 of the pairs are called autosomes and are not involved in determining sex.**

- **The 23rd pair are the sex chromosomes:**
  XX in females
  XY in males

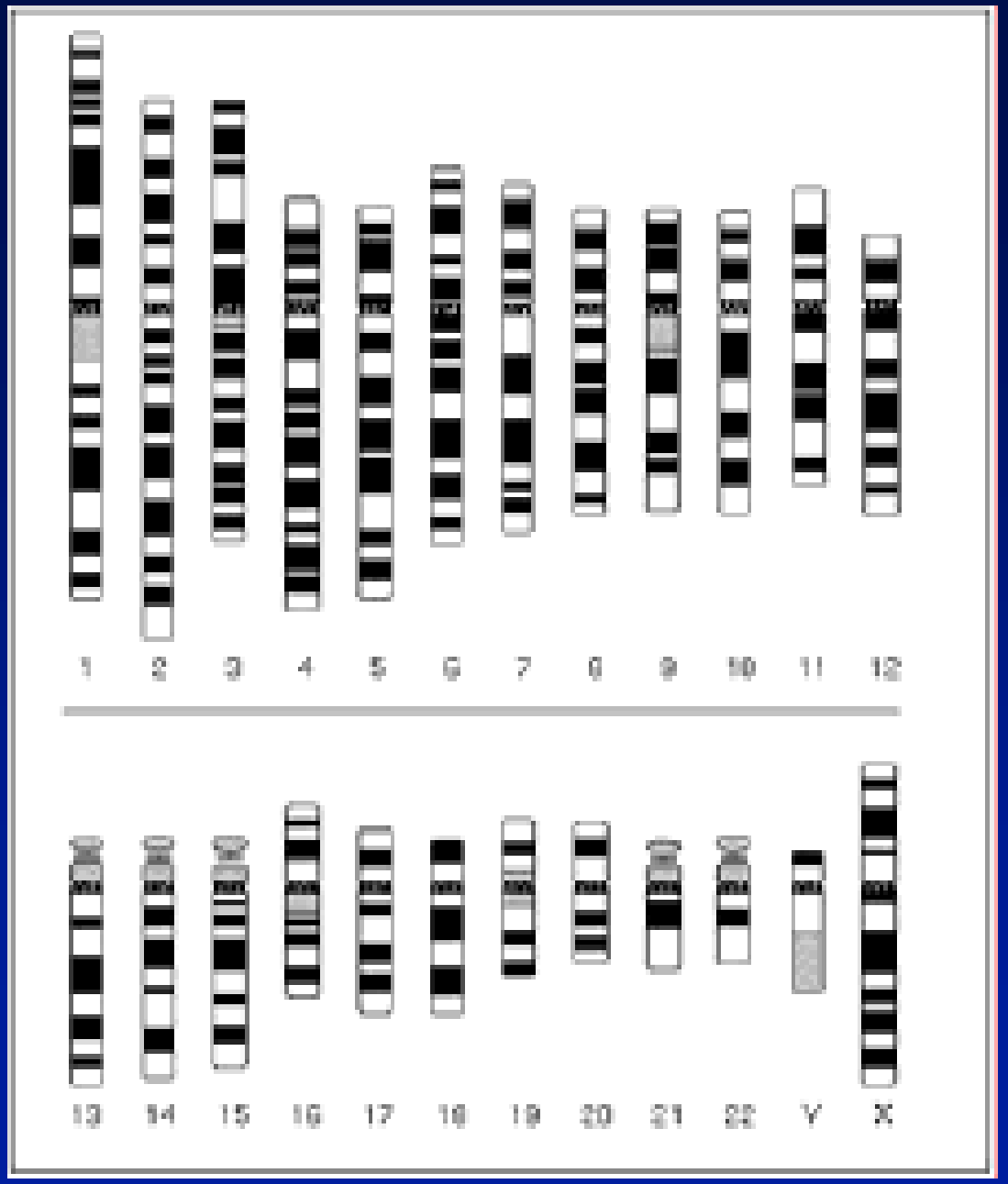
- **The chromosome constitution of an individual is the Karyotype. The normal human karyotype is 46, XY (male) or 46, XX (female).**

Normal Male Karyotype (46,XY)

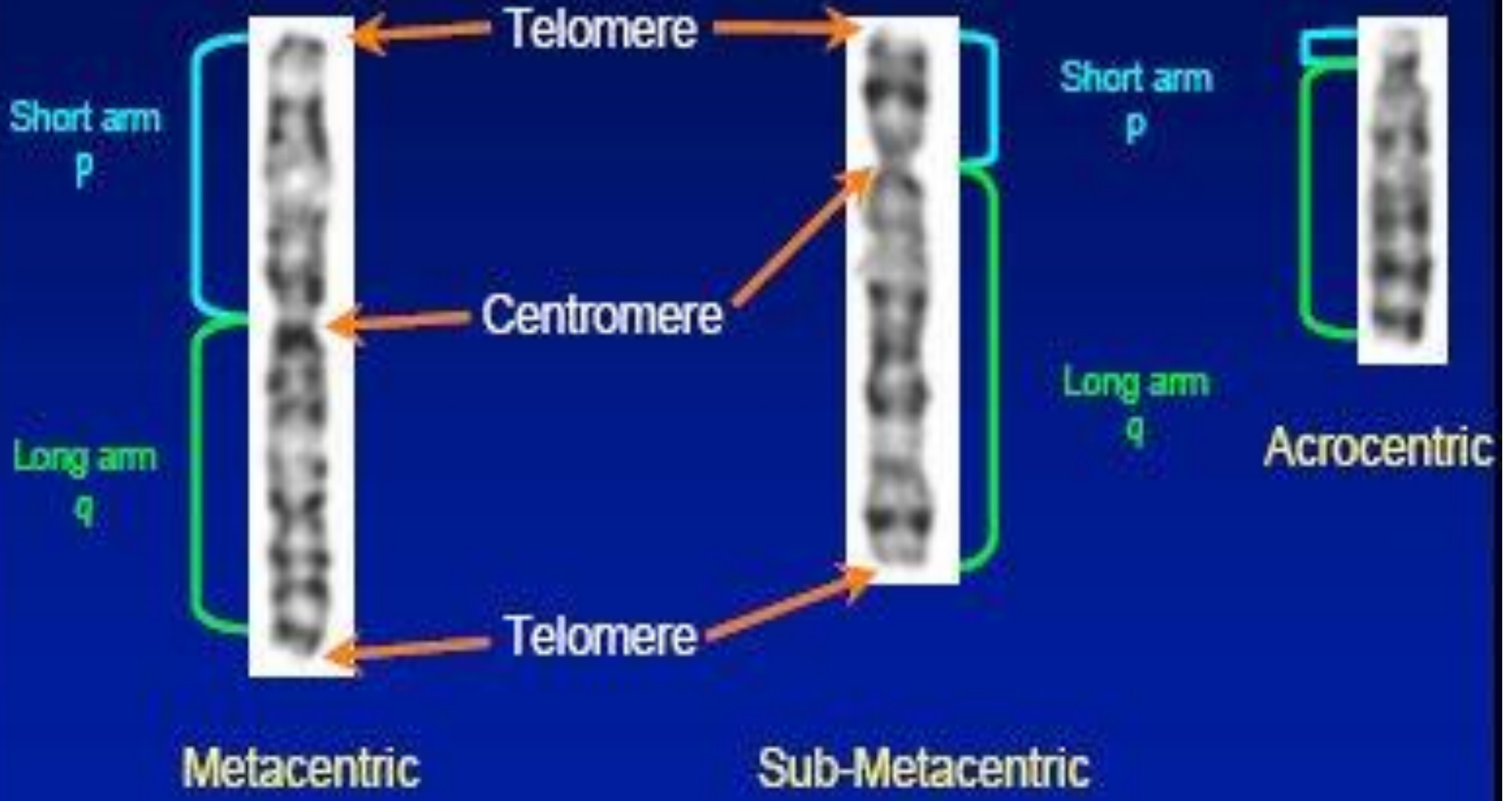


Chromosome Identification

Chromosomes are identified by their size, banding pattern and the position of the centromere



Naming of Parts



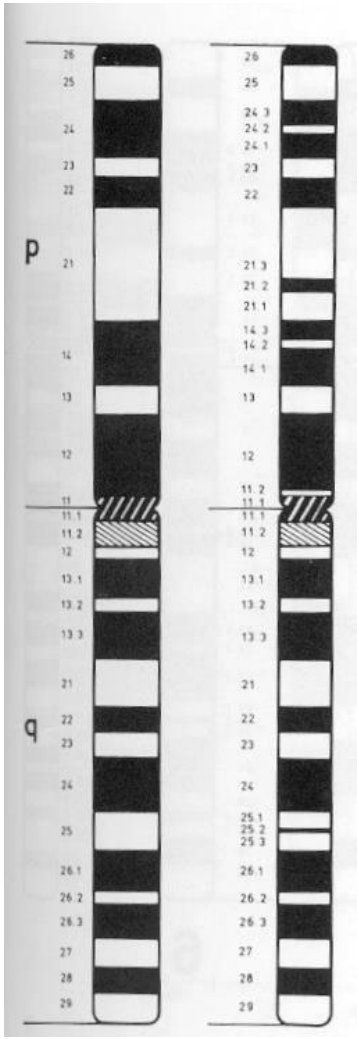
Chromosome nomenclature

- **Regions, Bands & Sub-bands**

- **Numbered consecutively from centromere to telomere**
- **Centromere is 10 (either p10 or q10)**

- **1p31.1:**
  - **chromosome 1**
  - **short arm**
  - **region 3 , band 1, sub-band 1**

Ideogram of Chromosome 3



The consequence of chromosome aberration

Chromosome disease:

Any syndrome characterized by malformations or malfunctions in any of the body's systems, and caused by abnormal chromosome number or constitution.

More than 100 chromosome diseases and over 10,000 abnormal karyotypes of chromosomes have been reported.

Characteristics of chromosomal disease :

- **mental retardation**
- **growth retardation**
- **congenital malformations**

Chromosomal abnormalities and disease

Chromosome aberration:

It refers to the numerical or structural changes of chromosome/s within germ cells or somatic cells.

Reasons of chromosome aberration

- Spontaneous aberration
- Induced aberration：
  - Chemical factors：medicine, pesticide, industrial poison, food additive
  - Physical factors：radiation
  - Biology factors：biological toxin, virus etc;
  - Maternal age

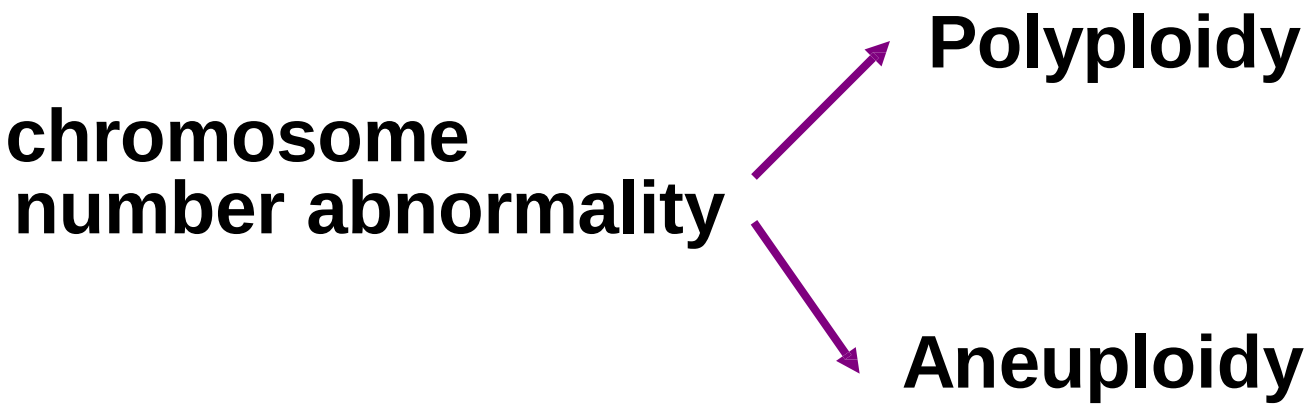
The types and mechanism of chromosome aberration

Types of chromosome aberration

- chromosome **number** abnormality
- chromosomal **structural** aberration

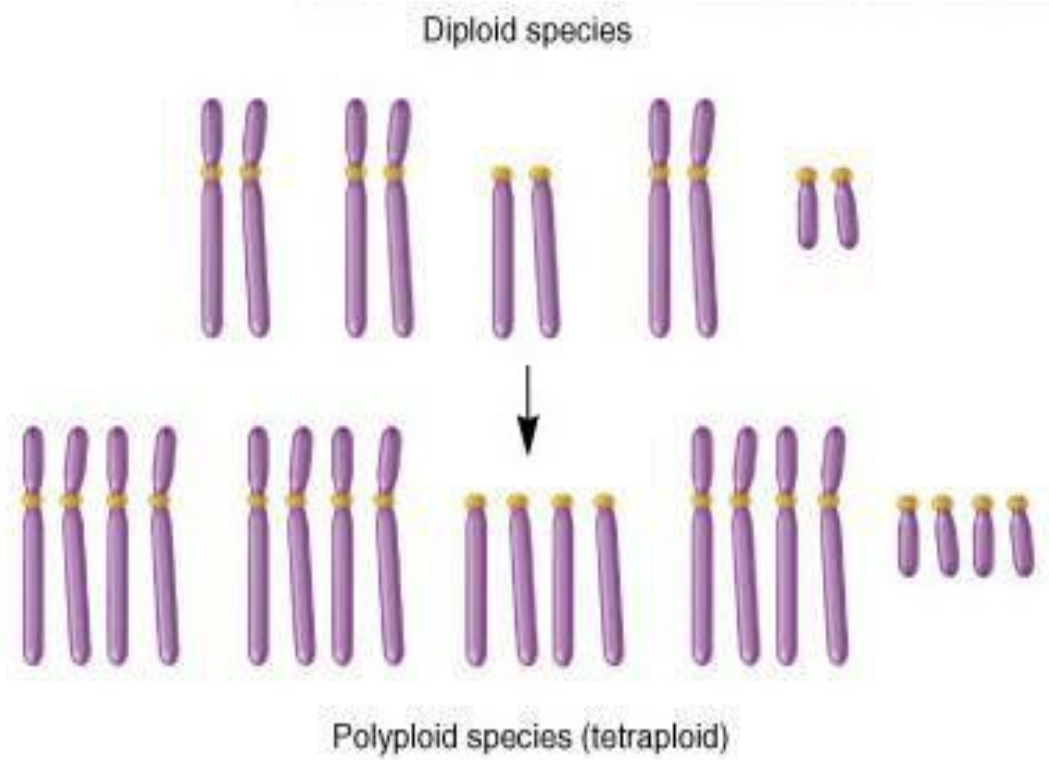
Changes in chromosome number and structure are important for health and evolution

The types and mechanism of chromosome number abnormality



Polyploidy

Polyploidy occurs when all the chromosomes are present in three or more copies. i.e. when the number of haploid chromosome sets is greater than two.



A common way for this to occur is for the mitotic spindle to fail, leaving all chromosomes in one cell..

The types of Polyploidy

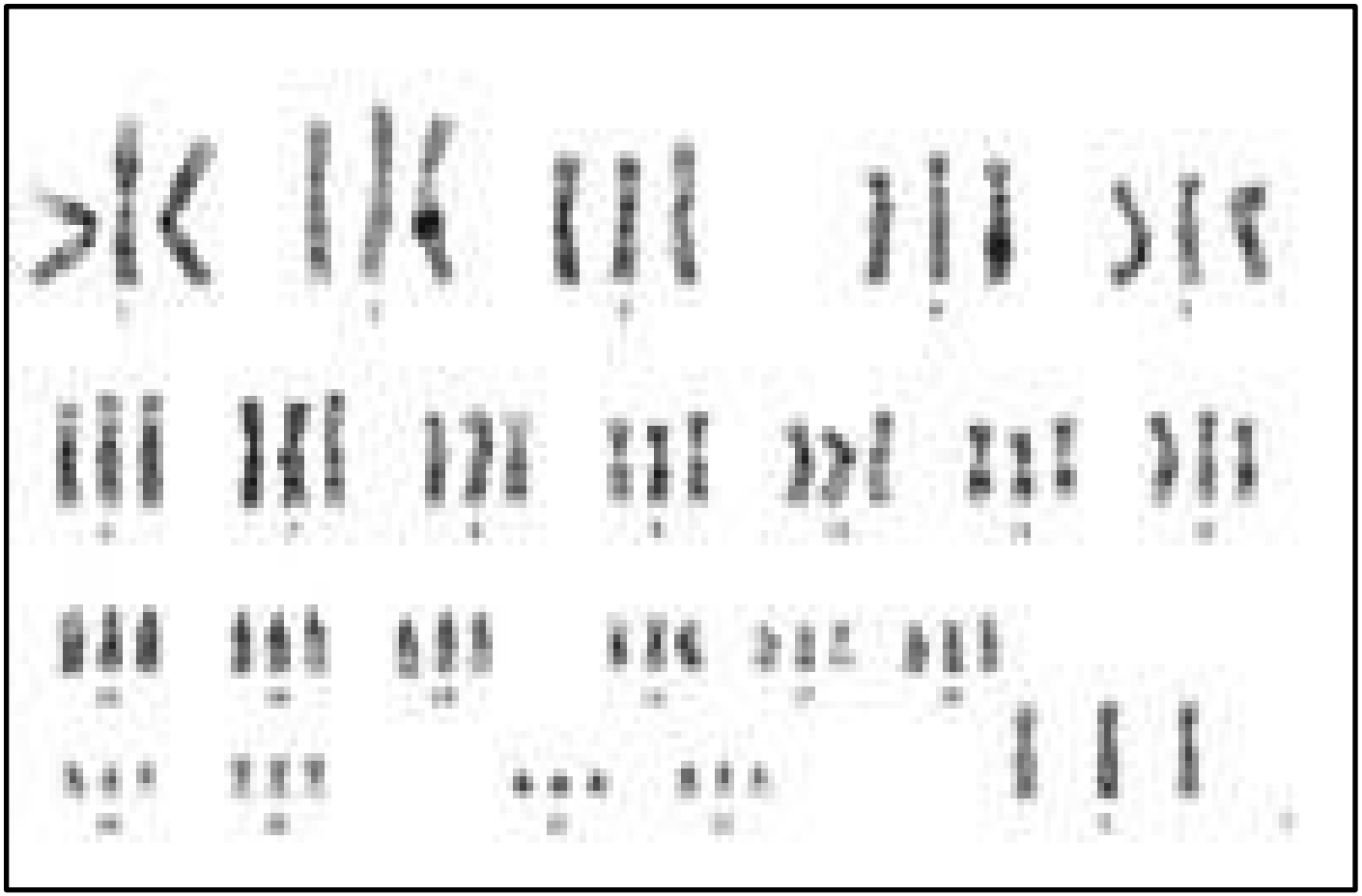
1. Triploidy :

t h e r e are three Chromosome Sets in patient's somatic cell , each pair of the chromosomes increases by one and a total of 69 chromosomes(3n).

2. Tetraploidy :

t h e r e are four Chromosome Sets in patients somatic cell , each pair of the chromosomes increases by two and a total of 92 chromosomes(4n).

The karyotype of triploid patient



The production mechanism of Polyploidy

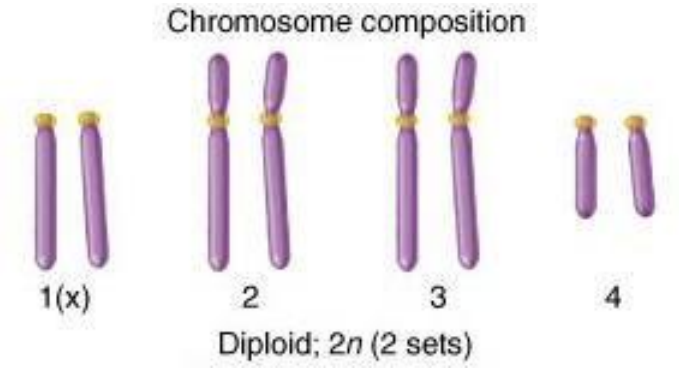
Polyploidy arise as a result of:

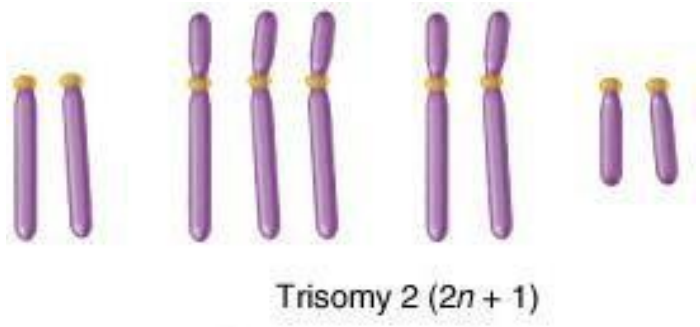
- **Fertilization by two sperms.**
- **A diploid sperm due to failure in meiosis.**
- **A diploid ovum due to failure in meiosis.**

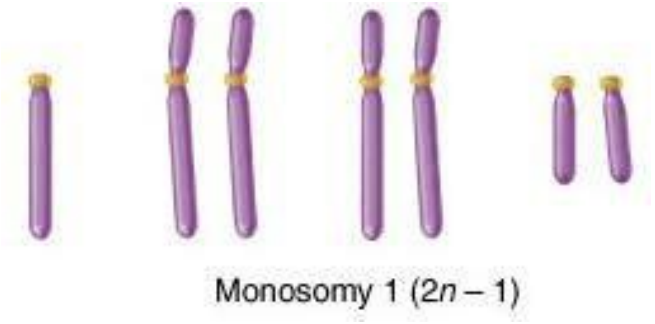
A proportion of the polyploid cells occurs in human bone marrow and also is a normal feature of regenerating liver and other tissues.

Aneuploidy

Aneuploidy occurs when one of the chromosomes is present in an abnormal number of copies (i.e. not an exact multiple of the haploid).







Trisomy and monosomy are two forms of aneuploidy.

The types of Aneuploid

Hyperdiploid：

there are one or several chromosomes more in somatic cells

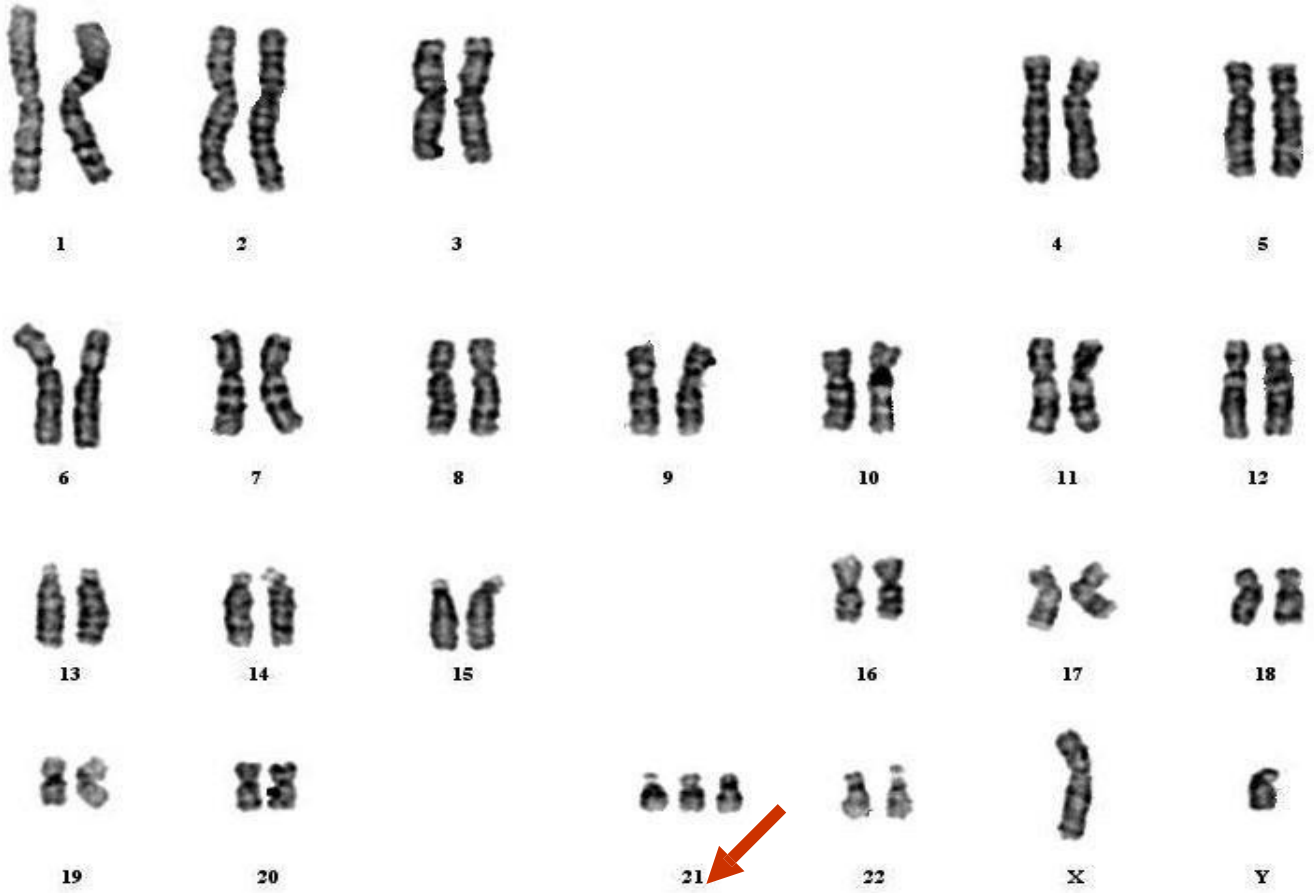
Trisomy：

having three chromosomes of a particular type

(2n+1), thus the number is 47 in human.

o

Trisomy 21 : 47,XY,+21



The types of Aneuploid

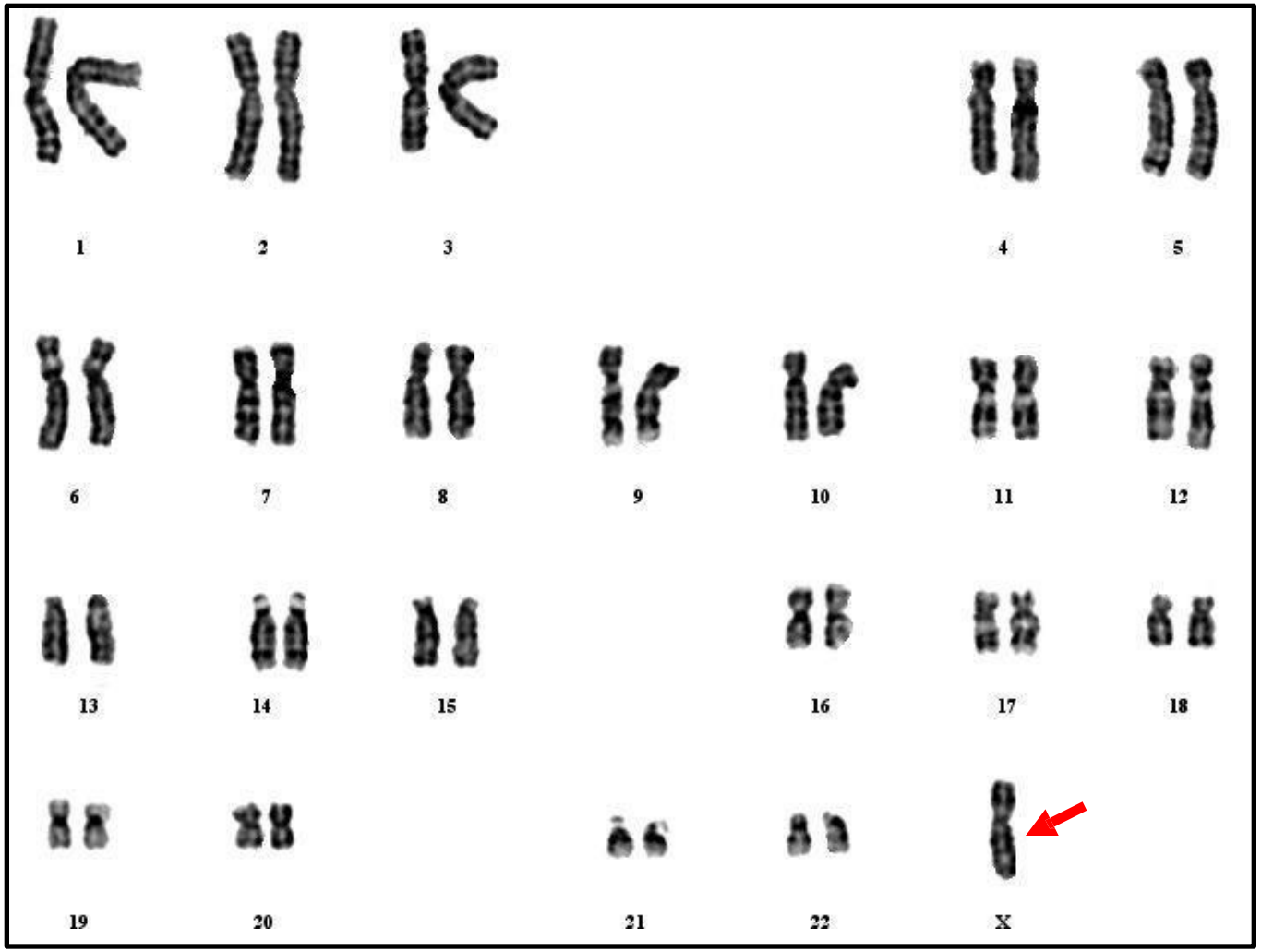
Hypodiploid:

there are one or several chromosomes less in somatic cells

Monosomy:

lack of one of a pair of chromosomes. (2n-1), thus the number is 45 in human.

Monosomy- 45,X



The production mechanism of Aneuploidy

Aneuploidy arise as a result of:

- **Failure of paired chromosomes /sister chromatids to disjoin at anaphase – non-disjunction**

- **Delayed movement of a chromosome at anaphase – anaphase lag**

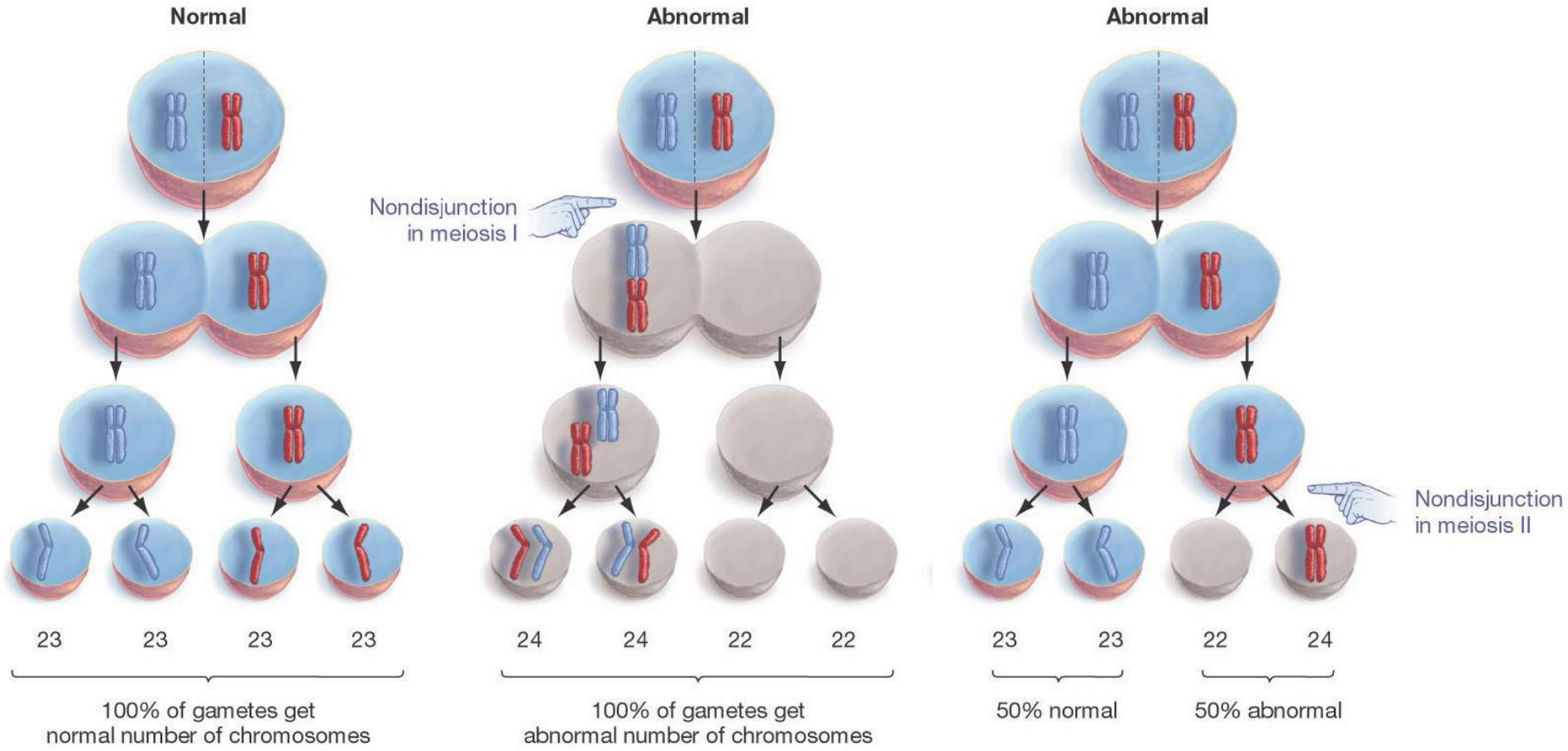
The mechanism of Aneuploid

Non-disjunction

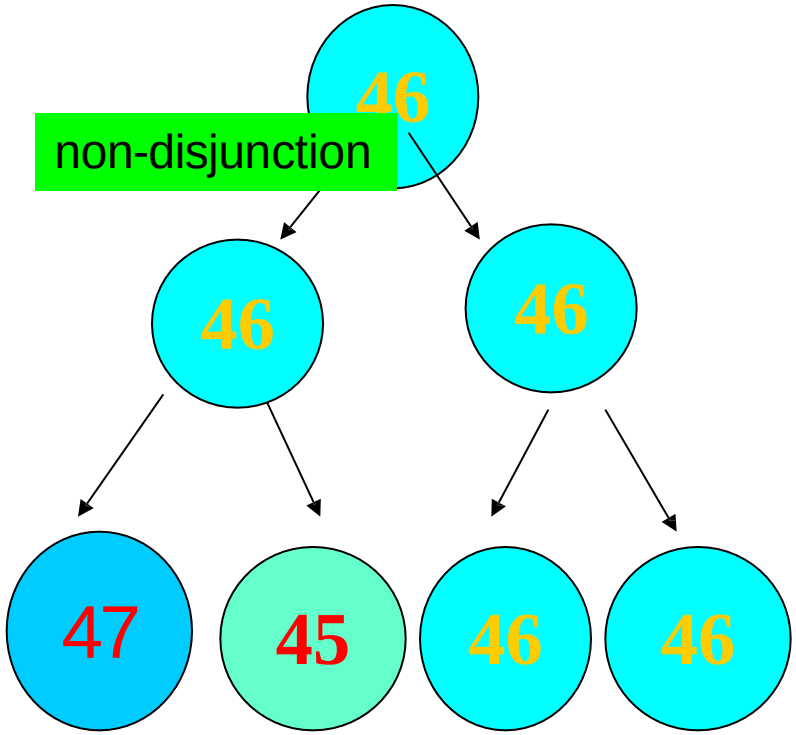
Non-disjunction can occur during meiosis

Non-disjunction can occur in the early cleavage phase of fertilized egg in mitosis

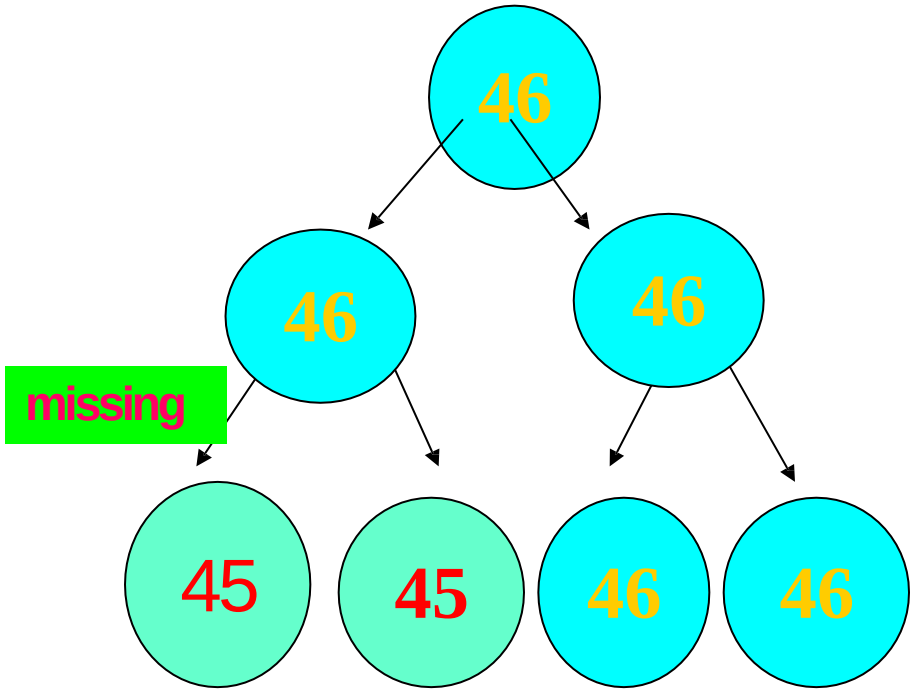
Chromosome Non-Disjunction in Meiosis Causes Aneuploidy



Mitotic Non-Disjunction Causes Chromosome Mosaicism



Disjunction in mitosis and the formation of mosaic in graphic



chromosome missing caused by the retardation in anaphase and the formation of mosaic in graphic

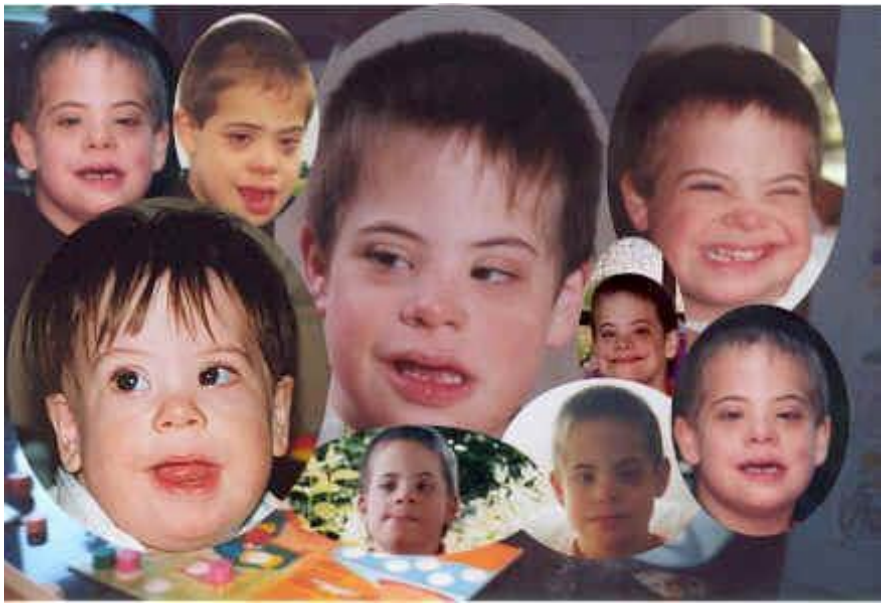
Mosaic：there are two or more chromosome number of different cells in an individual.

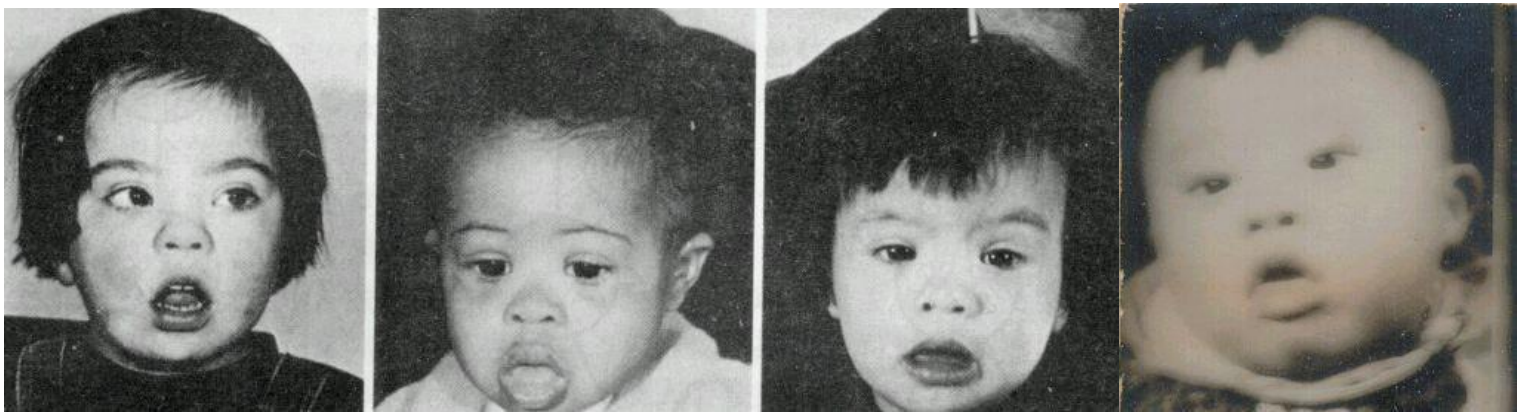
Chromosome disease

Trisomy 21

Down syndrome
(mongolism)

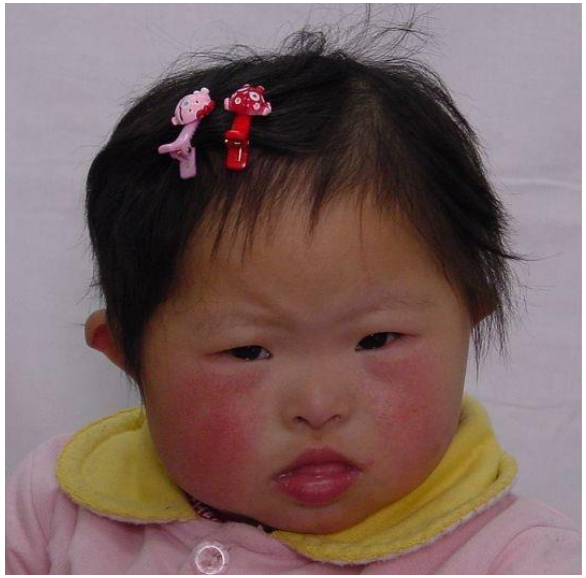
Clinical Manifestation :
Sluggish face is common





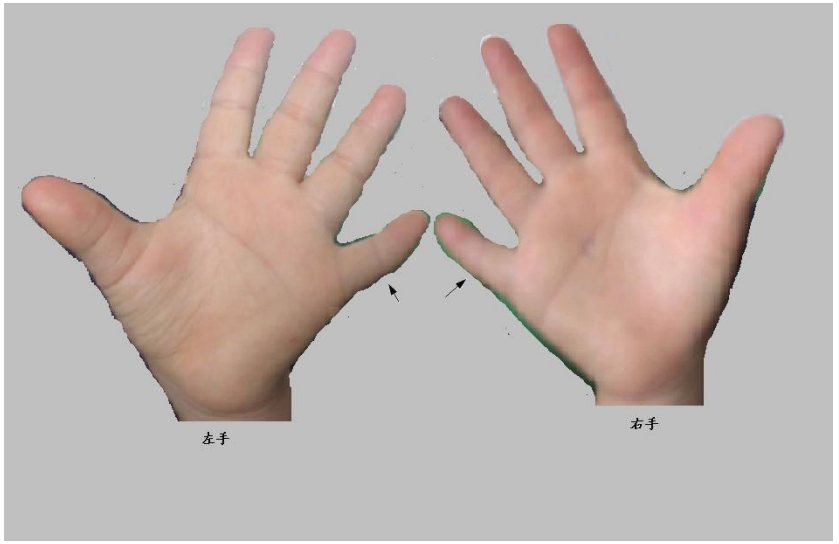
Down syndrome

Incidence 1/700
2/3 of down fetus spontaneously abort
Trisomy 21 in 94% of cases with extra chromosome from mother mostly(95%)
2% are mosaic

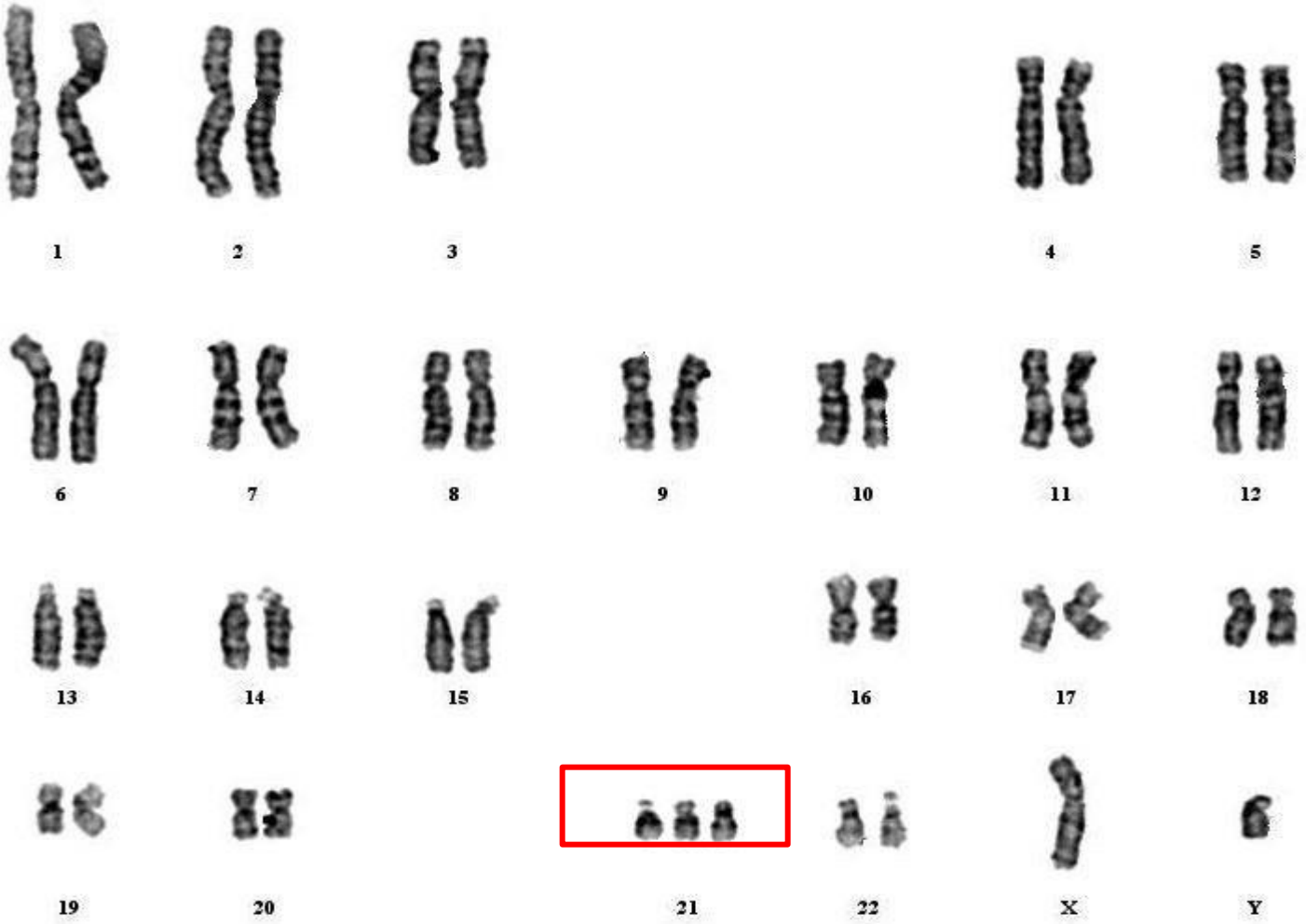


Clinical features

Severe mental retardation, growth retardation, Occipital flat, small finger wrinkle, male infertility female fertility casually.



Trisomy 21



47, XY, +21

Edward syndrome （Trisomy 18)

- **Prevalence is approximately**

1 in 25,000

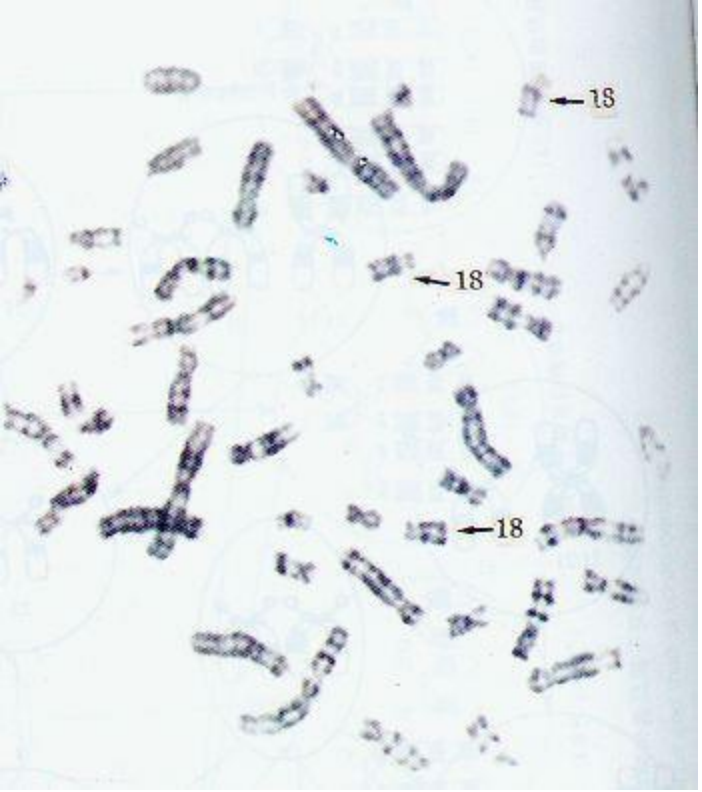
- **The preponderance of females compared**

with male

- **Prevalence is related with maternal age**
- **45% child patient die in one month**
- **90% child patient die in six months**

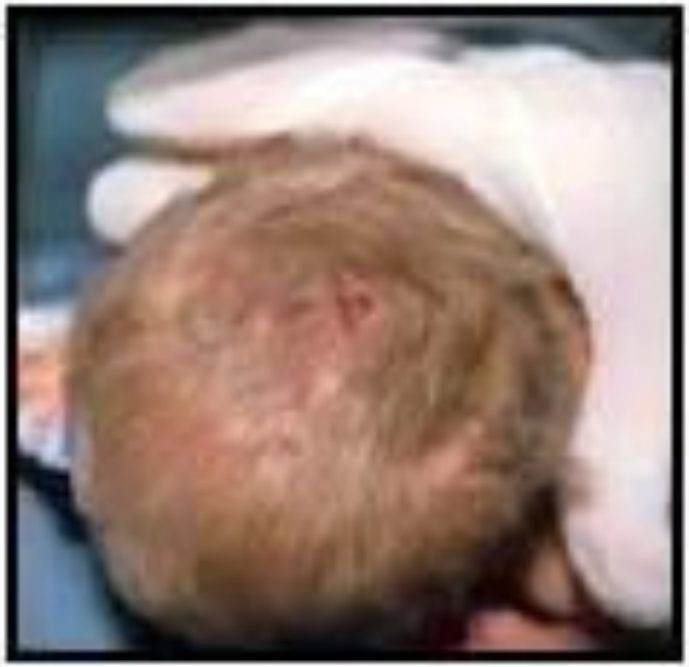
Clinical Manifestation ：

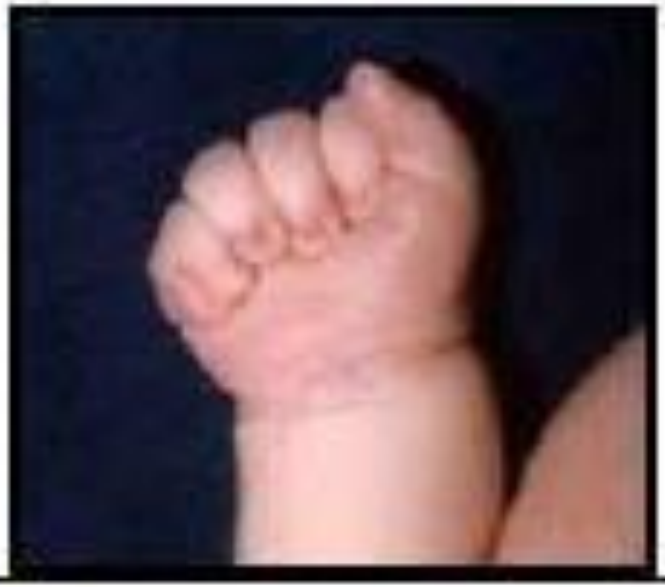
severe abnormity， die shortly after birth, intrauterine growth retardation， small eyeball， small mouth， short neck， severe mental retardation



Edward syndrome (Trisomy 18)

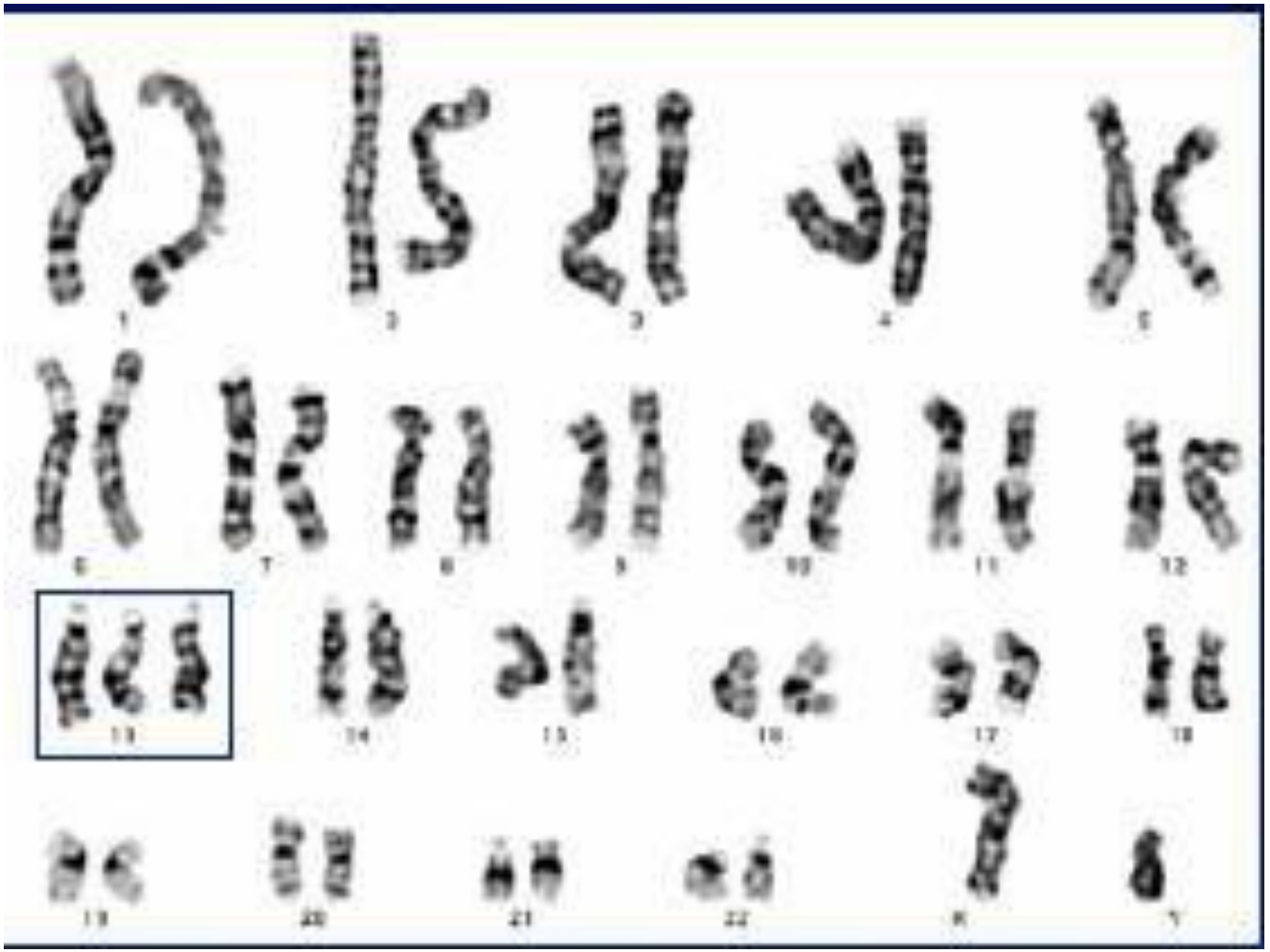
Trisomy 13 (Patau syndrome)

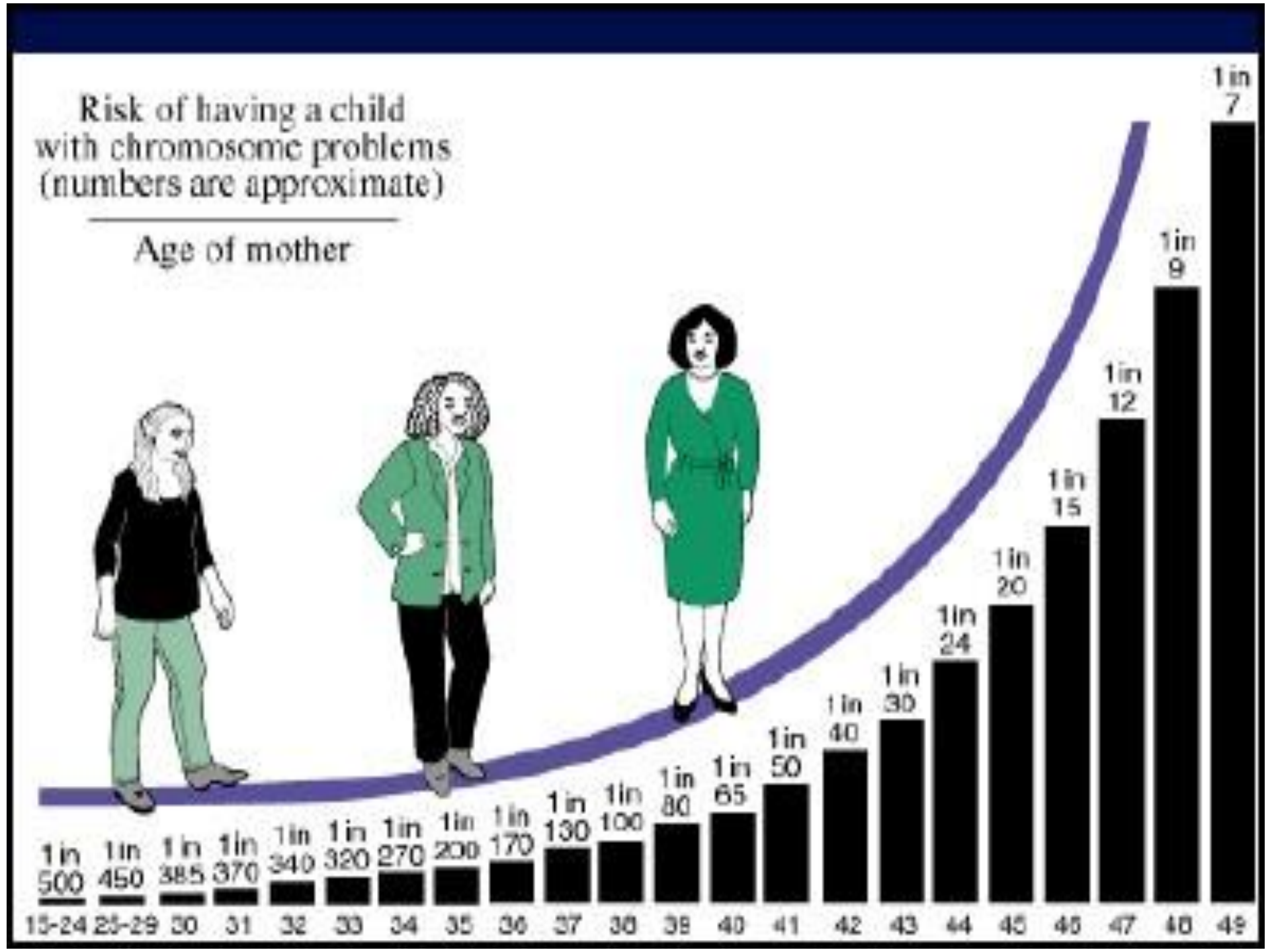




Midline malformations, scalp defect, polydactyly

Trisomy 13




Risk of having a child with chromosome problems (numbers are approximate)
Age of mother
1 in 500
1 in 450
1 in 385
1 in 370
1 in 340
1 in 320
1 in 270
1 in 200
1 in 170
1 in 130
1 in 100
1 in 80
1 in 65
1 in 50
1 in 40
1 in 30
1 in 24
1 in 20
1 in 15
1 in 12
1 in 9
1 in 7
15-24
25-29
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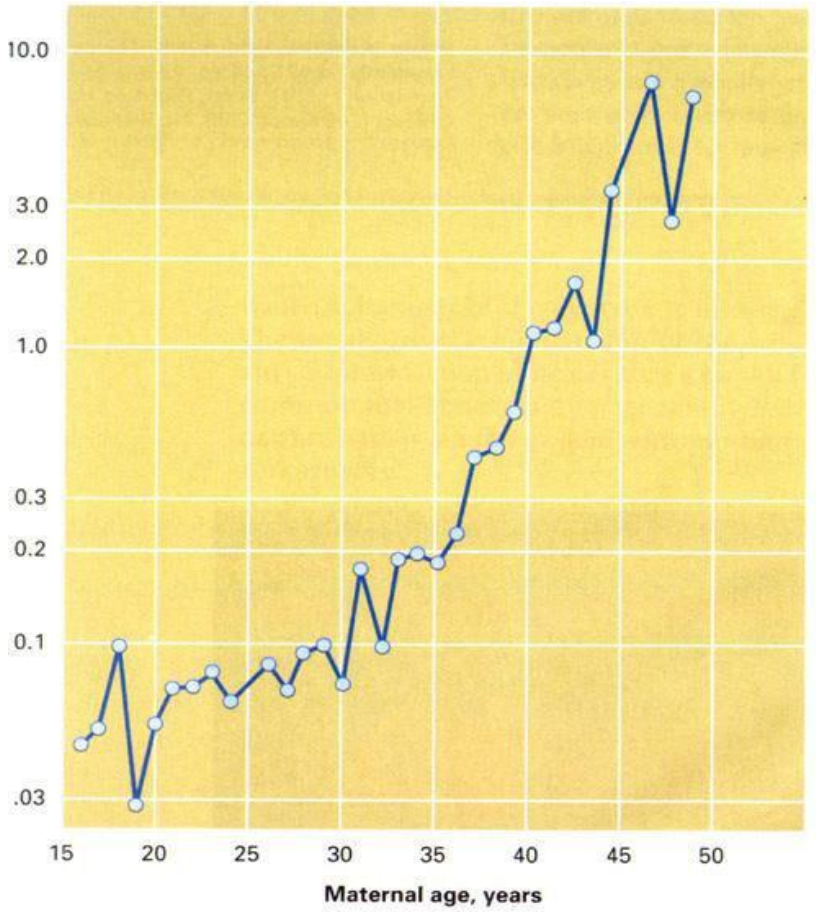
Reasons of chromosome aberration

Case：**Down syndromes and maternal age**

The hazard probability is 100 times than the normal women.



The Frequency of Chromosome Non-Disjunction And Down Syndrome Rises Sharply with Maternal Age

Mother's age	Chances of giving birth to a child with Down syndrome
20	1 in 1925
25	1 in 1205
30	1 in 885
35	1 in 365
40	1 in 110
45	1 in 32

Chromosomal Abnormalities: Structural Rearrangements

- Due to chromosome breakage and reunion in an abnormal way

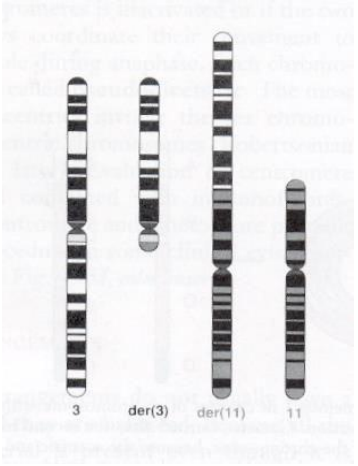
- Either:

  - ***Balanced*** (*usually* normal phenotype)
    - Inversion, Reciprocal translocation, Robertsonian translocation

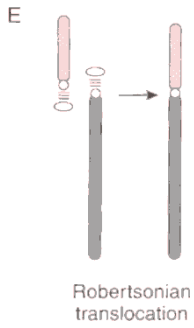
  - ***Unbalanced*** (abnormal phenotype)
    - Deletion, Duplication, Ring, Isochromosome

Balanced Structural Rearrangements - Translocations

- ***Reciprocal translocation*:**
  - Breakage of non-homologous chromosomes
  - Reciprocal exchange of broken-off segments



- ***Robertsonian translocation***:
  - 2 acrocentrics fuse near centromere
  - Loss of short arms
  - Still balanced because multiple copies of rRNA genes



Consequences of reciprocal translocations

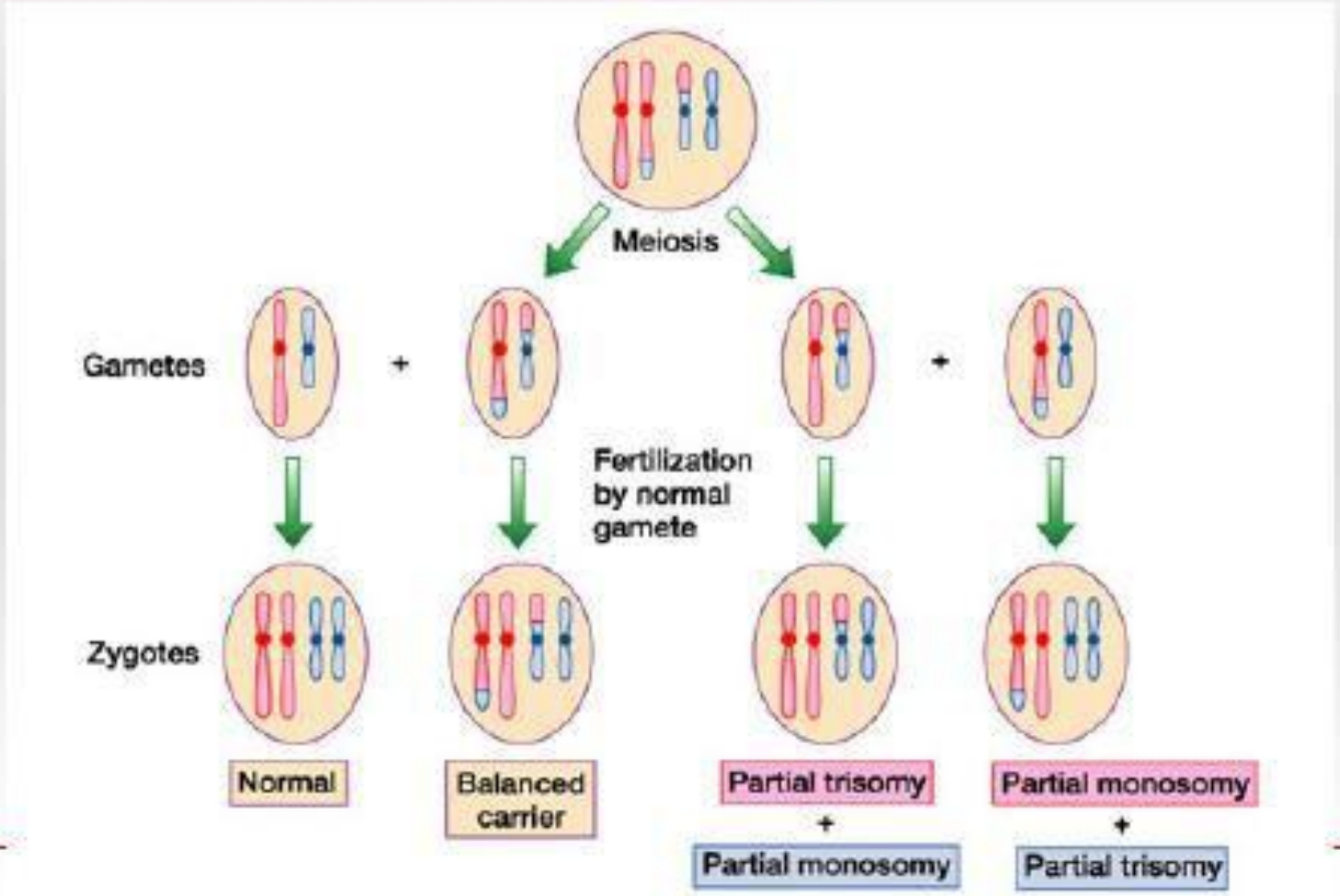
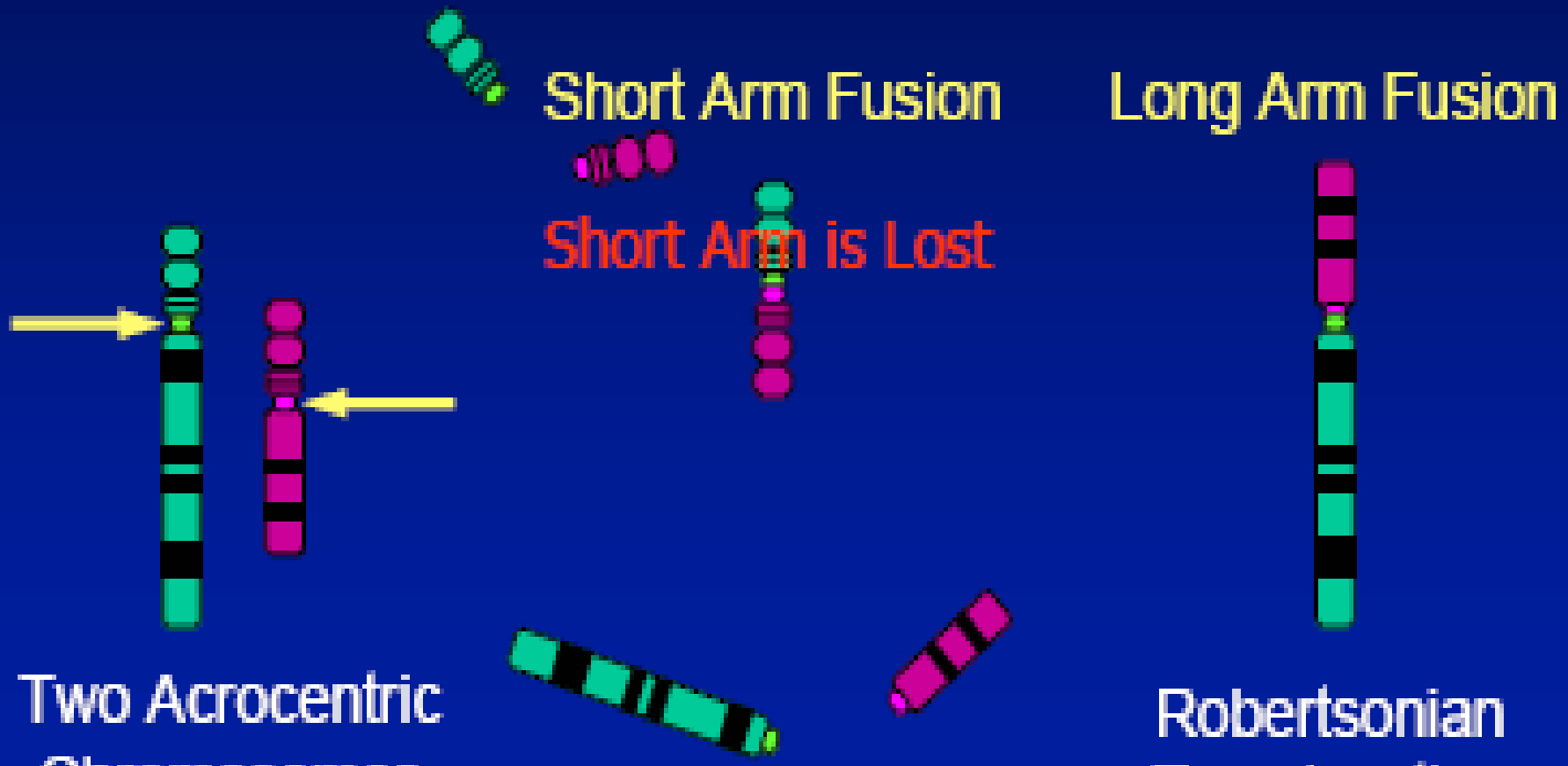


Figure 2-22 Human Molecular Genetics, 3/e. (© Garland Science 2004)

Robertsonian Translocation

- Translocation between acrocentric chromosomes. Short arms are lost and long arms fuse at centromere (5% of Down syndrome)



Consequences of Robertsonian fusions

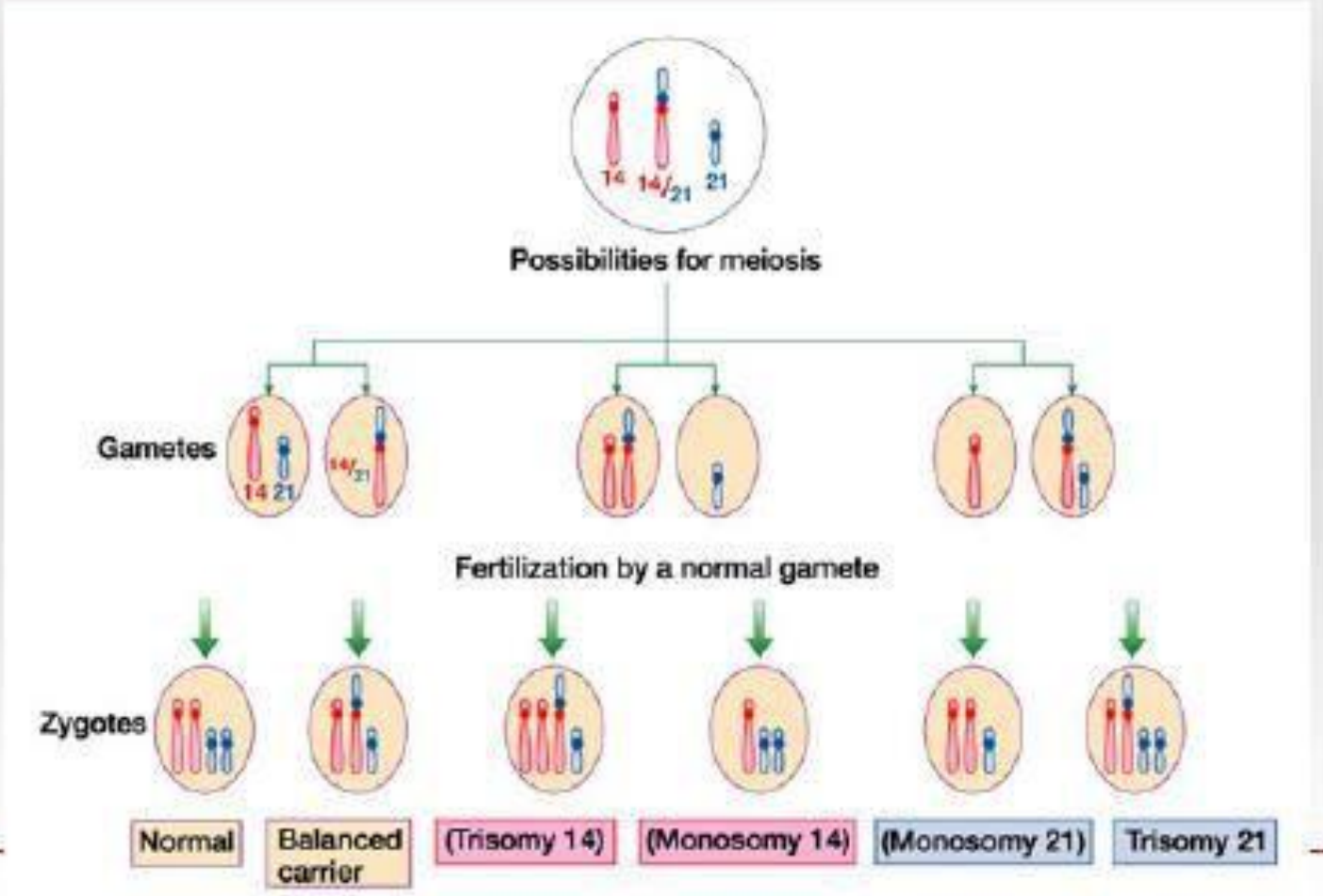


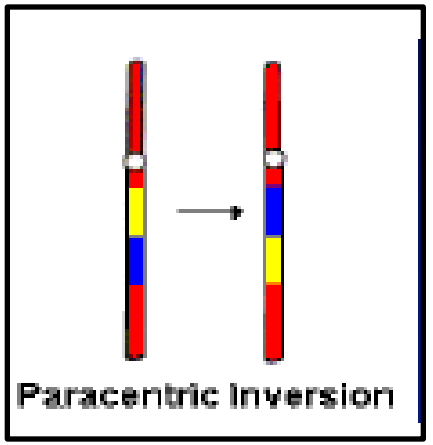
Figure 2-23 Human Molecular Genetics, 3/e. (© Garland Science 2004)

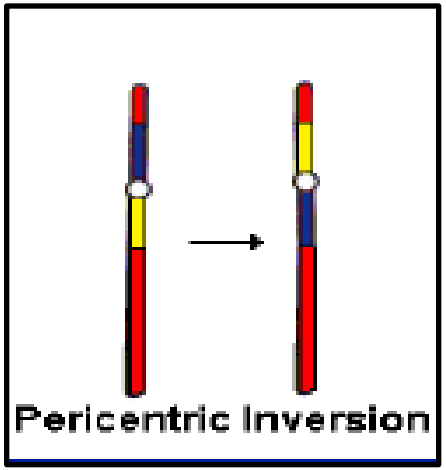
Balanced Structural Rearrangements
Inversion:

- ***Inversion:***
  - Chromosome undergoes 2 breaks
  - Segment between the breaks is inverted
- 2 types:

  - **Paracentric**
    - 2 breaks on one side of centromere; arm ratio unchanged
    - unbalanced offspring (recombinants) usually not viable (acentric or dicentric)
  - **Pericentric**
    - one break in each arm; often arm ratio changed
    - recombinants have duplications and deficiencies of chromosome segments
    - risk of carrier having viable recombinant: 5-10%

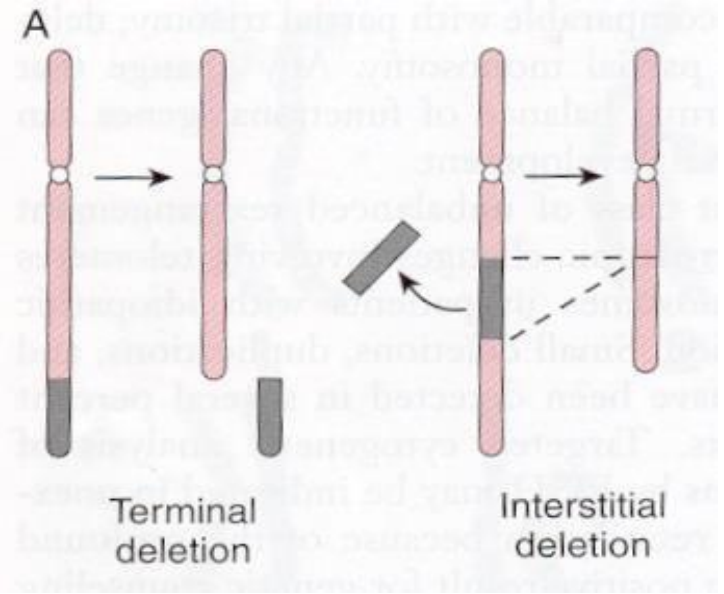
    eg: Allderdice syndrome



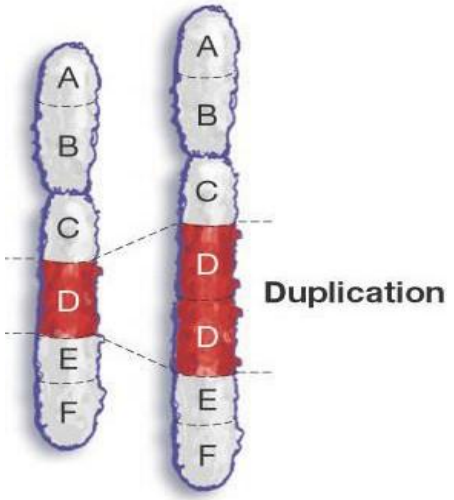


Unbalanced Structural Rearrangements - Deletion & Duplication:

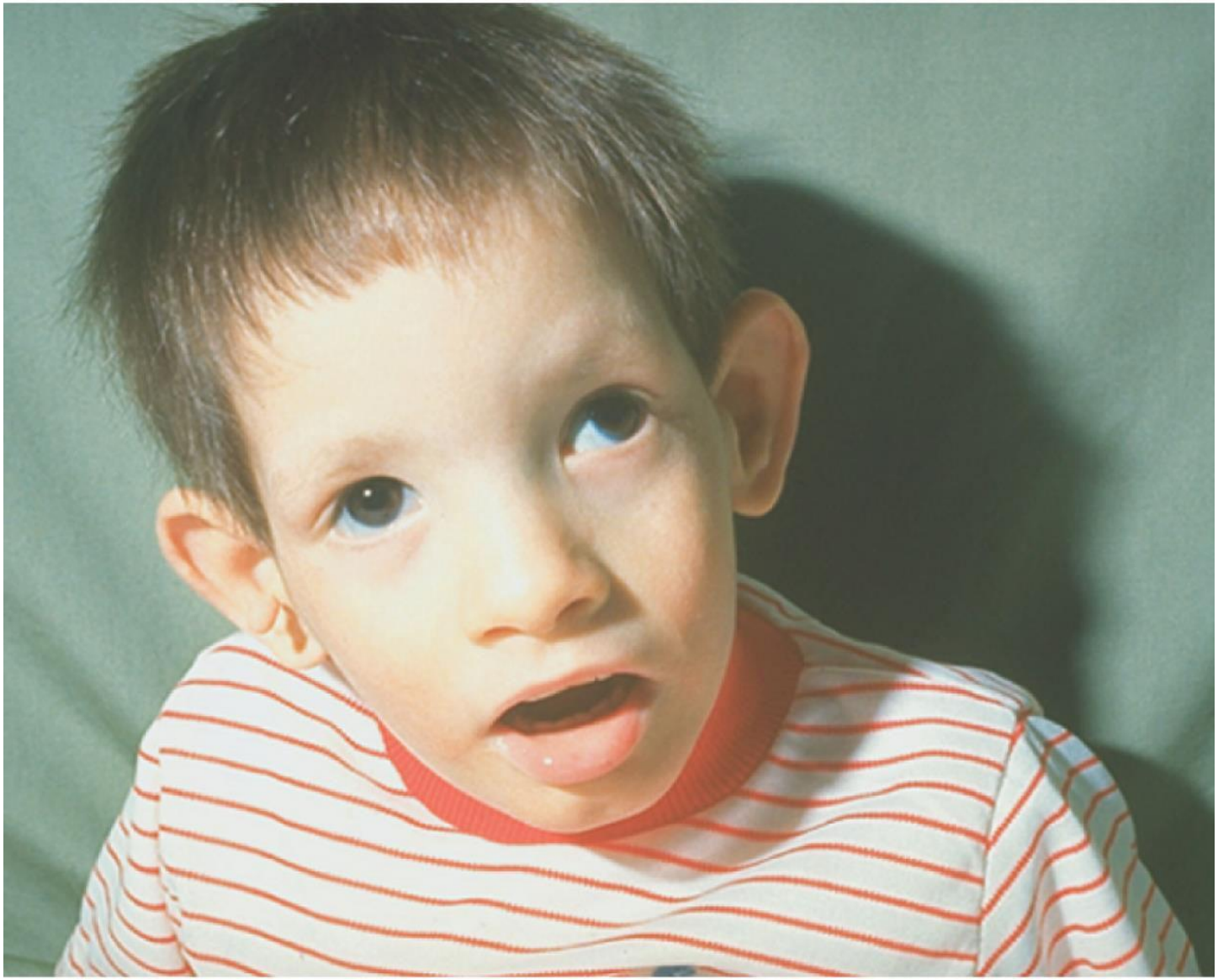
- **Deletion:**
  - Loss of a chromosome segment (5p-)
  - Terminal or interstitial
  - Must be at least 5 Mb to be seen cytogenetically
  - 46, XX del (5p) (p15)



- **Duplication**
  - 46, XY dup (1) (q22q25)

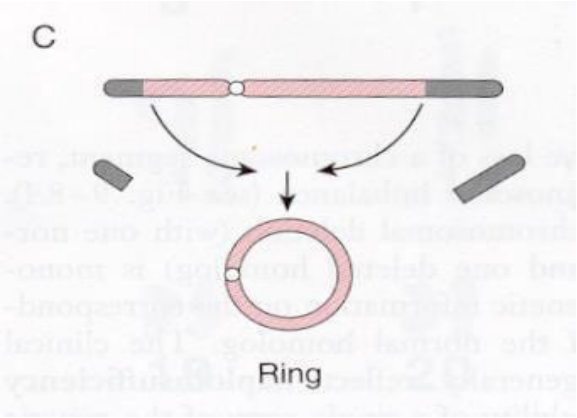


A Boy with Cri-du-Chat Syndrome – a Debilitating Disorder Caused by Chromosome Deletion

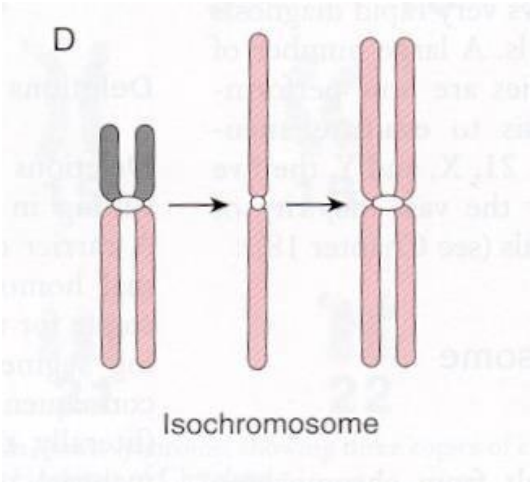


Unbalanced Structural Rearrangements: Ring and Isochromosome

- ***Ring chromosome***:
  - Chromosome undergoes 2 breaks
  - Broken ends reunite in a ring



- ***Isochromosome:***
  - One arm missing; other arm duplicated
  - Breakpoints are assigned to the centromere



Sex chromosome disease

Sex chromosome disease/s caused by the sex chromosome number or structure abnormality. Sex chromosome is 1 / 3 of the total number of chromosomes.

The prevalence is 1 in 500. due to secondary sex character, the majority in adolescent development show symptoms.

common features of sex chromosome disease

sex character development insufficient or abnormal.
mental retardation.

Sex chromosome disease

Klinefelter syndrome

prevalence in male is about 1 in 700 or 800 .

infertility male 1/10.

It is caused by an extra X chromosome

Clinical Manifestation

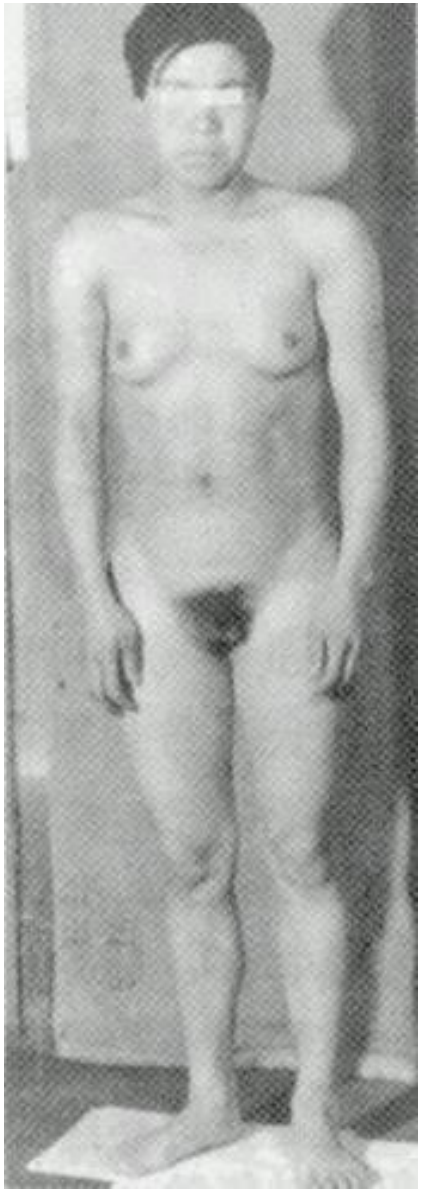
small penis and testis

tall statures and long arms and legs

sexual characteristics difference、

part female characteristics

poor beard growth



Turner syndrome

Karyotype： 45, X

The incidence rate of the female infant is 1 / 5 000

And accounted for 18% to 20% in spontaneous abortions.

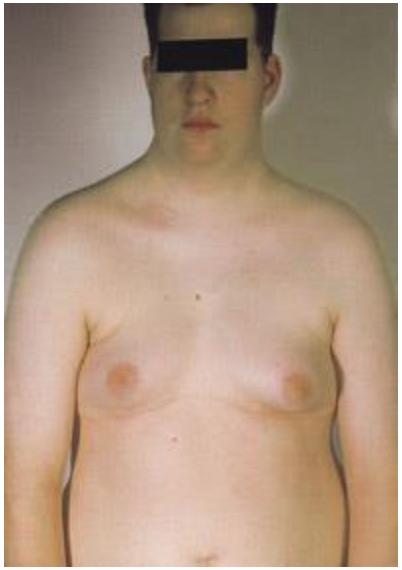
One of the X chromosomes is either missing or inactive.

Clinical features ：

These women have immature female appearance, do not develop secondary sex characteristics, and lack internal reproductive organs.

Sex Chromosome Aneuploid Conditions are Common

Sex Chromosomal			
XXY	1/1,000 (males)	Klinefelter	Sexual immaturity (no sperm), breast swelling
XYY	1/1,000 (males)	Jacobs	Tall
XXX	1/1,500 (females)	Triple X	Tall and thin, menstrual irregularity
X0	1/5,000 (females)	Turner	Short stature, webbed neck, sexually undeveloped



Learning Outcomes

Having gained a knowledge on the types of genetic disorders and a broad understanding of the types and the basis of chromosomal abnormalities that affect the humans, the student by completion of the lectures should be able to :

- **List the types of genetic disorders that could affect the humans.**
- **Briefly describe each of the above disorders; namely chromosomal, single gene, polygenic, mitochondrial and somatic disorders giving examples.**
- **Understand the basis of the numerical and structural chromosomal abnormalities leading to human disorders and give examples of each of the above.**
- **Outline the mechanism of non disjunction and translocation in the causation of chromosomal trisomies.**
- **Briefly explain the maternal age effect and its relevance to chromosomal trisomies.**