Ivana FELLNEROVÁ

# CHROMOSOMAL ABNORMALITIES

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# Lecture overview

- Cell division [mitosis, meiosis]
- Numerical [genomic] abnormalities
- Structural [chromosomal] aberration
- Prenatal diagnosis
- ISCN

# CELL DIVISION

## MITOSIS, MEIOSIS

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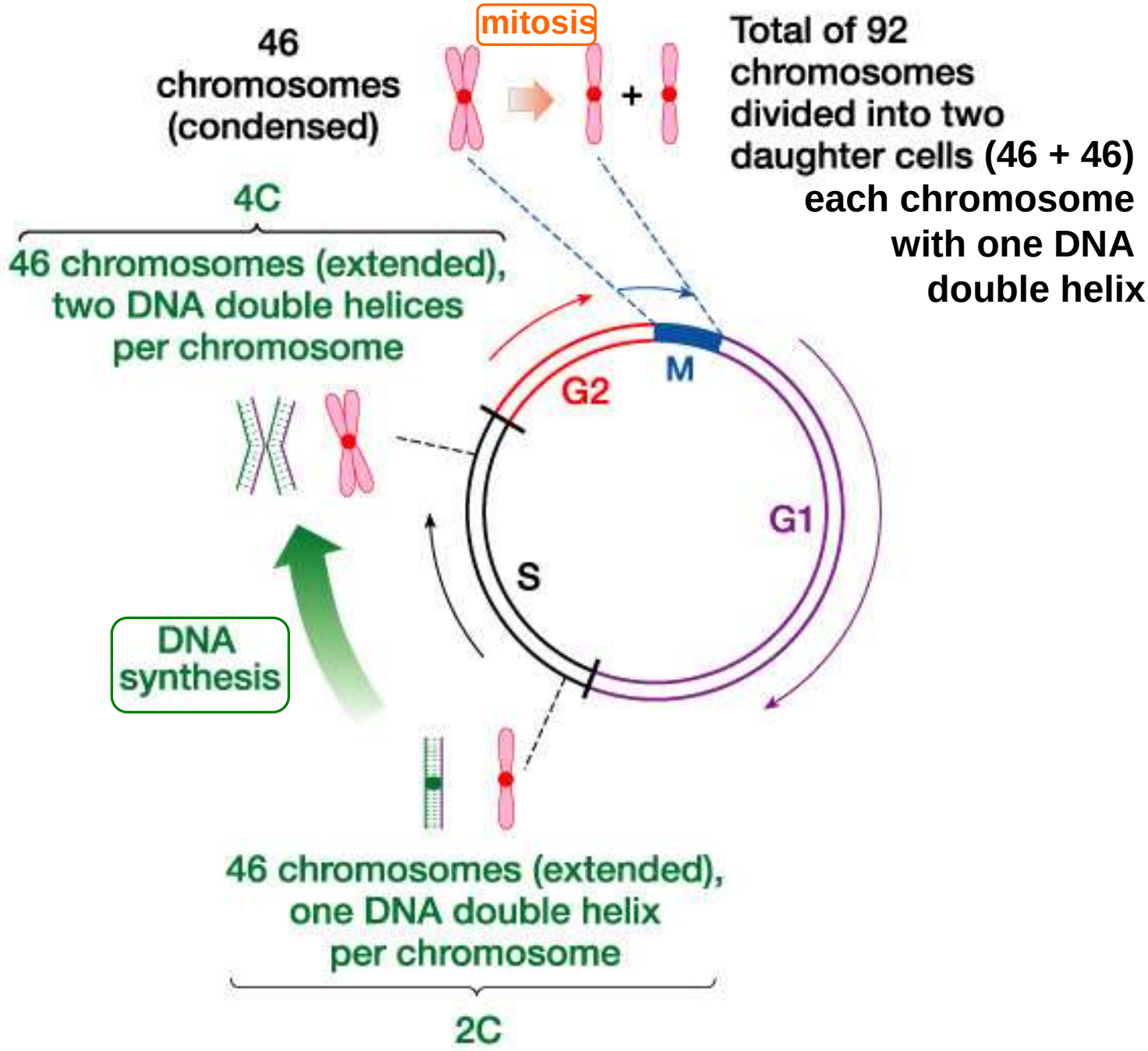
# CELL CYCLE

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# MITOSIS

## INTERPHASE

- Nuclear envelope intact
- No chromosomes visible

Mitosis

## Prophase

- Chromosomes condense and become visible
- Bipolar spindle develops

## Prometaphase

- Nuclear envelope dissolves
- Chromosomes begin to migrate to equatorial plane (metaphase plate) and are seen to contain two chromatids

## Metaphase

- Chromosomes fully condensed and located at metaphase plate

## Anaphase

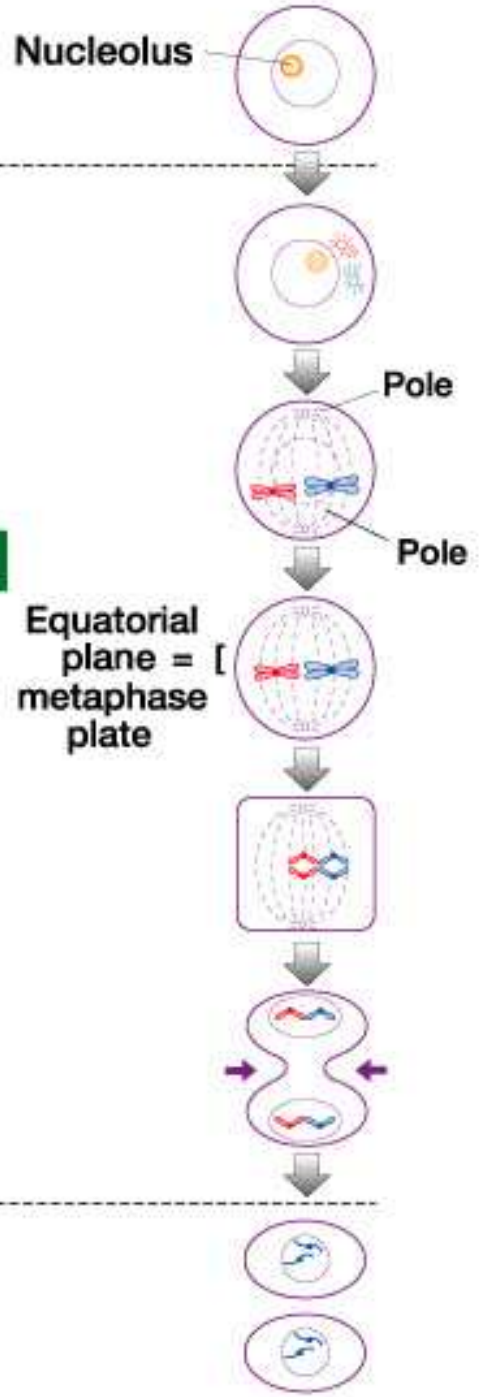
- Each centromere splits
- The two chromatids of each chromosome are pulled to opposite poles

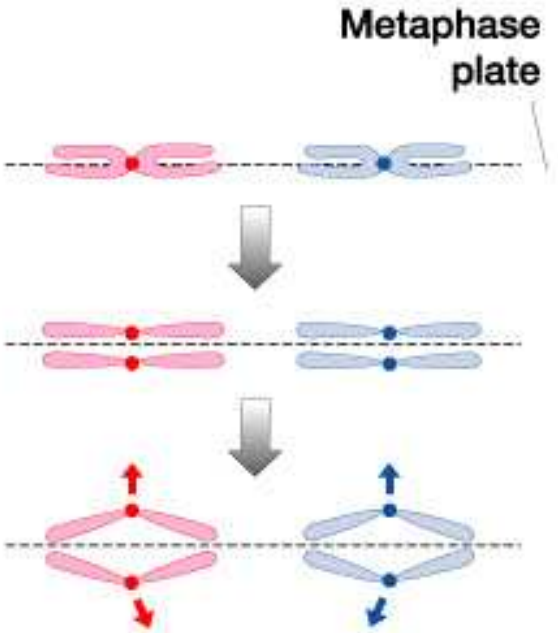
## Telophase

- Chromosomes reach poles and start to decondense
- Nuclear membrane reforms
- Cytoplasm starts to divide

## Cytokinesis

- Cytoplasm division completed to give two daughter cells

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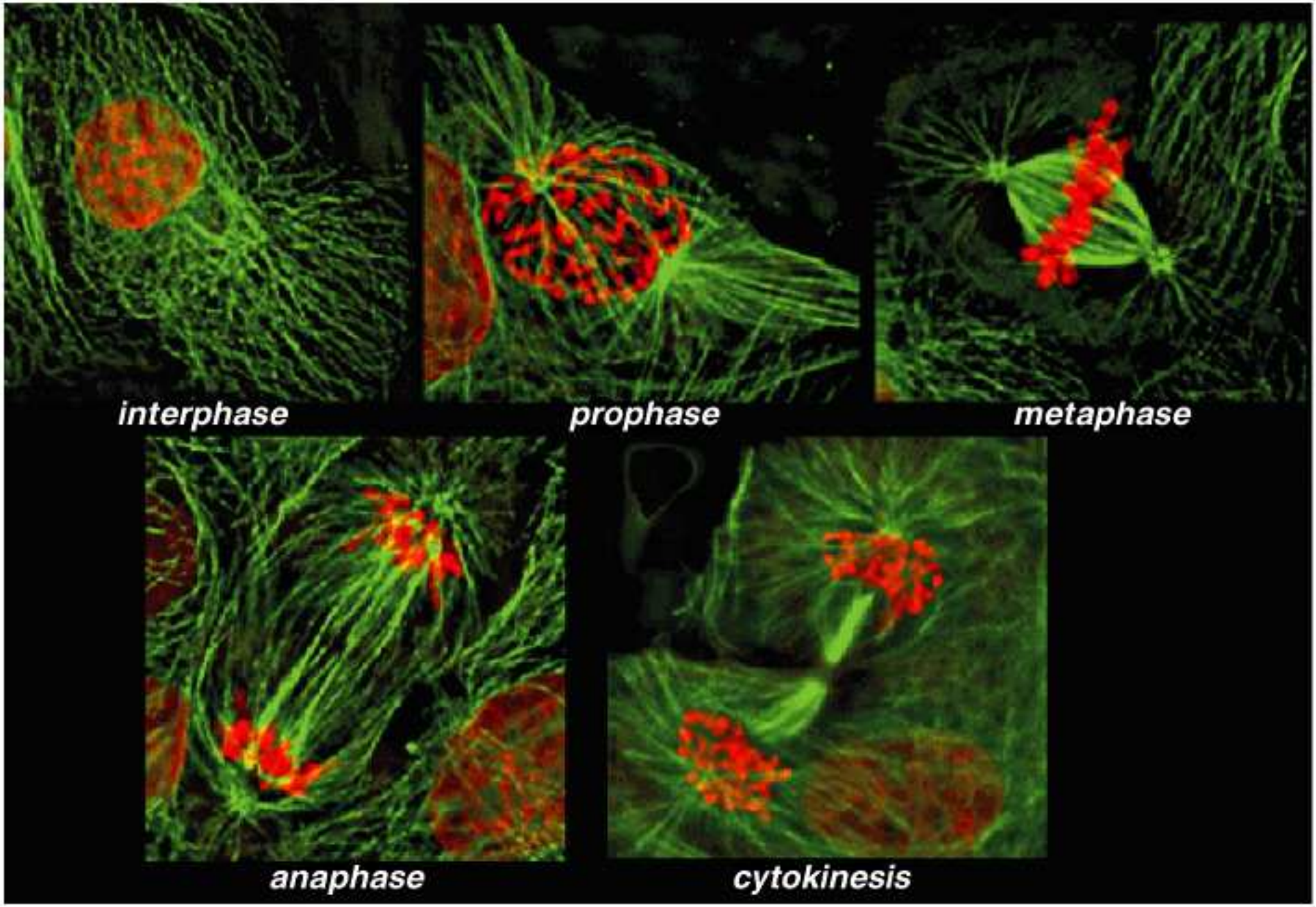
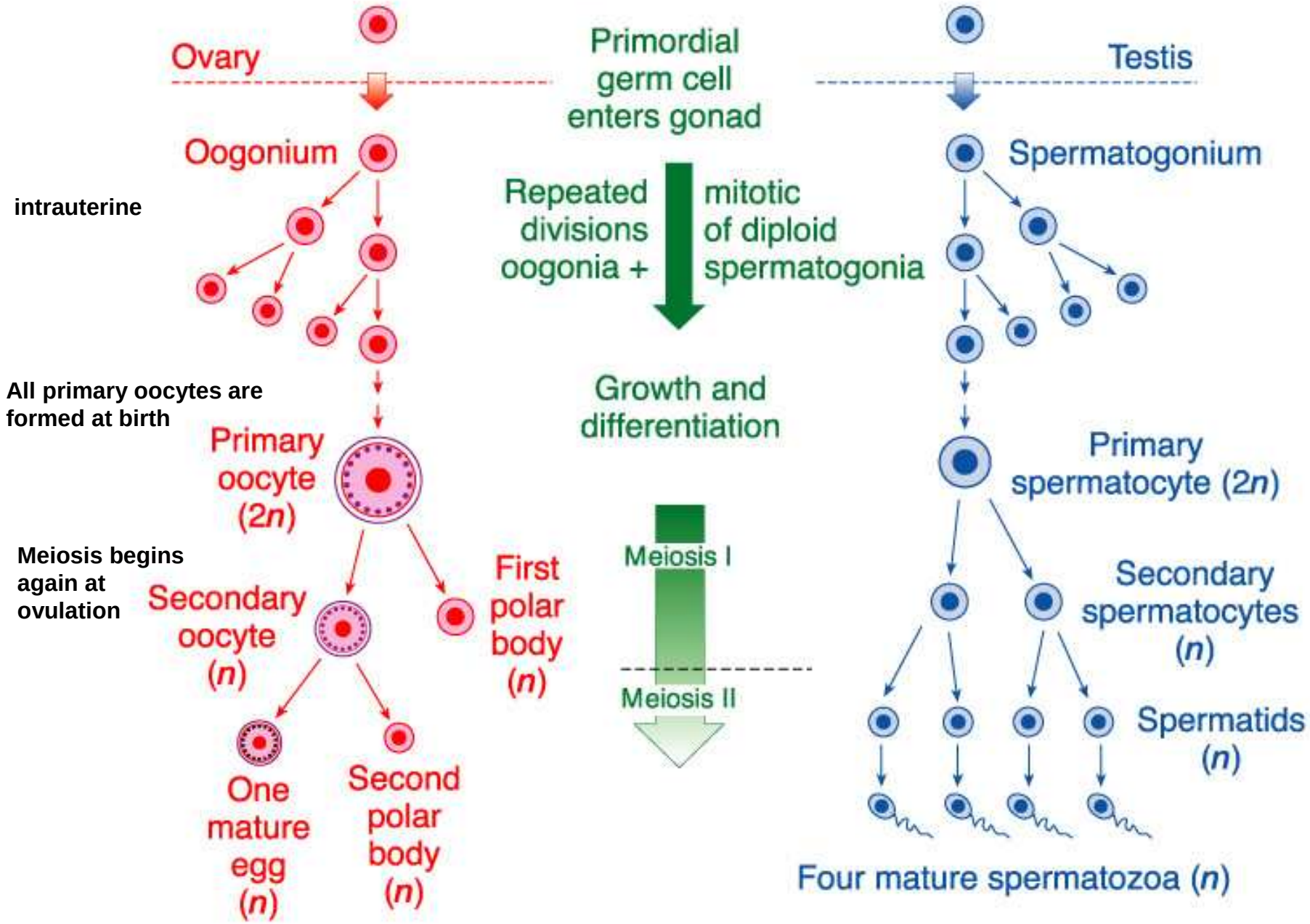

interphase
prophase
metaphase
anaphase
cytokinesis

# MEIOSIS (gametogenesis)



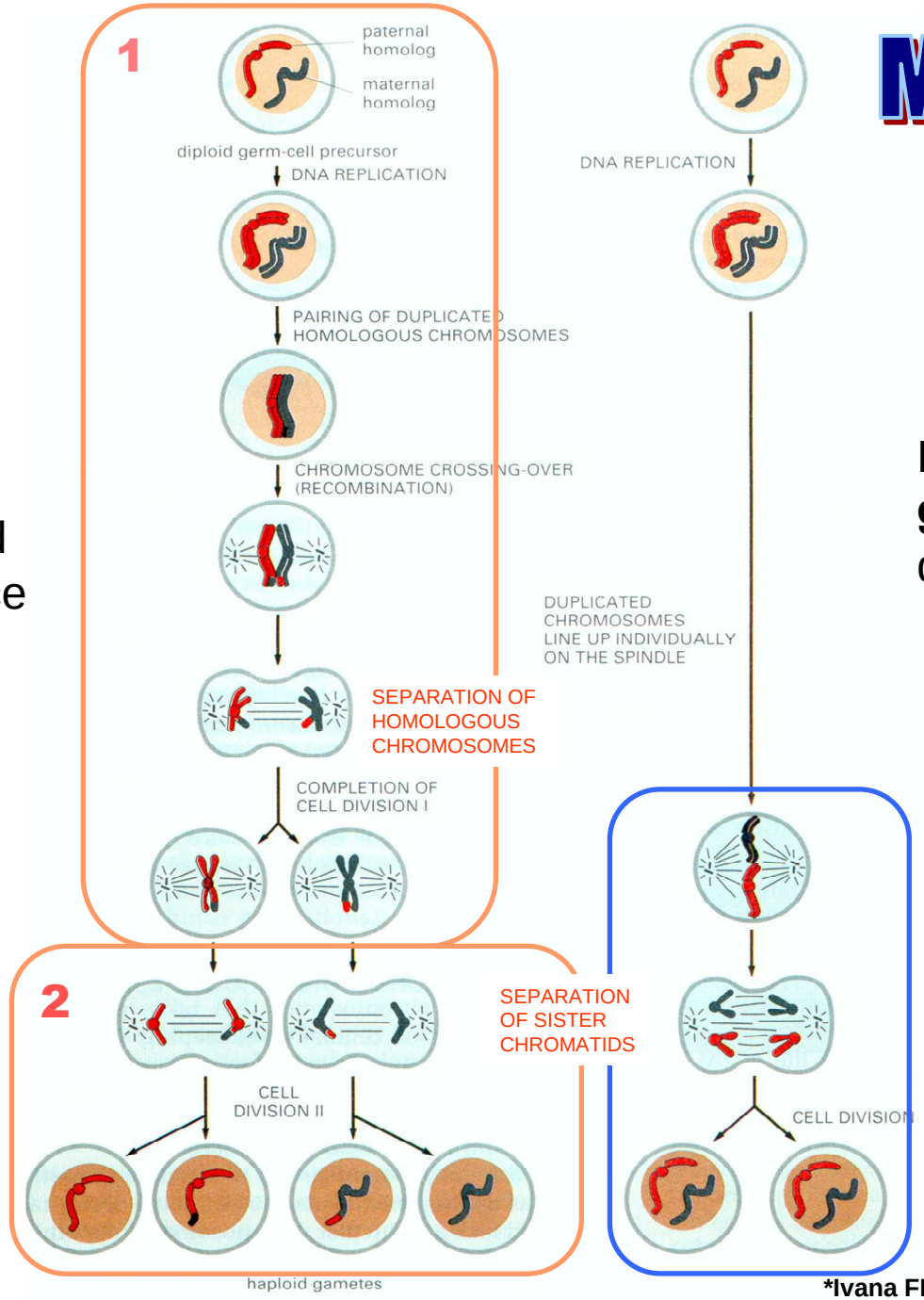
# MEIOSIS

Germ cell division [gametogenesis]

Essential for **reproduction** and species maintenance

**Two** successive **cell division** without intervening DNA replication

Production of four **haploid** germ cells




# MITOSIS

Somatic cell division

Essential for **growth** and development

human zygote = 1 cell
mature adult = $10^{14}$ cells

**Single** cell **division**

Production of two identical daughter cells

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# Chromosomal abnormalities

**[chromosomal malformations, anomalies, aberrations or defects]**

- **An error [mutation] in person's genome**
- **Any type of changes in the chromosome structure or number**
- **Often results in physical or mental abnormalities**

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# Chromosomal abnormalities

**Result from:**

- missrepair of broken chromosomes,
- by improper recombination,
- by malsegregation of chromosome during mitosis or meiosis.

**Constitutional abnormalities:**

All cells of the body have the abnormality. This results from a defective gamete or abnormal fertilization.

**Somatic abnormalities:**

Occur only in certain cells or tissues of the body. This results in a mosaic individual.

# Clasification of the

# HUMAN KARYOTYPE ABNORMALITIES

- **NUMERICAL [genomic] mutation:**

  **Changes of the chromosome number**

- **STRUCTURAL [chromosomal] aberration:**

  **Parts of chromosomes are lost, gained or moved to new position in the genome**

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# NUMERICAL ABNORMALITIES

## Changes of the chromosome number

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# Basic terms

**EUPLOID:**

organism with normal chromosome set. Greek: *eu* = “good”
*ploid* = “set”

**POLYPLOID:**

organism with multiple of haploid set [ triploidy 3n, tetraploidy 4n ]

**ANEUPLOID:**

organism with unbalanced set of chromosomes (monosomy, trisomy).
chromosome number that is not exact multiple of the haploid set

**MIXPLOIDY:**

organism with two or more genetically different cell linages

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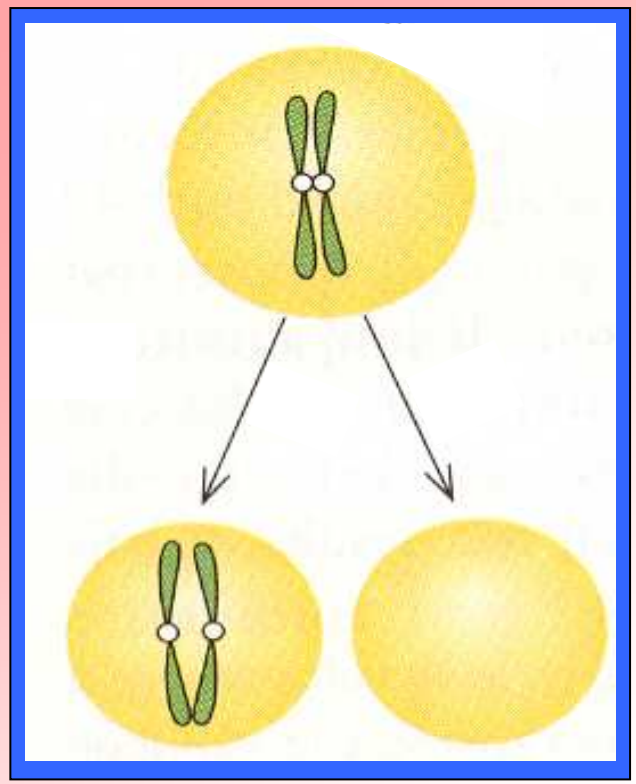
**The common mechanism by which disorder in chromosome number (aneuploidy) arises is called:**

# NON-DISJUNCTION

**= process when homologues chromosomes or sister chromatids fail to disjoin [ do not separate] into two daughter cells during cell division**



Depends on when nondisjunction take place:

- **<u>mitotic</u> nondisjunction**
- **<u>meiotic</u> nondisjunction**

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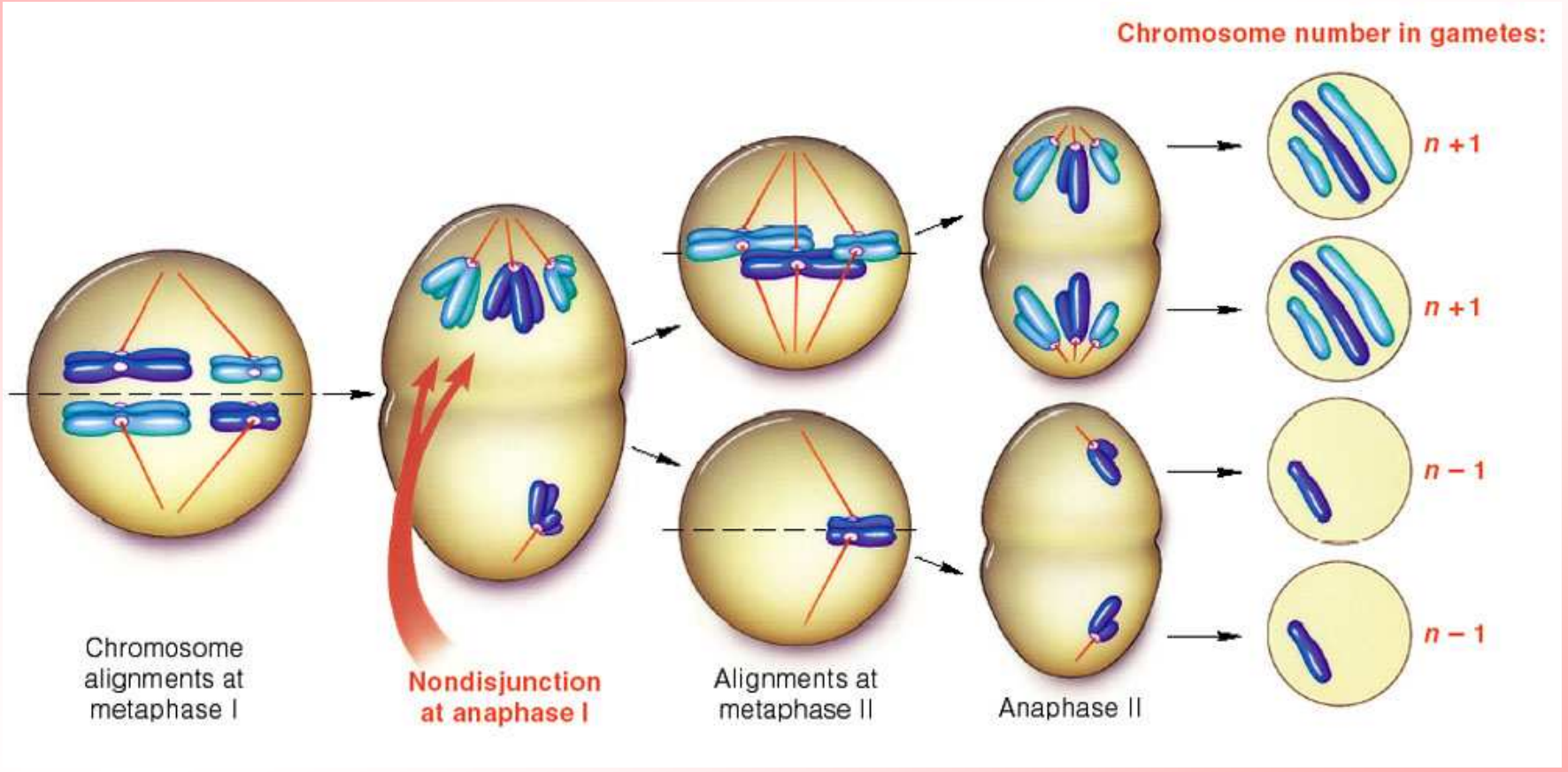
# Non-disjunction

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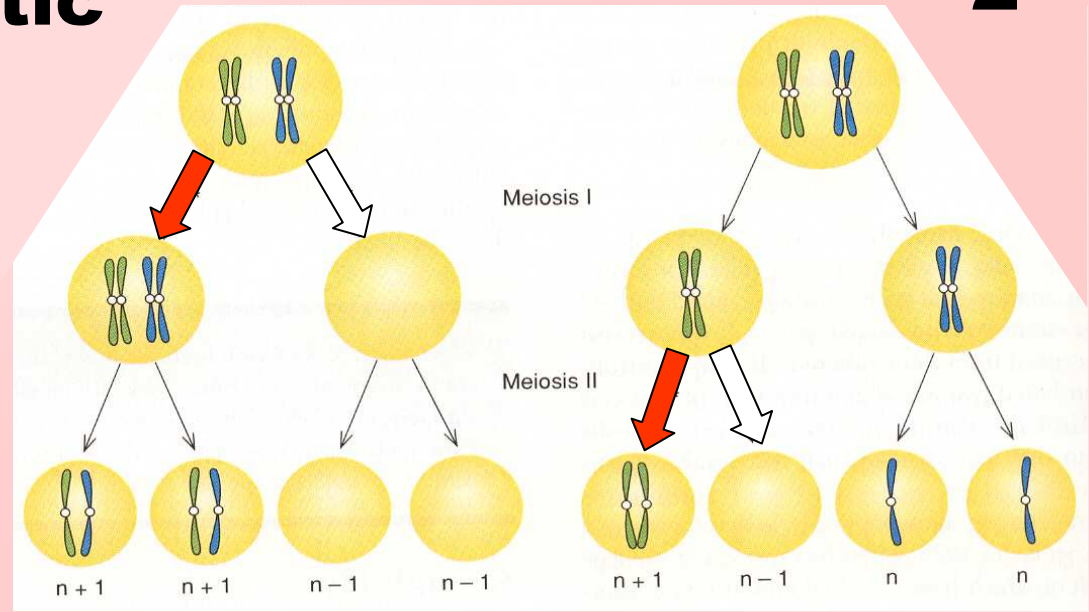
# MEIOTIC non-disjunction

## 1st meiotic division

**Homologues chromosomes** do not separate properly




## 2nd meiotic division

**Sister chromatides** do not separate properly

## ALL GAMETS ARE ABNORMAL

**half gametes carry both, half neither homologous chromosome**

## HALF GAMETS ARE NORMAL

**half gametes are abnormal one caries both, one neither chromosome**

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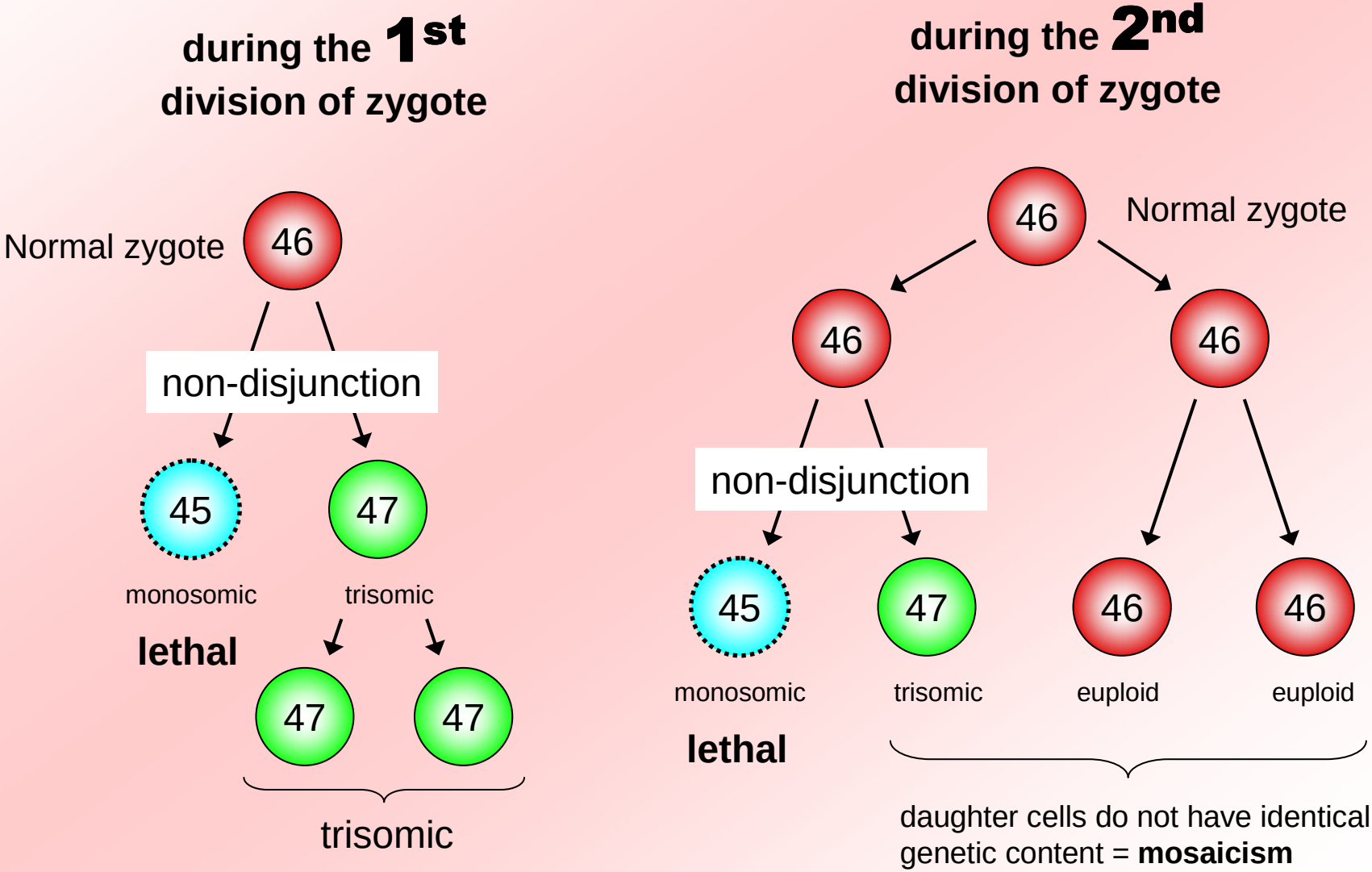
# MITOTIC non-disjunction



# Classification of NUMERICAL mutation

**POLYPLOIDY :** TRIPLOIDY (3n)
TETRAPLOIDY (4n)

**ANEUPLOIDY:** AUTOSOMAL aneuploidy
- Down syndrome [trisomy 21]
- Edwards syndrome [trisomy 18]
- Patau syndrome [trisomy 13]

SEX CHROMOSOME aneuploidy
- Turner syndrome [XO female]
- “Superfemale” [XXX female, trisomy X]
- Klinefelter syndrome [XXY male]
- “Supermale” [XYY, male]

**MIXPLOIDY:** MOSAICISM

CHIMERA

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# 1. POLYPLOIDY

**Polyploidy individual has more than two sets of chromosome.**

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**3 sets = triploidy 3n (69 XXX, 69 XXY, 69 XYY)**
**4 sets = tetraploidy 4n**

## How polyploidy arise?

1. Multiple fertilization (polyspermy): two sperm fertilize an egg
2. Errors in meiosis : producing unreduced diploid gametes
3. Errors in mitosis that cause a somatic doubling of the chromosome number

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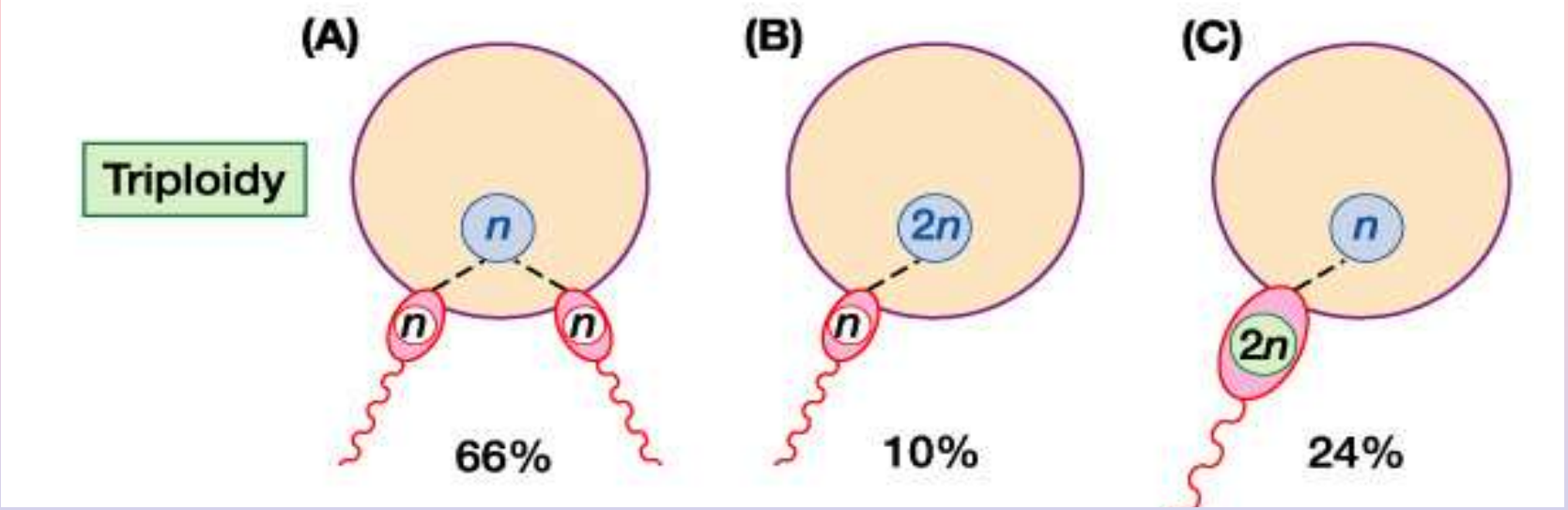
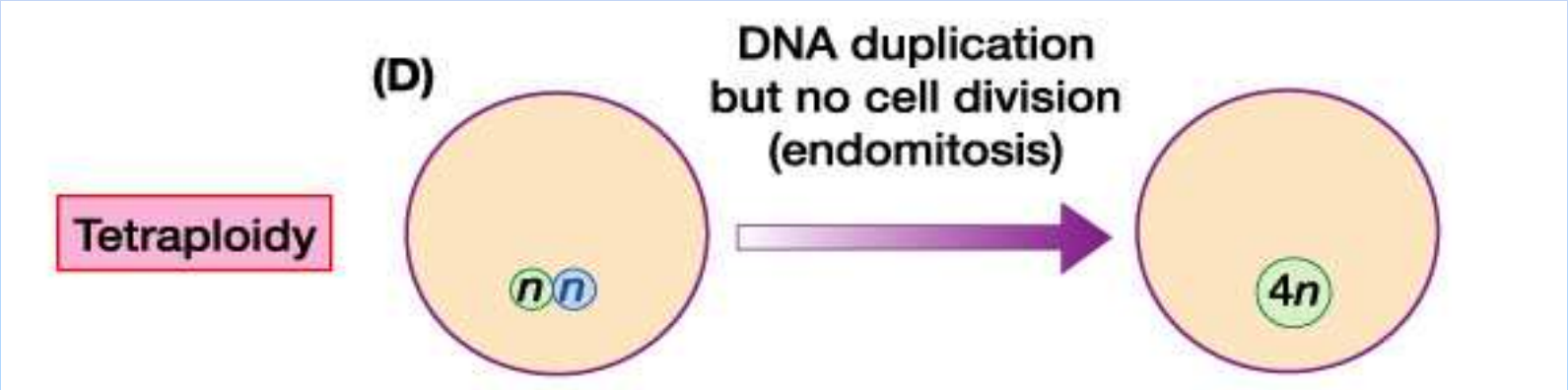
[A] Multiple fertilization

[B,C] Error in meiosis
Producing unreduced diploid gametes




[ D ] Error in mitosis [endomitosis]: doubling of the chromosome number while the first zygotic division does not complete

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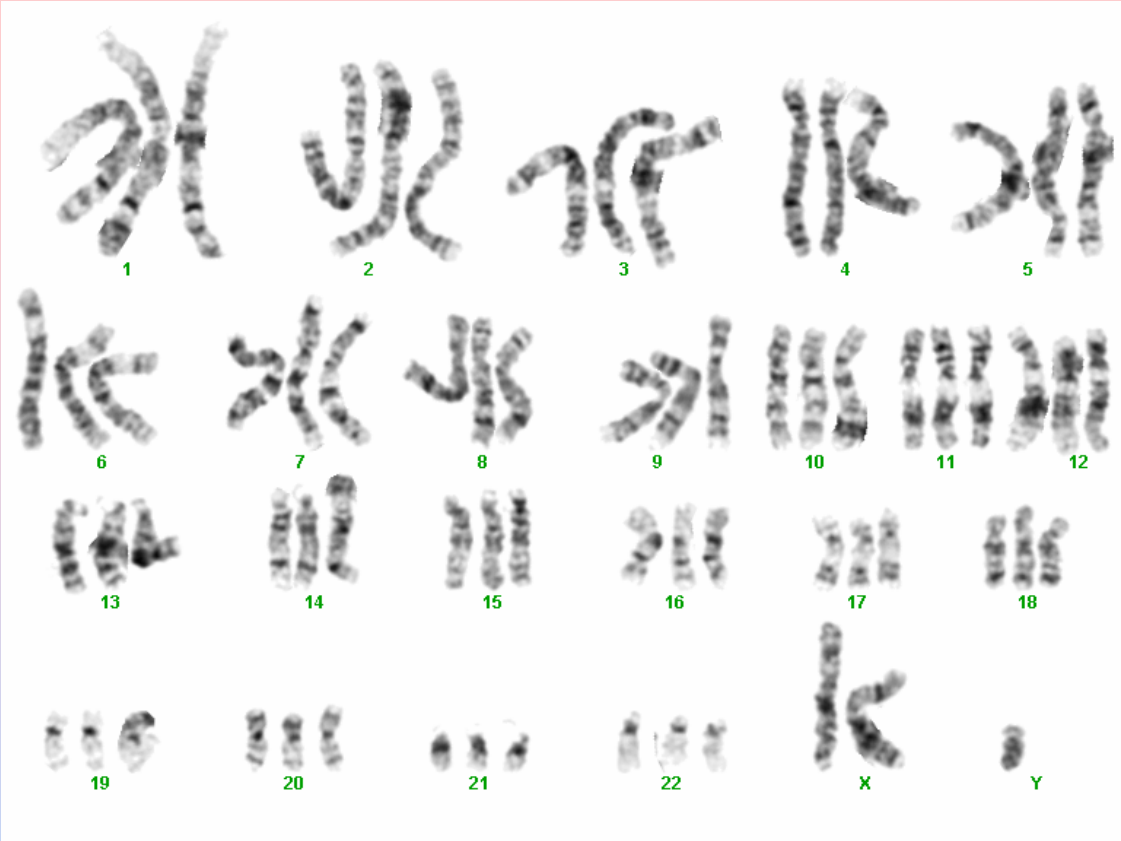
# TRIPLOIDY




- Mostly results from dispermy
- 99% of triploid conception is lethal as embryo or fetus.
- 1% infant survives for a few days
- Triploidy seen in about 1 in 10 000 live births

# 2. MIXPLOIDY

**Two or more genetically different cell linages whitin one individual.**

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**MOSAICISM**

Genetically different cell population arise from one zygote

- Aneuploid mosaics (e.g. 2n/2n+1 are common) due to non-disjunction or chromosome lag in early mitotic division of zygote

- Polyploid mosaics (e.g. 2n/3n are occasionaly found) mostly arise by fuzion of the second polar body with one of cleavage nuclei of normal diploid zygote

**CHIMERISM**

**Genetically different cell population originate from different zygotes. More rare.**

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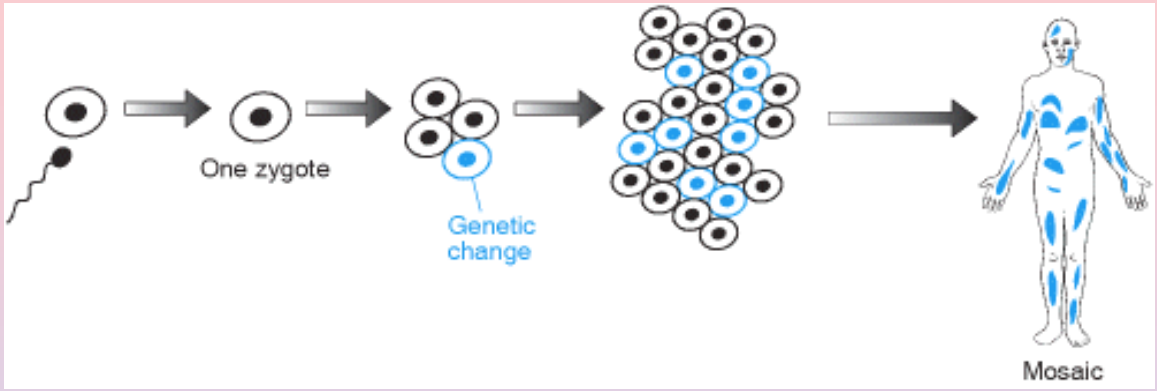
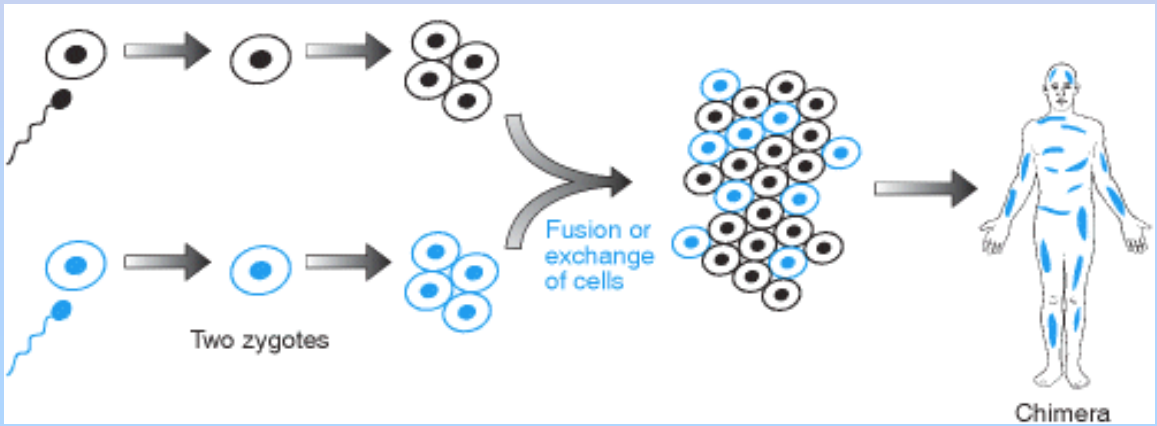
# MOSAIC




The individual that has a mixture of different cell lines derived from a **single zygote**

# CHIMERA

The individual that has two or more genetically different cell lines



# 3. ANEUPLOIDY

**Any chromosome number that is not exact multiple of the haploid se [23].**
**Cells have extra chromosomes or chromosome missing**

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**Monosomy** = condition where one chromosome is missing (mostly lethal in very early embryogenesis
**Trisomy** = condition where one extra chromosome is abbreviated

## A. AUTOSOMAL aneuploidy
changes of somatic chromosome number

## B. SEX- CHROMOSOME aneuploidy
changes of sex chromosome number

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# AUTOSOMAL aneuploidy

**Autosomal MONOSOMY - lethal condition**

**Autosomal TRISOMY - most are lethal; few exception:**

- **Down syndrome [trisomy 21]**
- **Edwards syndrome [trisomy 18]**
- **Patau syndrome [trisomy 13]**

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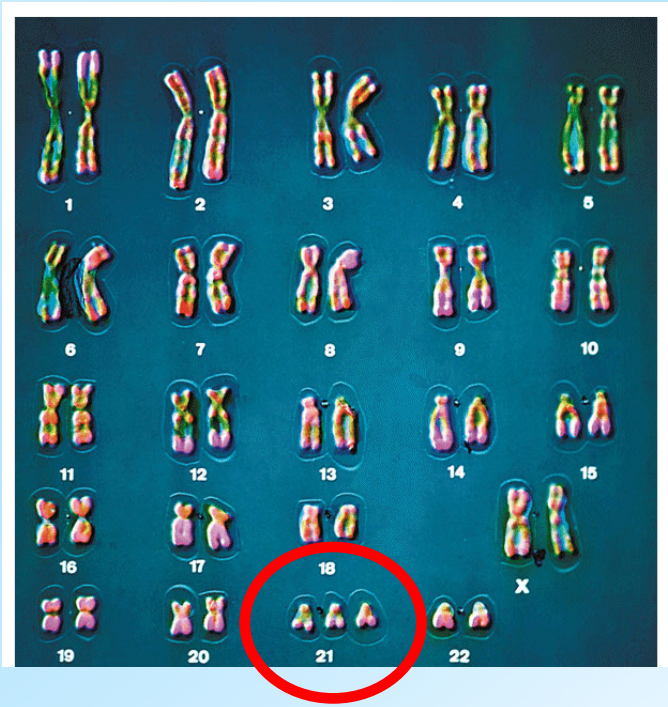
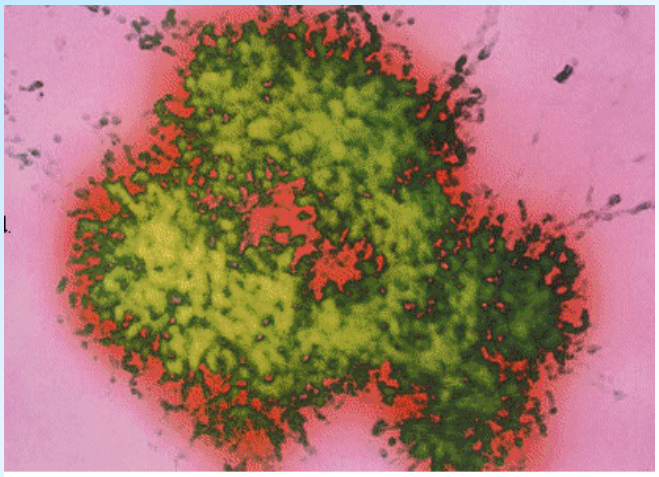
# DOWN syndrome:

**The most common chromosomal abnormalities in live born children: 1 in 800 live births**

**First chromosomal abnormality Discoverd in humans (1959)**

**Trisomy 21**



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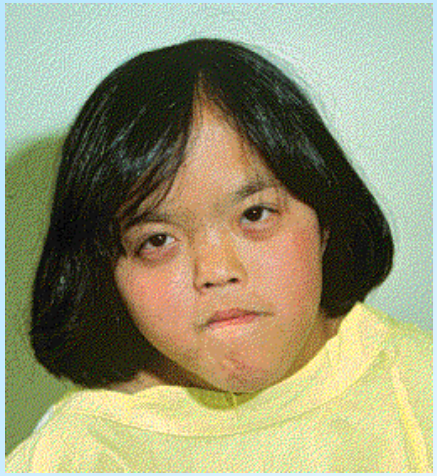
# DOWN syndrome:

**Trisomy 21**

- Mild to moderate range of retardation [their skills can be increased by right education]
- Heart and digestive system defect [sometime may need surgery]
- All parts of the body are shortened
- Face is broad and flat with small nose
- Eyes with slanting eyelids



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# Cytogenetic cause of

# DOWN syndrome:

Trisomy 21

**~ 92 % of cases are numerical: trisomy 21**

**KARYOTYPE: 47,XX,+21 or 47,XY,+21**

In 90 % in trisomy 21 additional chromosome comes **from the mother's egg**
[error in oogenesis: maternal non-disjunction meiosis I ]

**~ 4 % Robertsonian translocation:**

**~ 2 - 4 % of cases are mosaicism:**

**KARYOTYPE: 46/47,+21**

Error in mitosis: mitotic non-disjunction. Cases of mosaic Down's syndrome
Is likely less severe because some of the cell are normal.

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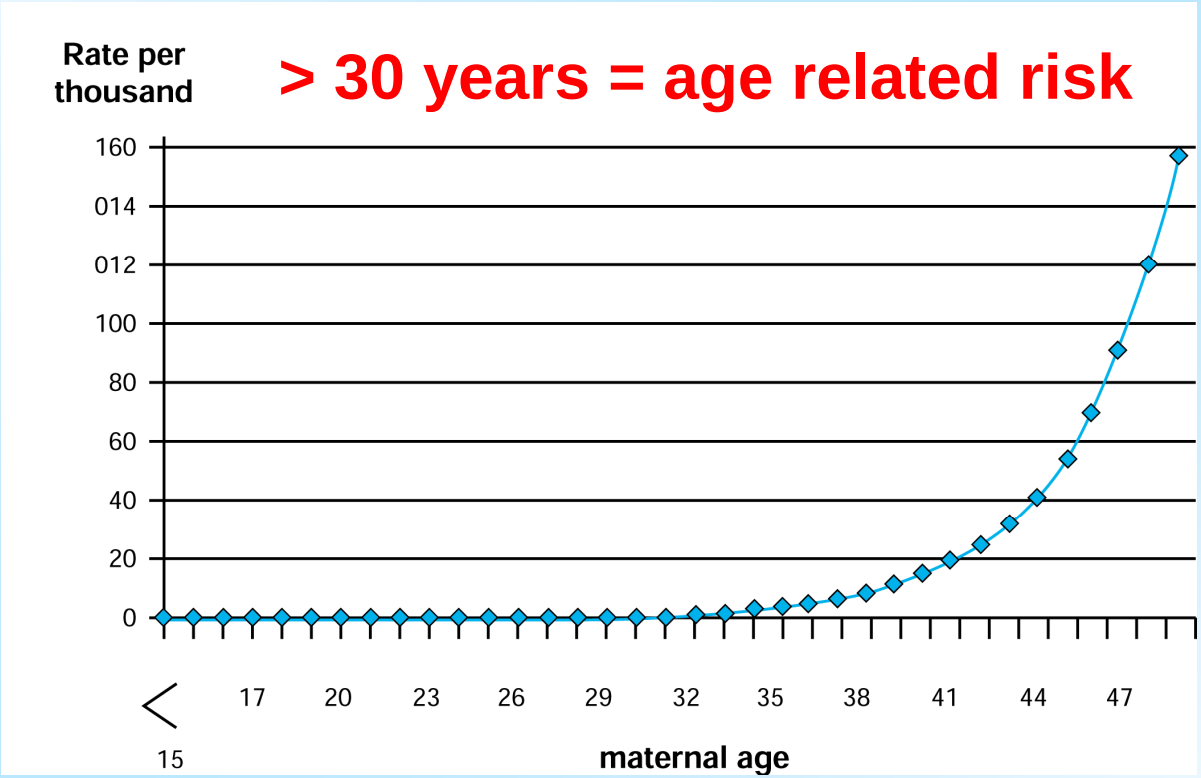
# DOWN syndrome

Trisomy 21

## Risk: Late maternal age effect




**Older females are more likely to carry embryos with chromosomal abnormalities.**

30 years = 1/900

35 years = 1/385

40 years = 1/100

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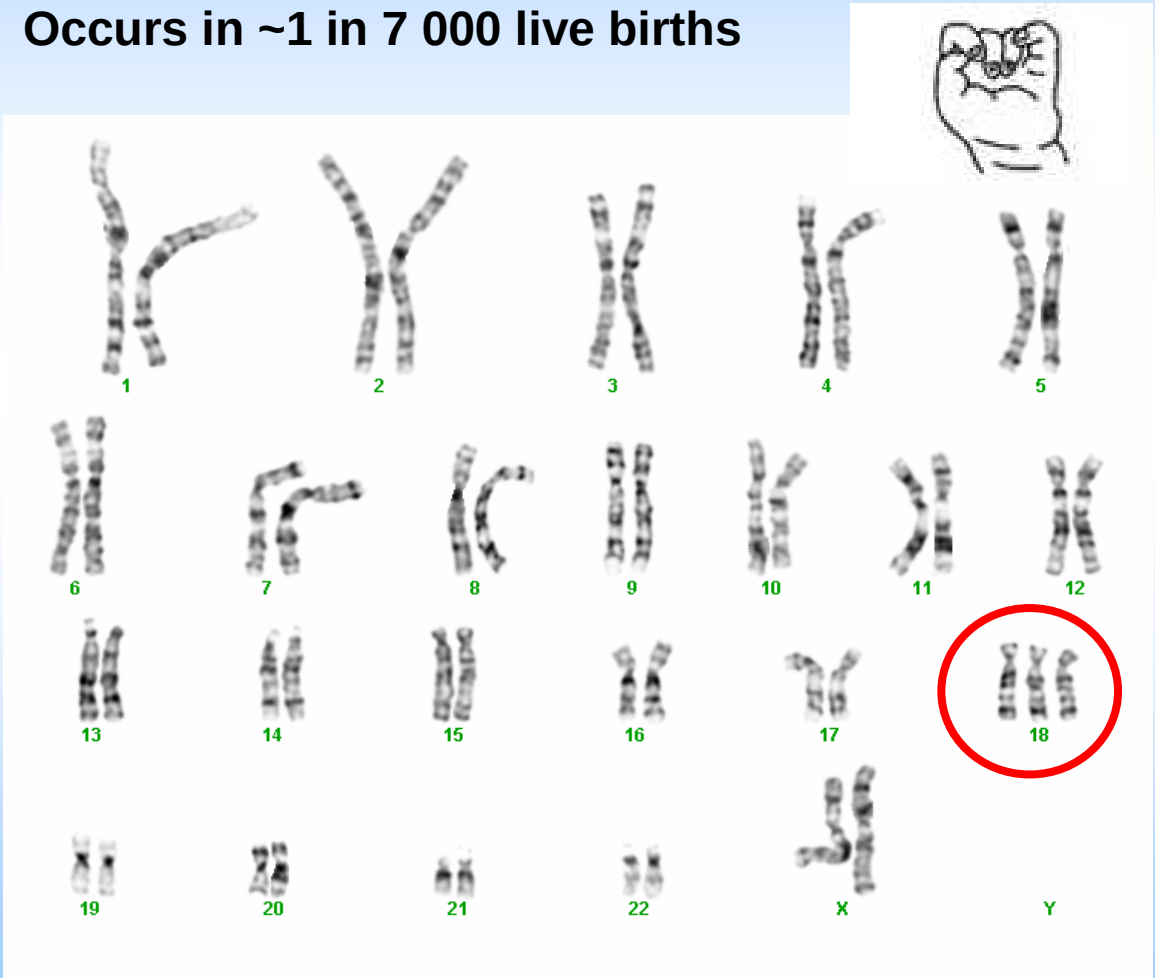
# Edwards syndrome

**Trisomy 18**

**Occurs in ~1 in 7 000 live births**




For unknown reason 80 % of all trisomy 18 are female

## Associated with:

- **Mental and physic retardation**
- **Skull and facial abnormalities**
- **Defect in all organs (malformation of heart, hands, feet)**
- **Advanced maternal age is a risk factor**

**Survival: 2 – 4 months**

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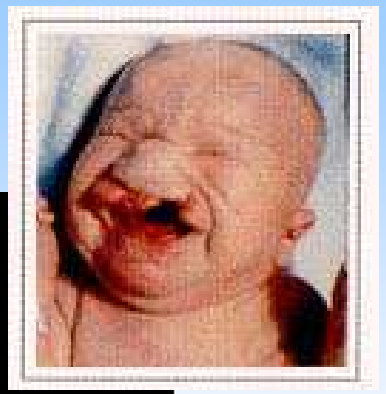
# Patau syndrome



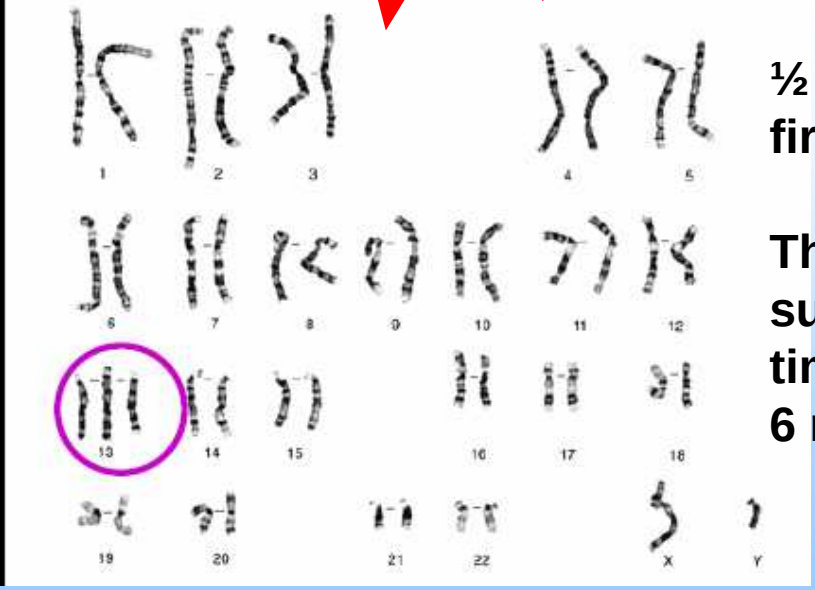
**Occurs in ~ 1 in 15 000 live births**

http://ghr.nlm.nih.gov/condition=patausyndrome

## What's your diagnosis?

- Infant born with multiple birth defects including cleft lip/palate, heart defect, extra fingers/toes, brain abnormalities

**Trisomy 13**



**½ die in first month**

**The mean survival time is 6 month**

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More tolerated than somatic aneuploidy

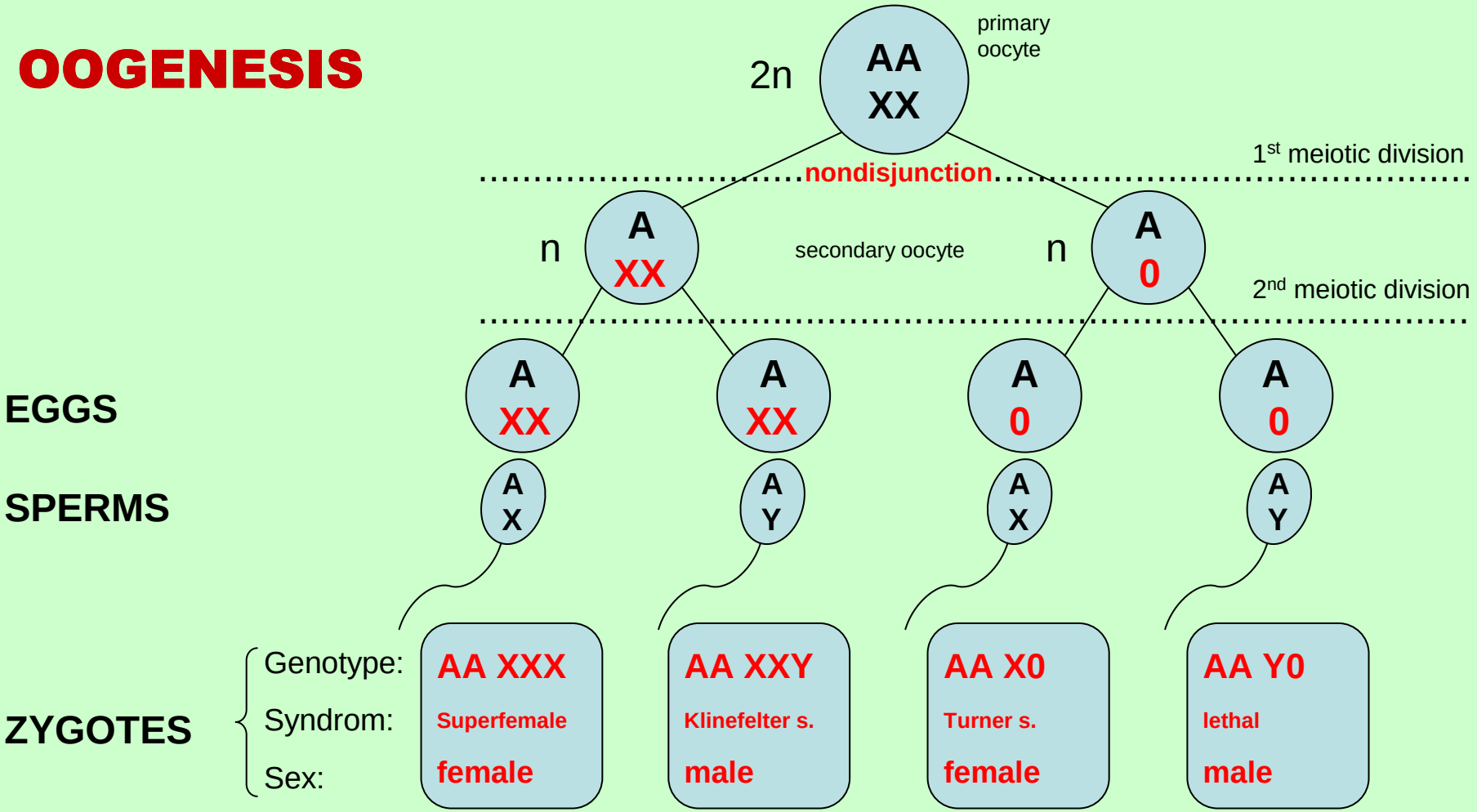
# SEX CHROMOSOME aneuploidy

- Turner syndrome [XO female]
- “Superfemale” [XXX female, trisomy X]
- Klinefelter syndrome [XXY male]
- Jacob´s syndrome “Supermale” [XYY, male]

**YO inviable, at least one X needed for survival**

# How sex-chromosome aneuploidy arise ?

1. Non-disjunction during oogenesis (in meiosis):

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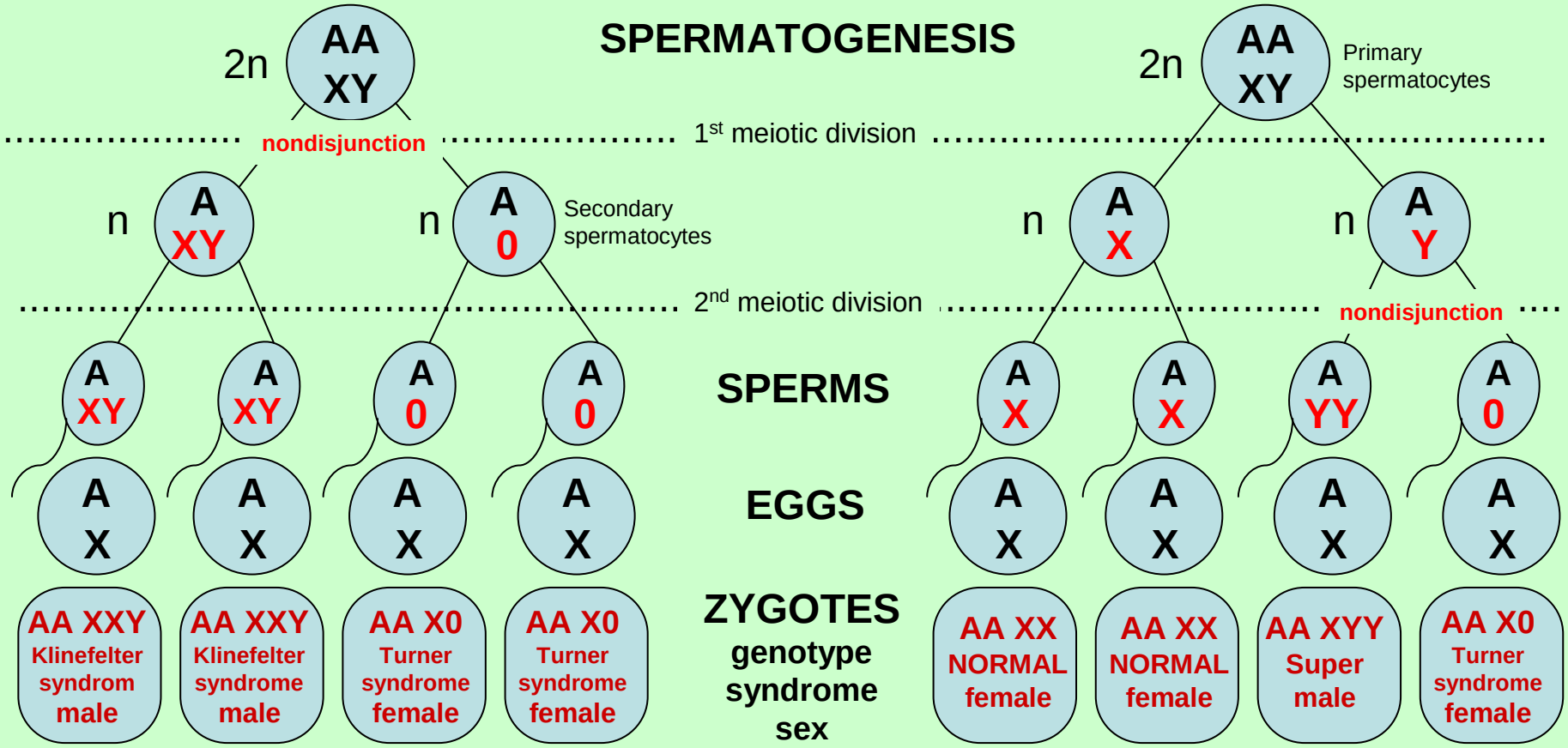
# How sex-chromosome aneuploidy arise ?

2. Non-disjunction during spermatogenesis (in meiosis):

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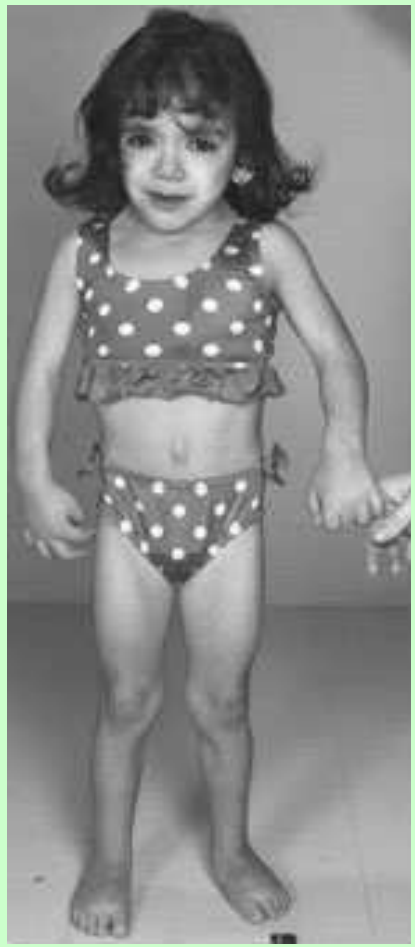
# TURNER syndrome


**Most common sex chromosome abnormality of human female**

~ 97 % die before birth
The incidence is 1 in 2 500 female births



**Turner syndrome girl treated with growth hormones and estrogen lead fairly normal life**

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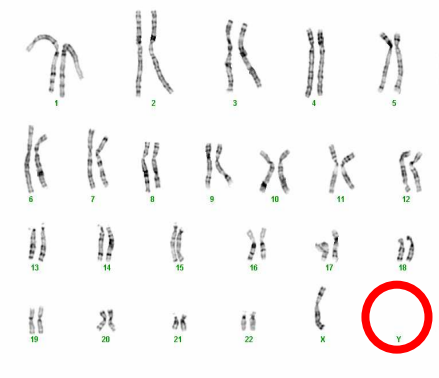
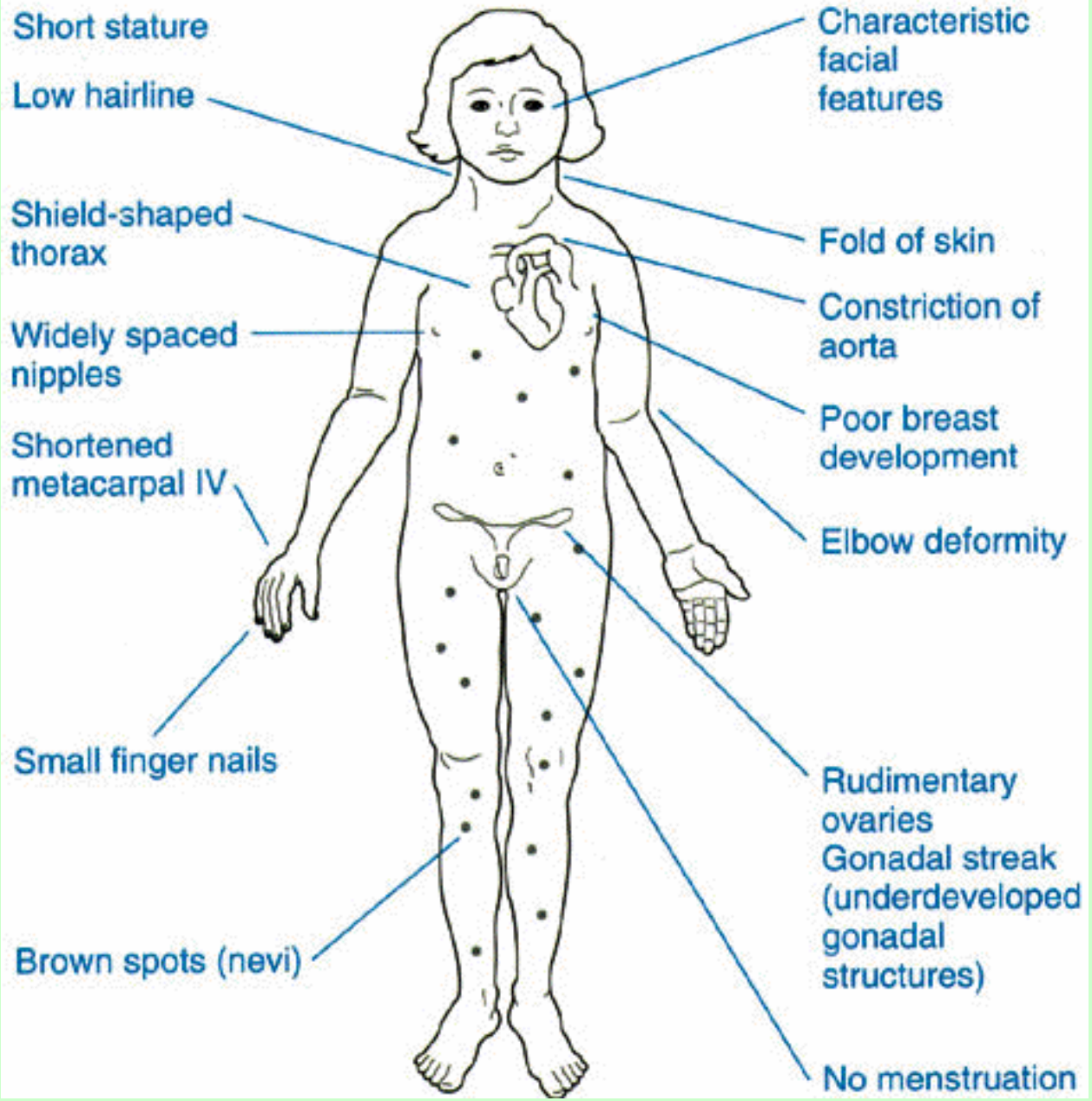
# Turner Syndrome

## XO (45, X )



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## Cytogenetic cause of

# TURNER syndrome

| | | |
|---|---|---|
| 45,X | | 55% |
| 46,X with abnormal X | | 15% |
| | Deletion<br>Isochromosome<br>Ring | |
| Mosaic | | 30% |
| | X/XX<br>X/XY<br>X/XXX etc. | |

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# "SUPERFEMALE"

## Females With Multiple X Chromosomes

**47, XXX** – Mostly normal females.

**48, XXXX**

**49, XXXXX**

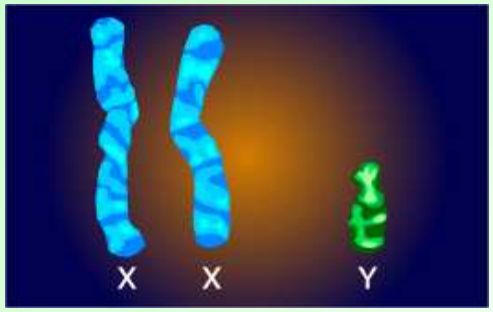
These tend to have underdeveloped secondary sex characteristics, sterility and mental retardation.

# Klinefelter Syndrome


**The Incidence of Klinefelter syndrome:**
**~ 1 in 1000 male births**

**The extra chromosome X was gained either:**

From diploid egg [XX] or sperm [XY]
[meiotic nondisjunction]
or
during early fetal development
[mitotic nondisjunction]

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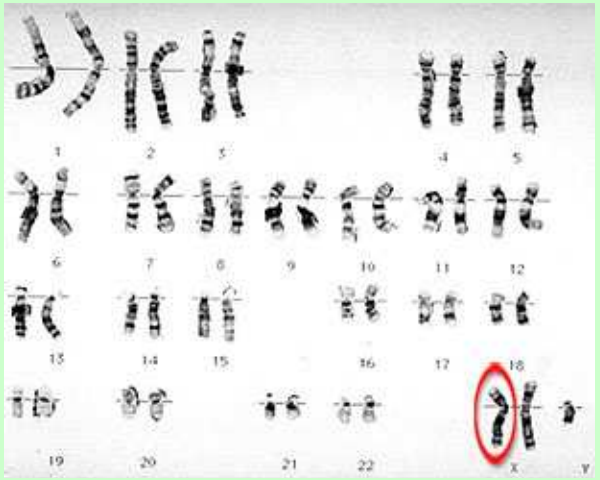
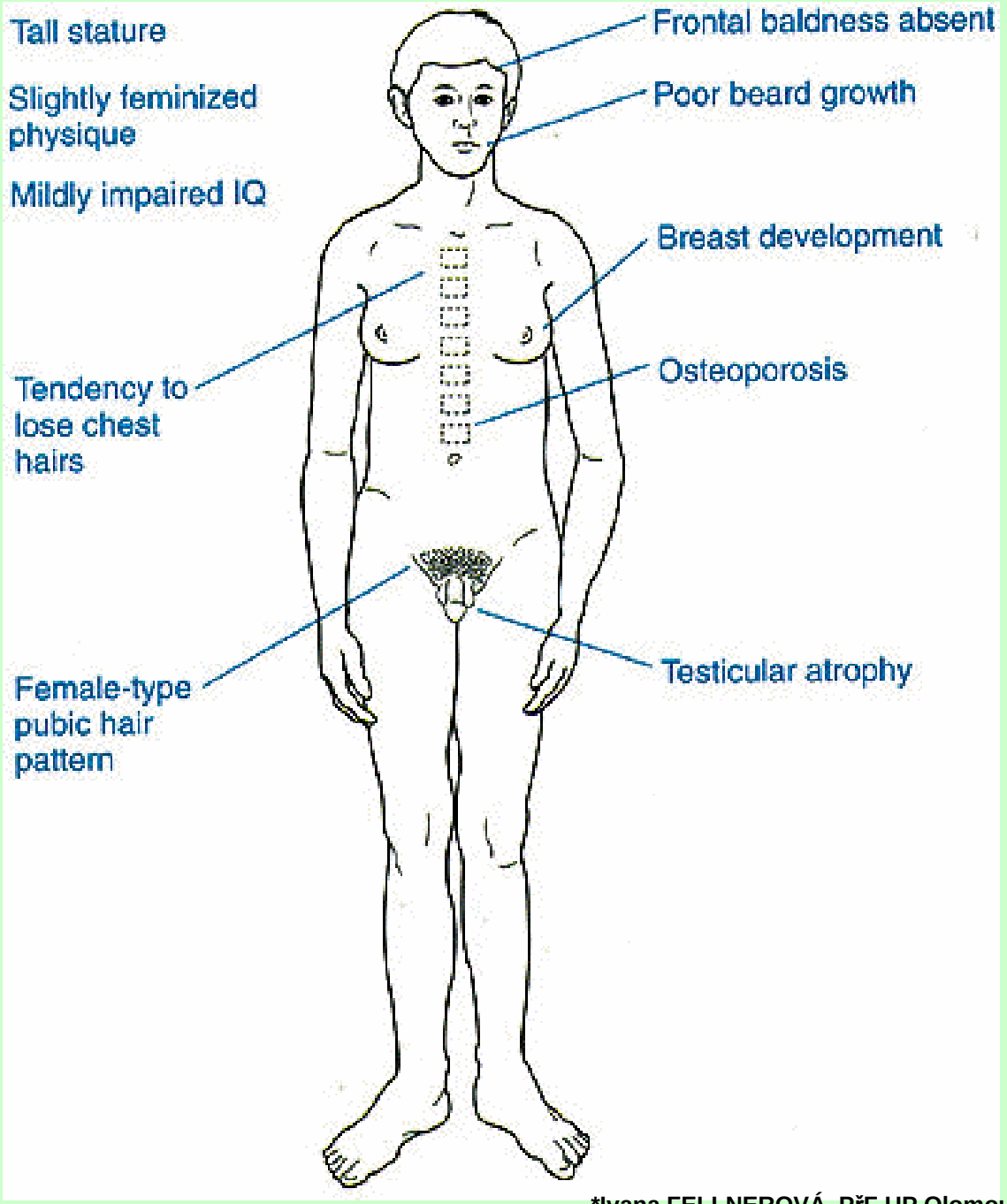
# Klinefelter Syndrome

## (47,XXY)



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# "SUPERMALE"

## Males With Multiple X Chromosomes

48, XXXY
48, XXYY
49, XXXXY
49, XXXYY

All are similar to XXY Klinefelter syndrome, but usually with more severe effects.

# Jacob's Syndrome


- know that 96% of all XYY males are apparently normal

- Modest phenotype includes
  - tendency to have great height
  - acne problems
  - speech and reading problems

- Studies suggesting some increase in aggressive behaviors remain controversial.

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# Clinical consequences of numerical abnormalities:

- Autosomal monosomies are more devastating than trisomics. Trisomic embryos survive longer than monosomic ones.

- Sex chromosome aneuploids is less devastating than in autosomal aneupoilds. This is because of X-inactivation mechanisms and the fact that Y carries very few genes that determine male sex.

# STRUCTURAL ABNORMALITIES

**Parts of chromosome are lost, gain or mowed**

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# Classification of STRUCTURAL rearrangement

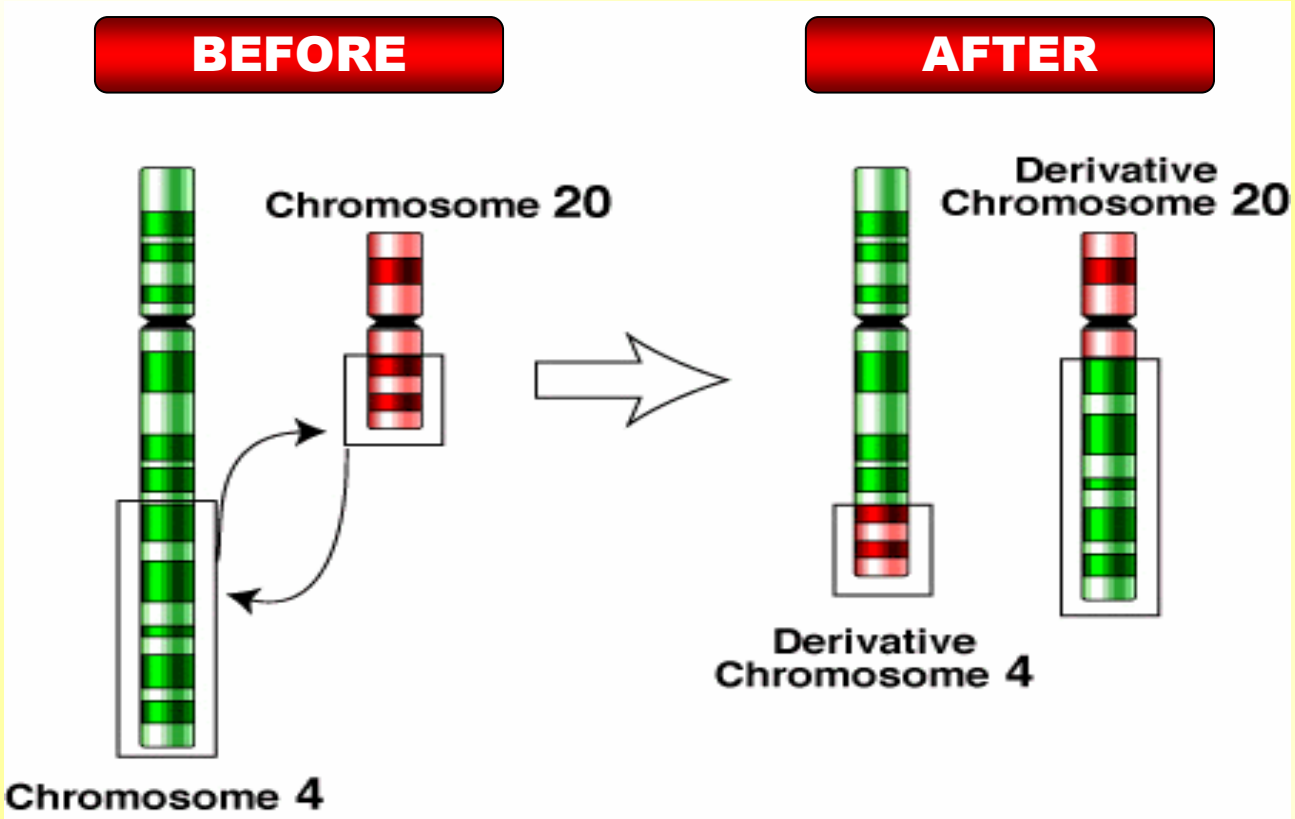
**Chromosome breakage with subsequent reunion in a different configuration**

- **BALANCED:**
  Neither loss nor gain chromosome material, just mowing to new position
  - **Reciprocal translocation**
  - **Inversion**
  - **Insertion**

- **UNBALANCED:** Lost or gain genetic material:
  - **Robertsonian translocation**
  - **Deletion**
  - **Duplication**
  - **Insertion**
  - **Isochromes**

# Reciprocal Translocation

BALANCED




Two non-homologous chromosomes has been broken and rejoined in the wrong configuration
(chromosomal segment has been transferred from one chromosome to another)

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# Reciprocal Translocation

- Balanced translocation [neither loss nor gain of genetic information]
- the exchange of chromosome material between 2 non-homologous chromosomes
- usually no phenotype effect (unless there is a position effect resulting in gene disruption)
- reproductive consequences


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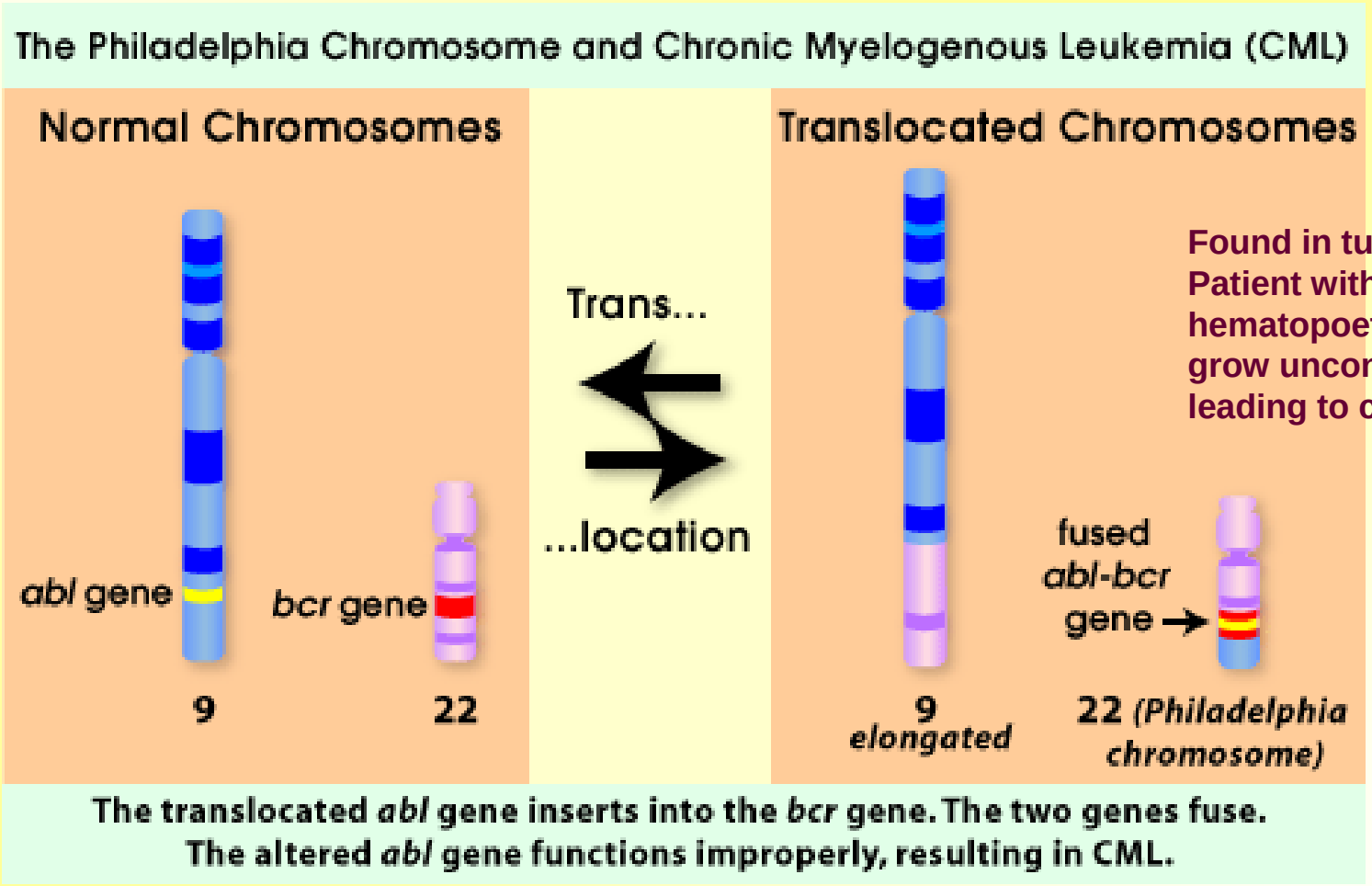
# Case of reciprocal translocation

BALANCED

Part of the q arm of chromosome 22 has been translocated onto the long arm of chromosome 9. The small distal portion of chromosome 9 i s translocated to chromosome 22.creating **PHILADELPHIA CHROMOSOME**




**Found in tumor cells. Patient with CML produce hematopoetic cell which grow uncontrollably leading to cancer**

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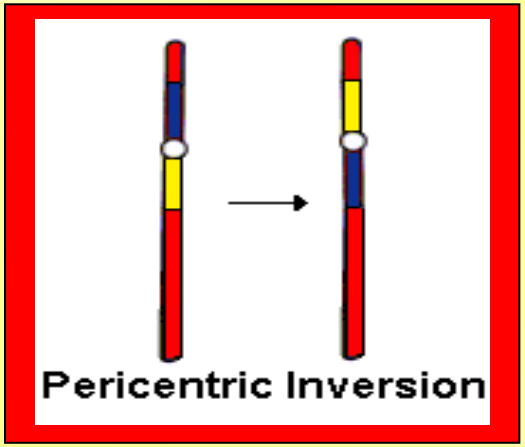
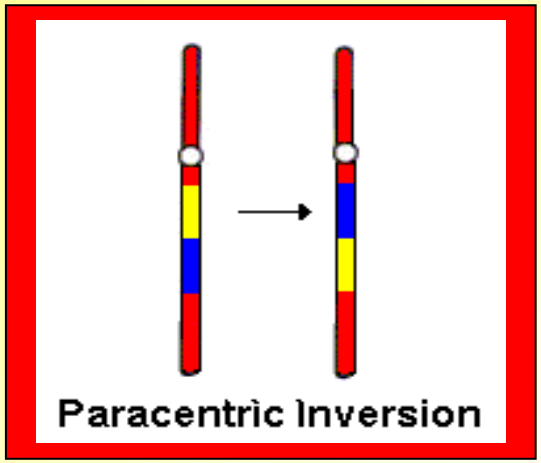
# Inversion

BALANCED

- An inversion consists of two breaks in one chromosome.
- The area between the breaks is inverted (turned around), and then reinserted
- Only 5-10 % cause health problems, often have reproductive problems




inverted area
includes the centromere




inverted area
excludes the centromere

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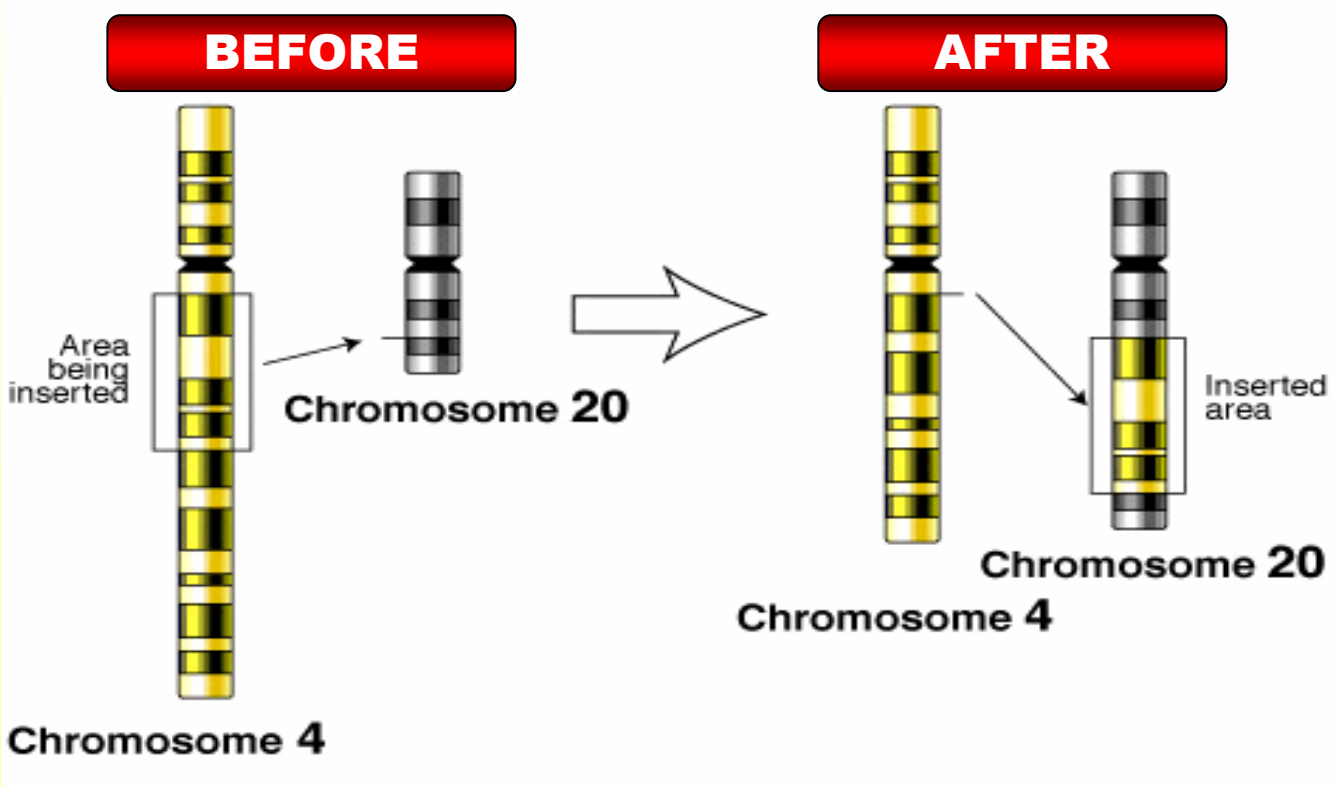
# Insertion


**Two breaks in one chromosome [ # 4]**
**Area between breaks has been moved out of original chromosome and has been inserted into different chromosome**

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# Unbalanced rearrangements

- Loss or gain of chromosome material
- Many different types
  - Translocations [nonreciprocal, Robertsonian]
  - Deletions
  - Duplications
  - Insertion
  - Isochromes
- Abnormal phenotype association

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# Robertsonian Translocation

- Named after W. R. B. Robertson who first identified them in grasshoppers in 1916
- Most common structural chromosome abnormality humans

  Frequency = 1/1000 livebirths
- A special case of „almoust balanced“ translocations involves any of two **acrocentric** chromosomes: 13, 14, 15, 21 and 22
- Two types of Robertsonian translocation
  - **Homologous acrocentrics involved**
  - **Non-homologous acrocentrics involved**

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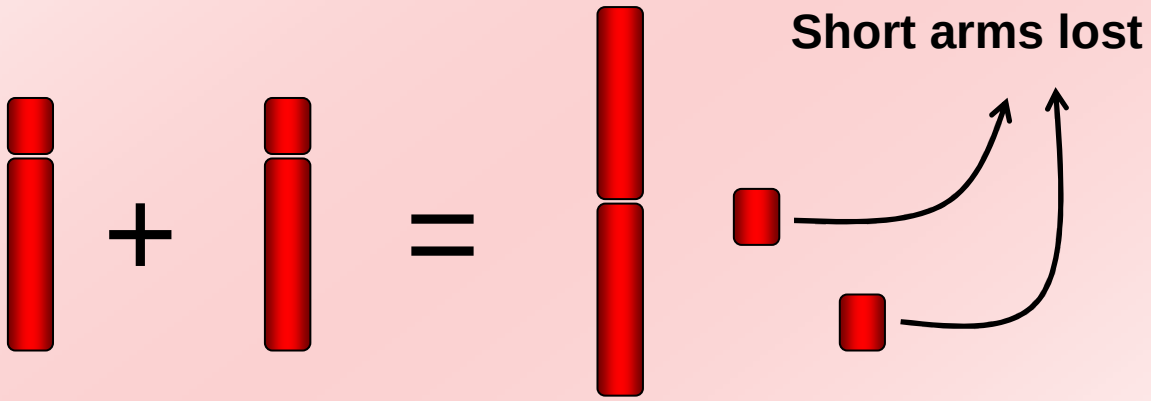
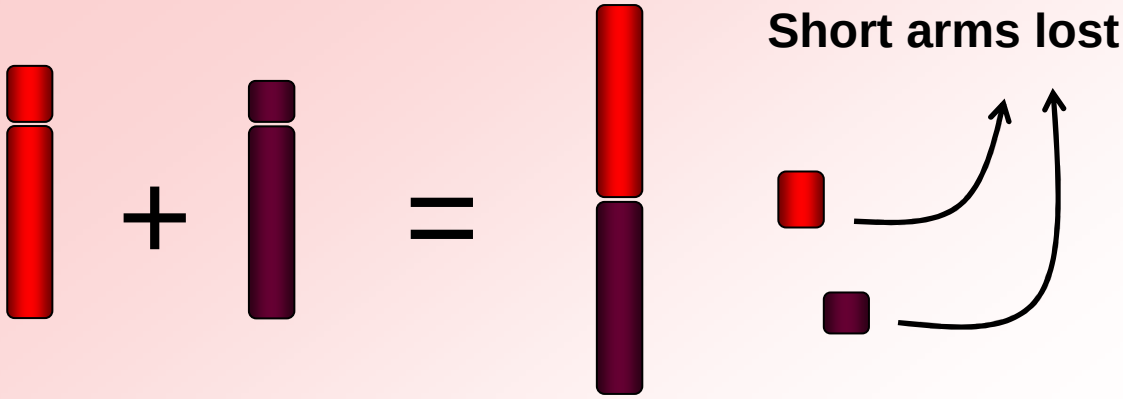
# Robertsonian Translocation

**Homologous**
**acrocentric, chromosome**
**i.e. 14**




**Non-Homologous**
**acrocentric chromosome**
**i.e. 14 & 21**

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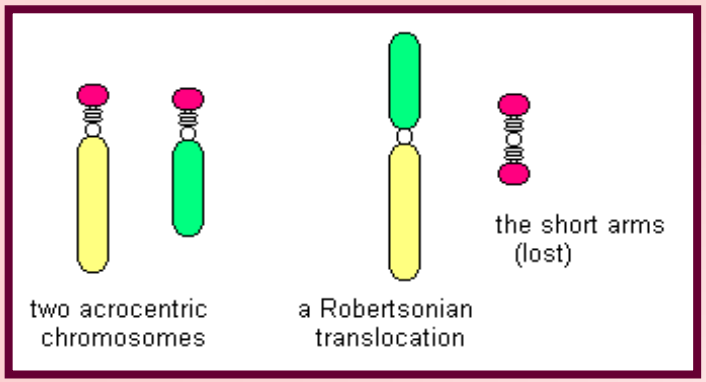
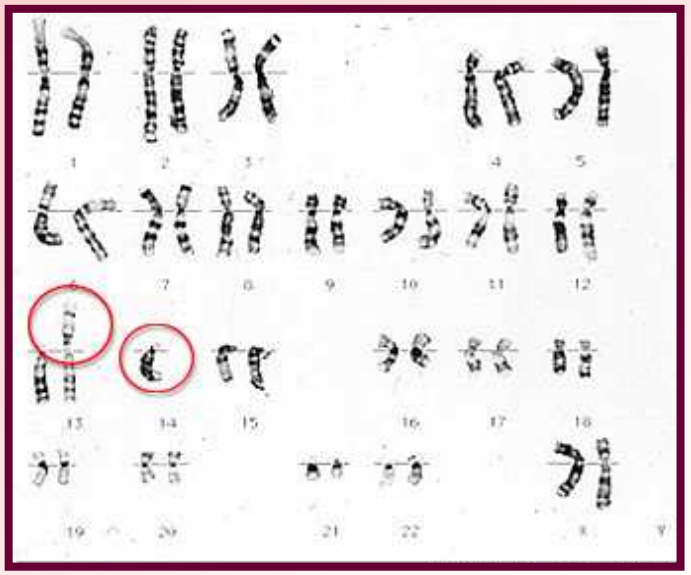
# Robertsonian Translocation

- a fusion between the centromeres of two acrocentric chromosomes forming a single derivate chromosome
- The short arms ( p ) are lost withouth phenotype efect (loss of the short arms does not matter – contain few, if any, genes)
- Carriers have difficulties at meiosis (modal chromosome number 45)



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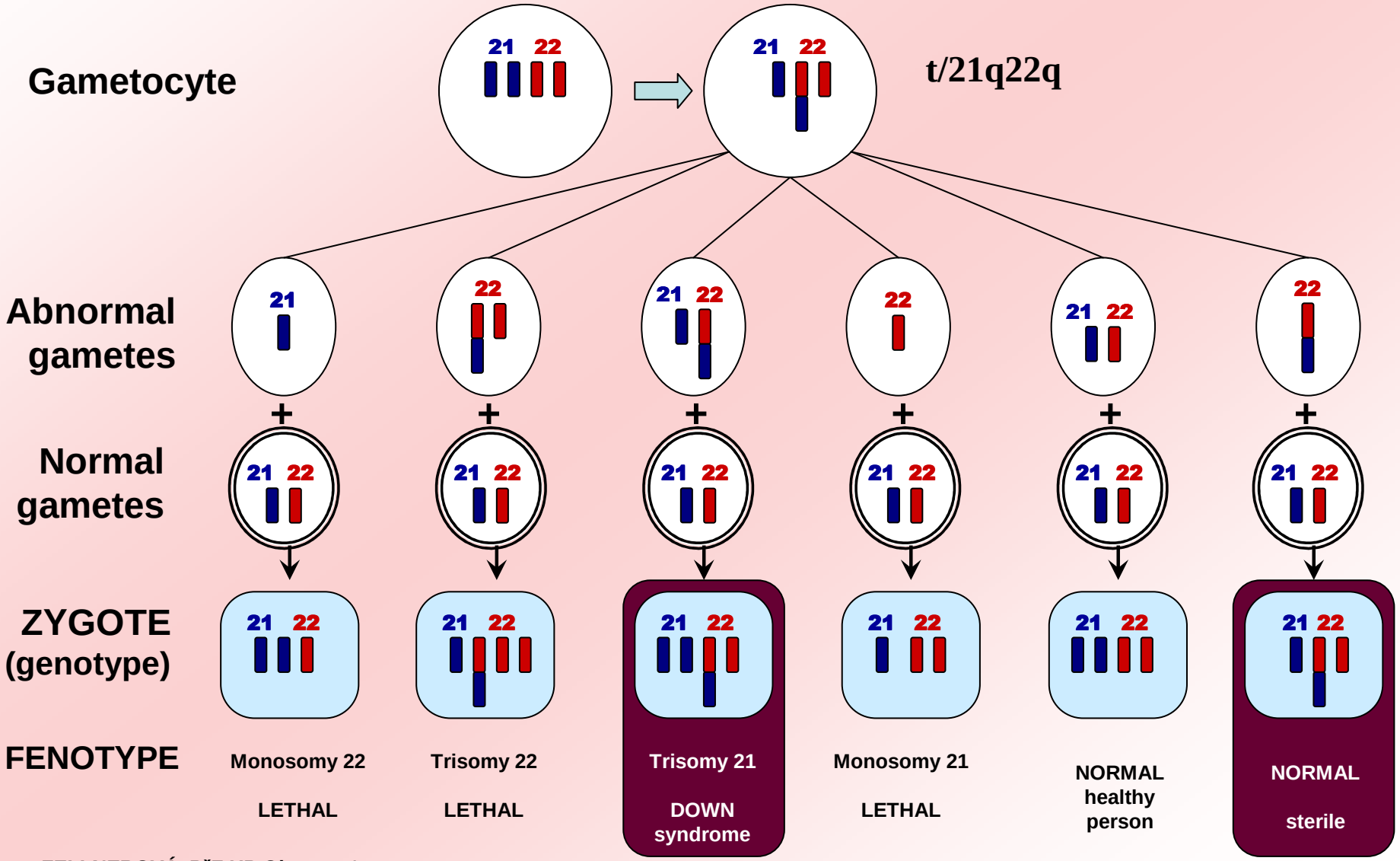
# Case of Robertsonian Translocation

**Fusion of q arm of acrocentric chromosomes # 21 and 22**

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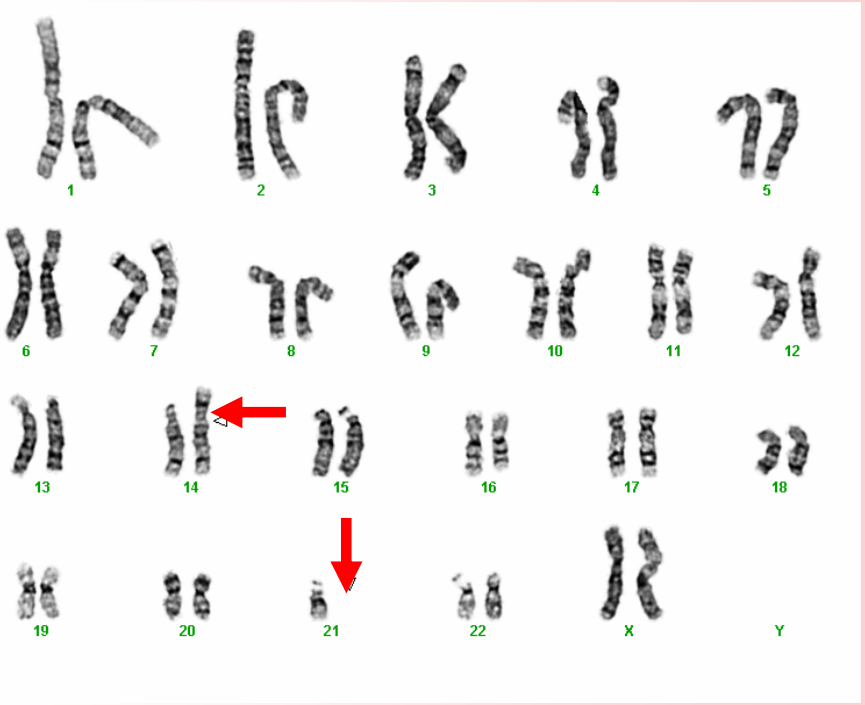
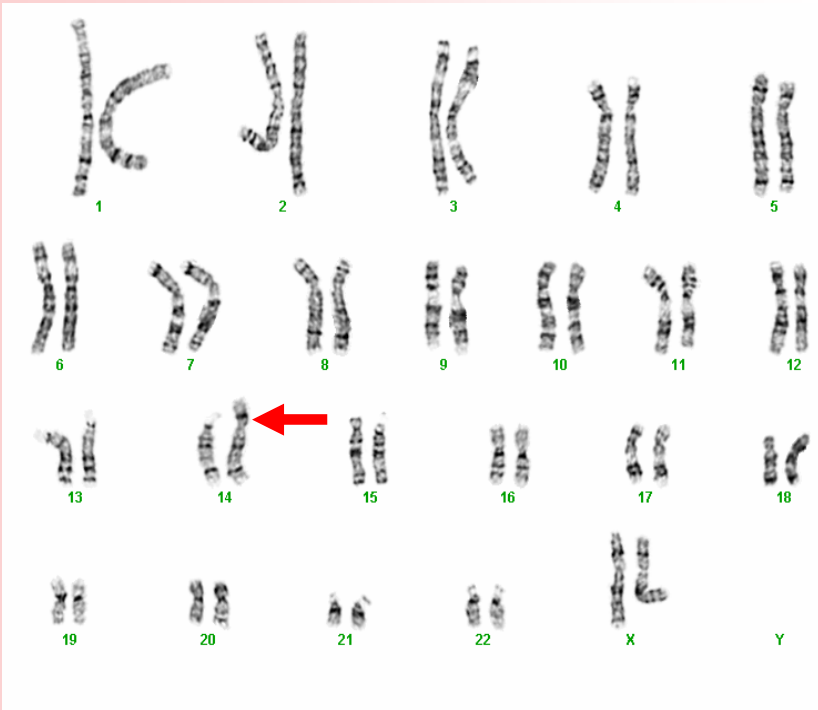
# Karyotype of Robertsonian Translocation

**A balanced chromosome 14 & 21 Robertsonian translocation**




**An unbalanced chromosome 14 & 21 Robertsonian translocation - trisomy 21, Down syndrome**

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# DELETION

- Part of chromosome[s] – large or small - has been deleted
- Can occur at any chromosome, any band and any size
- Consequences depend on how big a piece is missing and what gene are missing

**Terminal deletion:** one break point [extend to the telomere]

Cri-du-chat syndrom

**Interstitial deletion:** two break points

Williams syndrome – the elastin gene on chromosome 7 is deleted

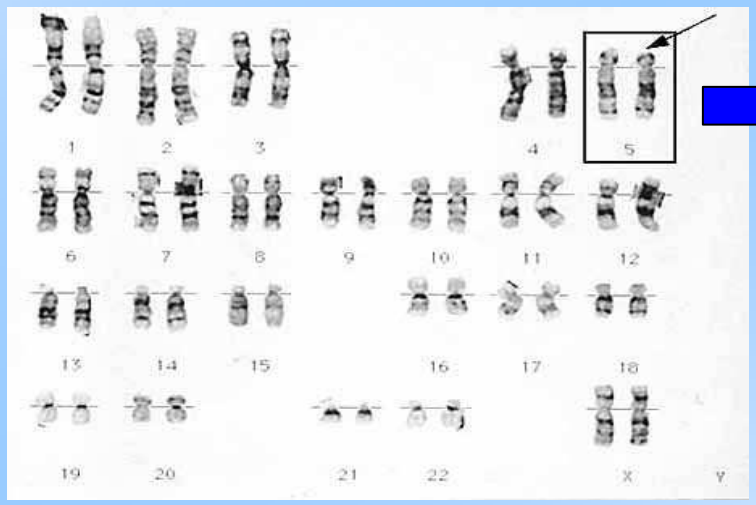
# Cri-du-chat syndrom

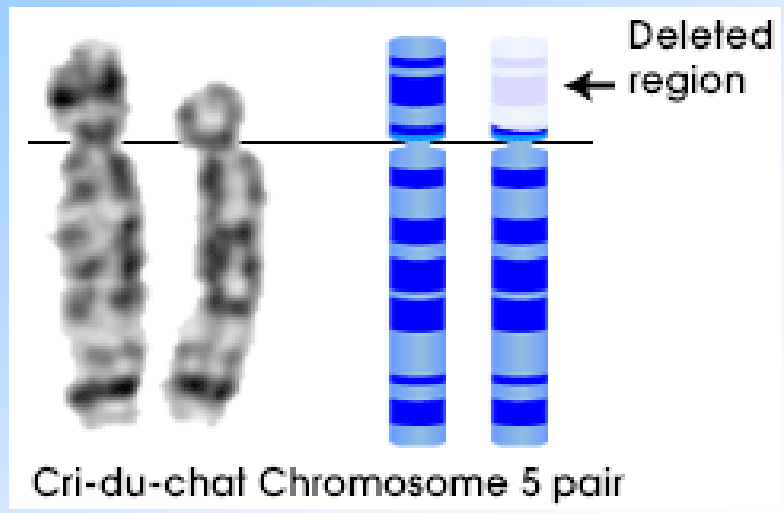
## Chromosome 5 terminal deletion

French for cry-of-the-cat
[refers to the distinctive cry of children caused by abnormal larynx]

~ 1 in 50.000 live births

Most common deletion syndrome
In humans

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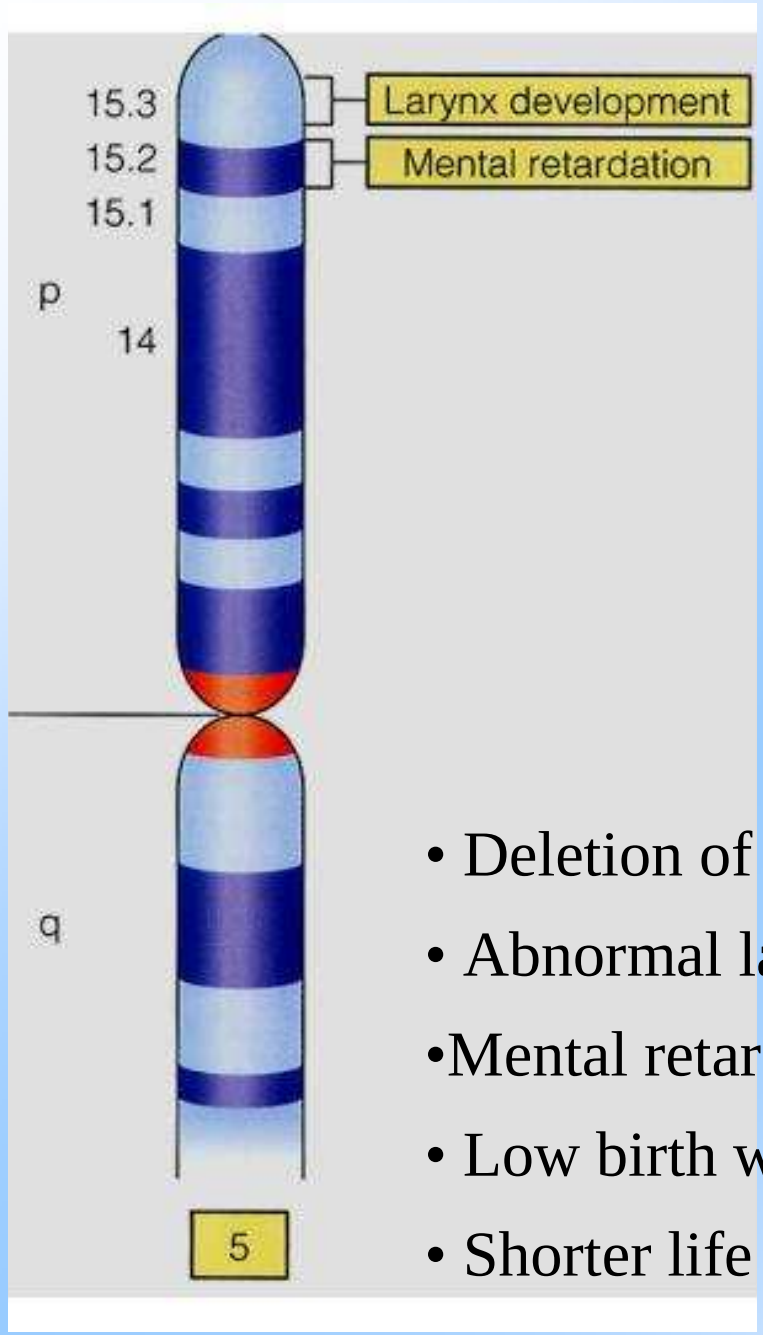
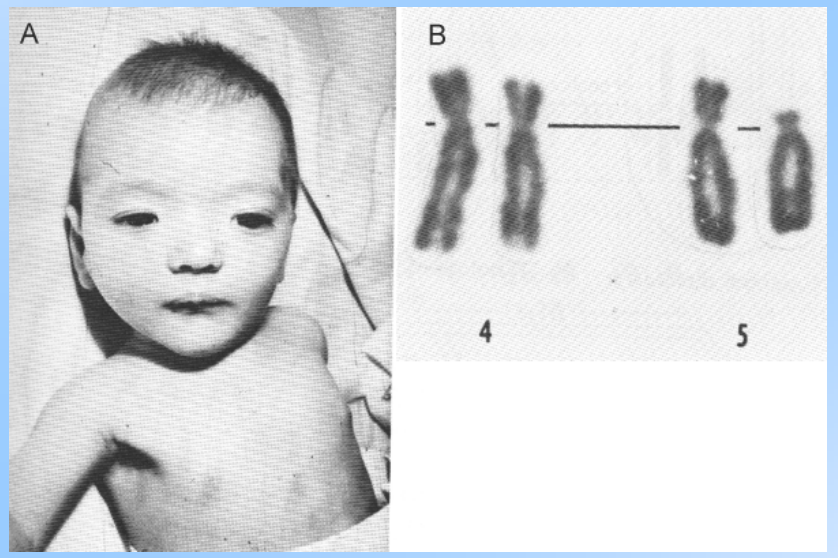
# Cri du Chat Syndrome

## ("Cry of the Cat" in French)




- Deletion of part of short arm of chromosome 5
- Abnormal larynx development
- Mental retardation, learning disability
- Low birth weight
- Shorter life span but most normally life expectancy

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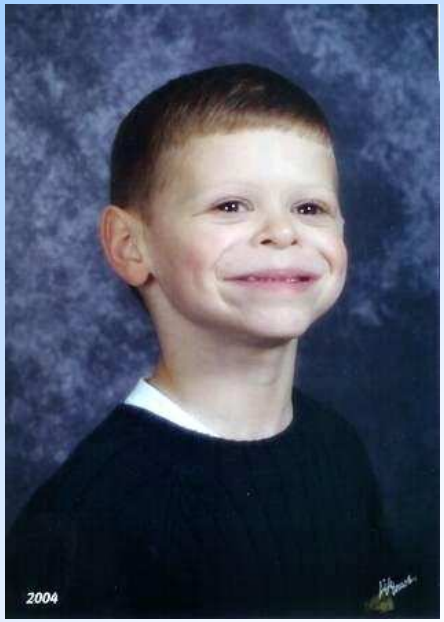
# Williams syndrome

## Chromosome 7 interstitial deletion

- Caused by very small deletion on the long arm of chromosome 7.
- Deletion include elastin gene which code a protein that gives the blood vessels the stretchiness
- The lack of the elastin protein, people with Williams syndrome have disorder of circulatory system

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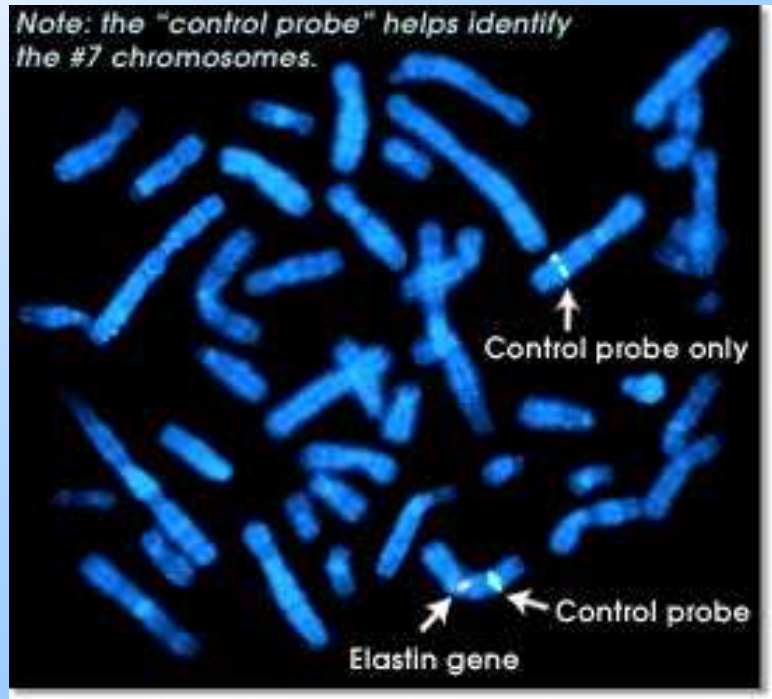
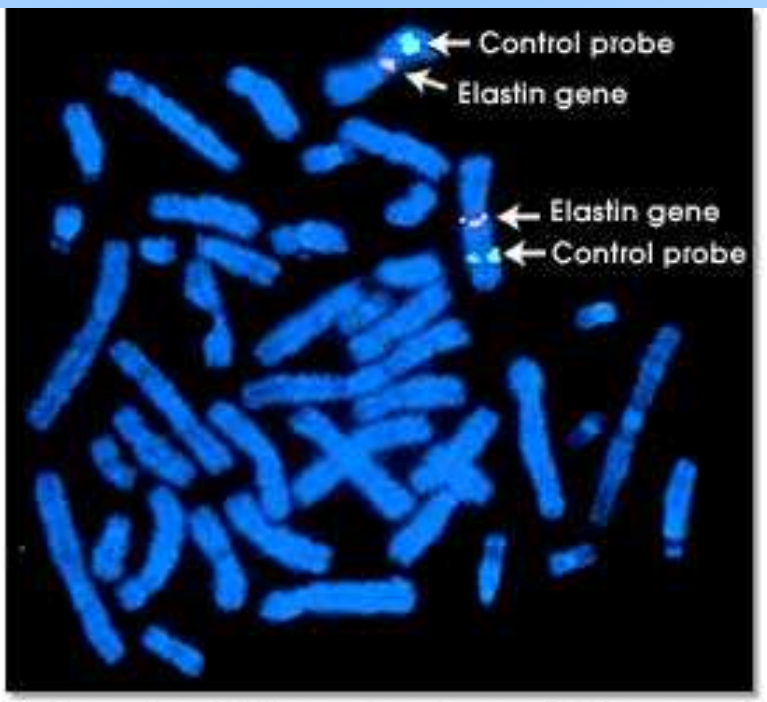
# Williams syndrome

The chromosomal deletion that causes Williams syndrome is so small that it cannot be seen by routine cytogenetic methods.
Deletion can be observed using a molecular cytogenetic technique - FISH




Positive Williams Syndrome FISH assay
(*Chromosome 7*)
The elastin gene is found on only one chromosome. The other copy carries an elastin gene deletion.




Negative Williams Syndrome FISH assay
(*Chromosome 7*)
The elastin gene is found on both chromosomes. This individual does not have Williams Syndrome.

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# FISH

## **F**luorescent **I**n **S**itu **H**ybridization

**It is a molecular cytogenetic technology utilizing fluorescently labeled DNA probes to detect or confirm gene or chromosome abnormalities, that are beyond the resolution of routine [convention] cytogenetic**

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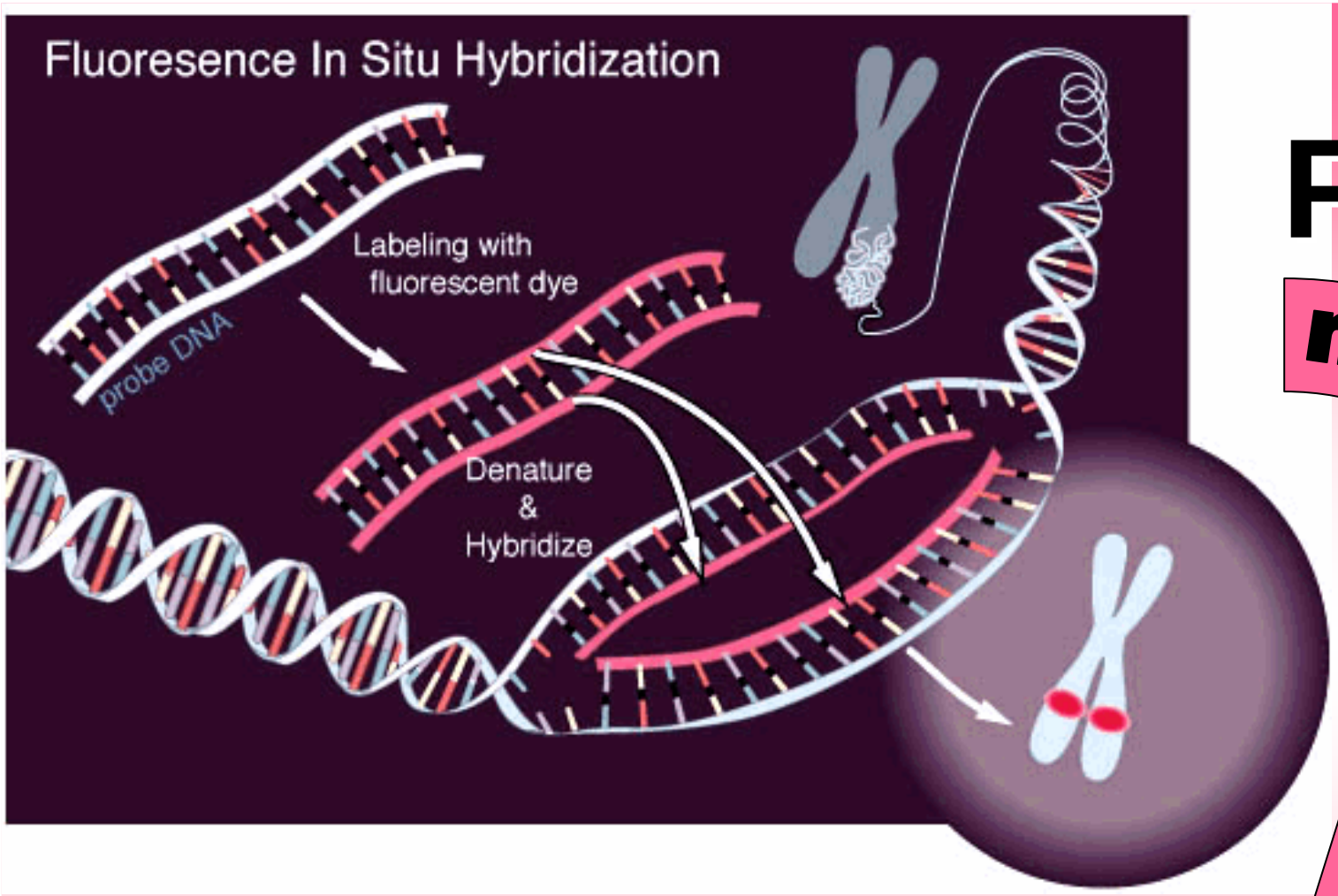


# FISH

## methodology

1. Making DNA probe complementary to known sequence
2. Labeling the probe with fluorescent marker
3. Denaturizing both, the probe and the sampling DNA: mix, hybridize
4. Wash of excess probe that did not bind to tested chromosome
5. Sample DNA is tested for presence or absence of the fluorescent signal

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# PRENATAL DIAGNOSIS

**Use for chromosomal analysis**

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# Cell used for chromosomal analysis

**Any cell with a nucleus**

- Lymphocytes
- Skin cells
- Tumor cells
- **Amniotic cells** ⟸
- **Chorionic villi** ⟸
- Rare fetal cells from maternal blood

# Condition that may suggest the use of prenatal diagnosis

- Advanced maternal age (>35)
- Previous child with chromosomal aberration
- Parent with chromosomal rearrangement
- X-linked biochemical disorder carrier

There are two different aproach to sampling cells of fetus:

# Amniocentesis


a. During amniocentesis, a long needle is used to withdraw amniotic fluid containing fetal cells.

# Chorionic villi

b. During chorionic villi sampling, a suction tube is used to remove cells from the chorion, where the placenta will develop.

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# Amniocentesis

- Done through the belly
- Performed at 14th – 17th weeks of pregnancy
- Colect fetal cells from amniotic fluid
- Detection by culturing fetal cells
- Slight risk of spontaneous abortion

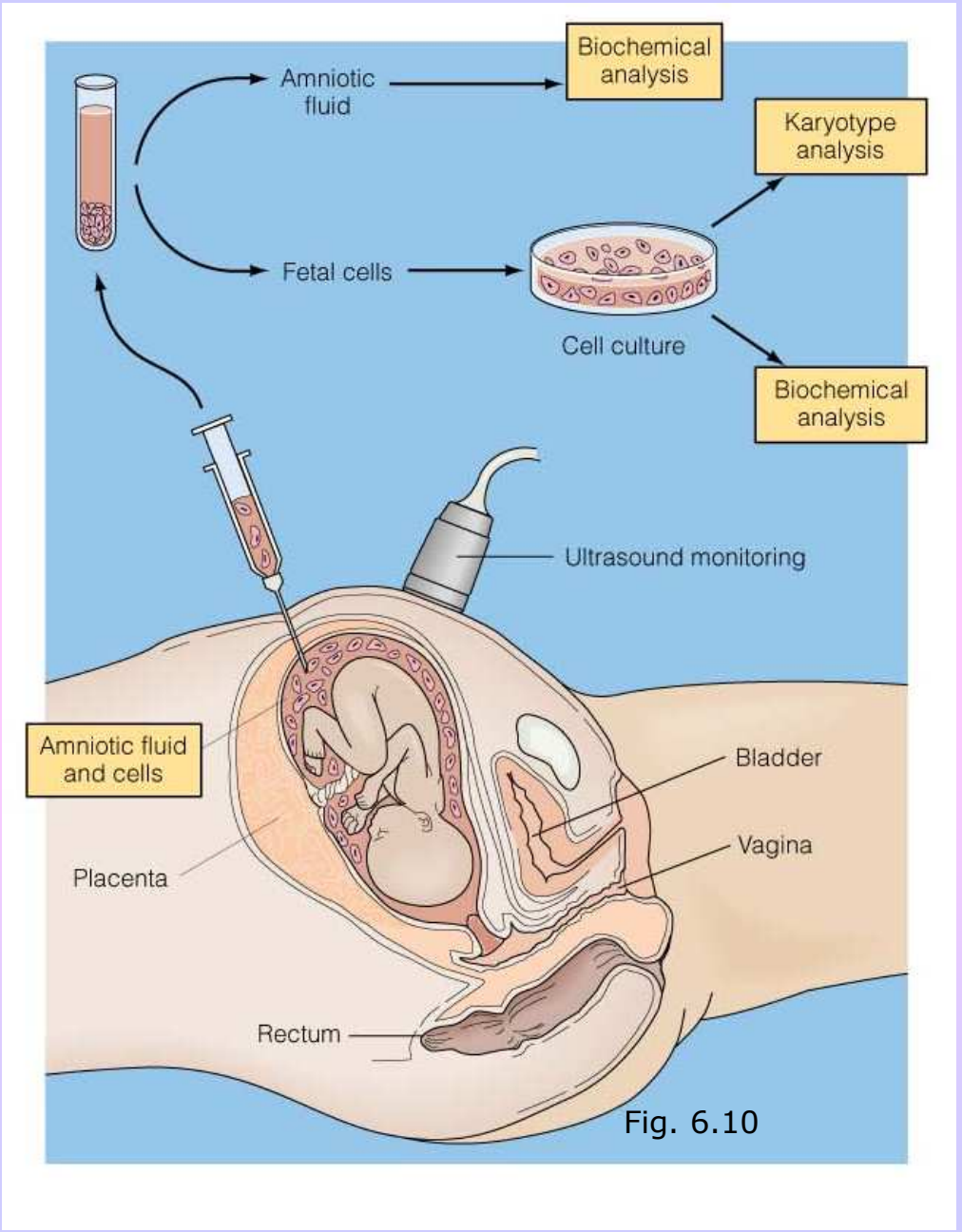

Fig. 6.10

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# Chorionic villus sampling

- Done through the cervix
- Performed at 5th – 10th weeks of pregnancy
- Uses a thin suction tube to sample chorionic cells from the placenta
- The cell do not be culturing; karyotyping can be done immediately
- Somewhat risky for mother and fetus

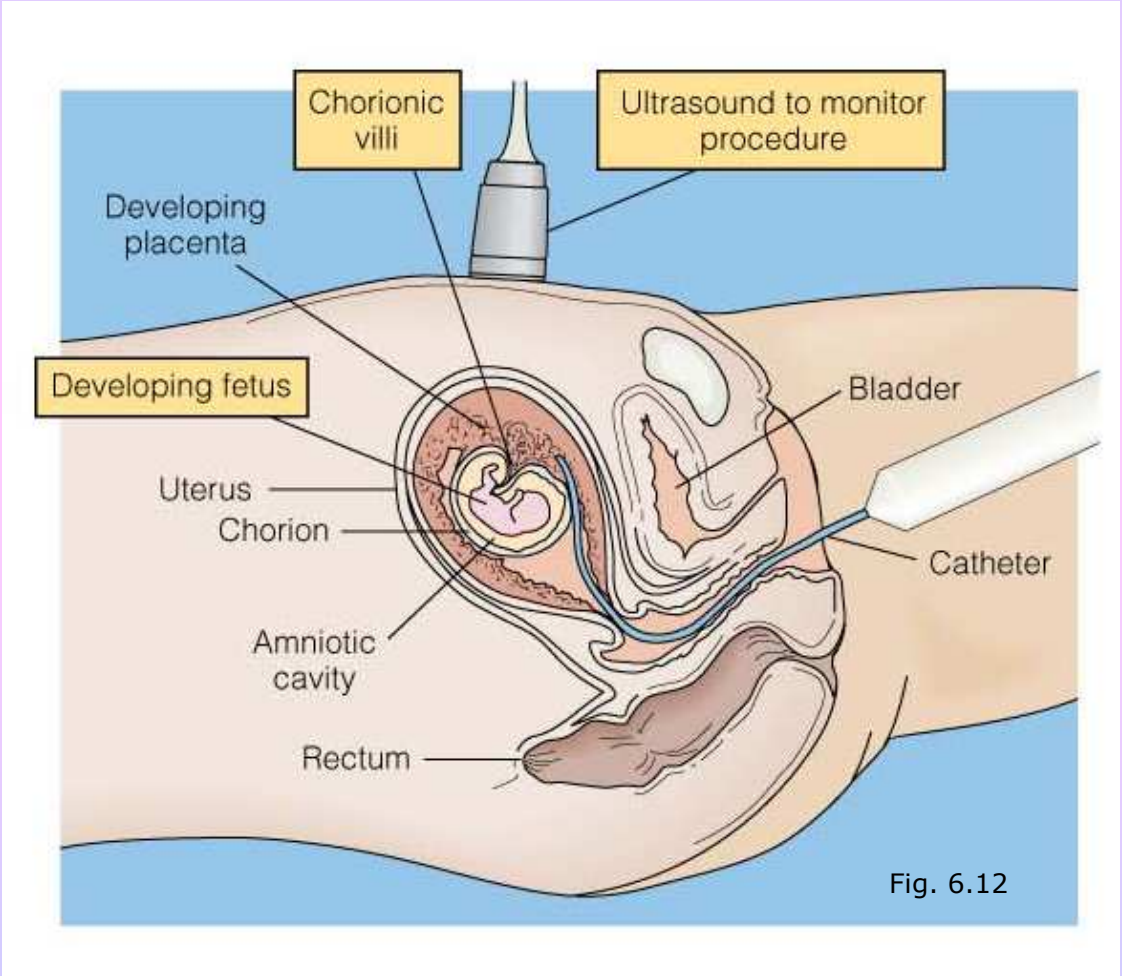

Fig. 6.12

# ISCN

# INTERNATIONAL SYSTEM for HUMAN CYTOGENETIC NOMENCLATURE

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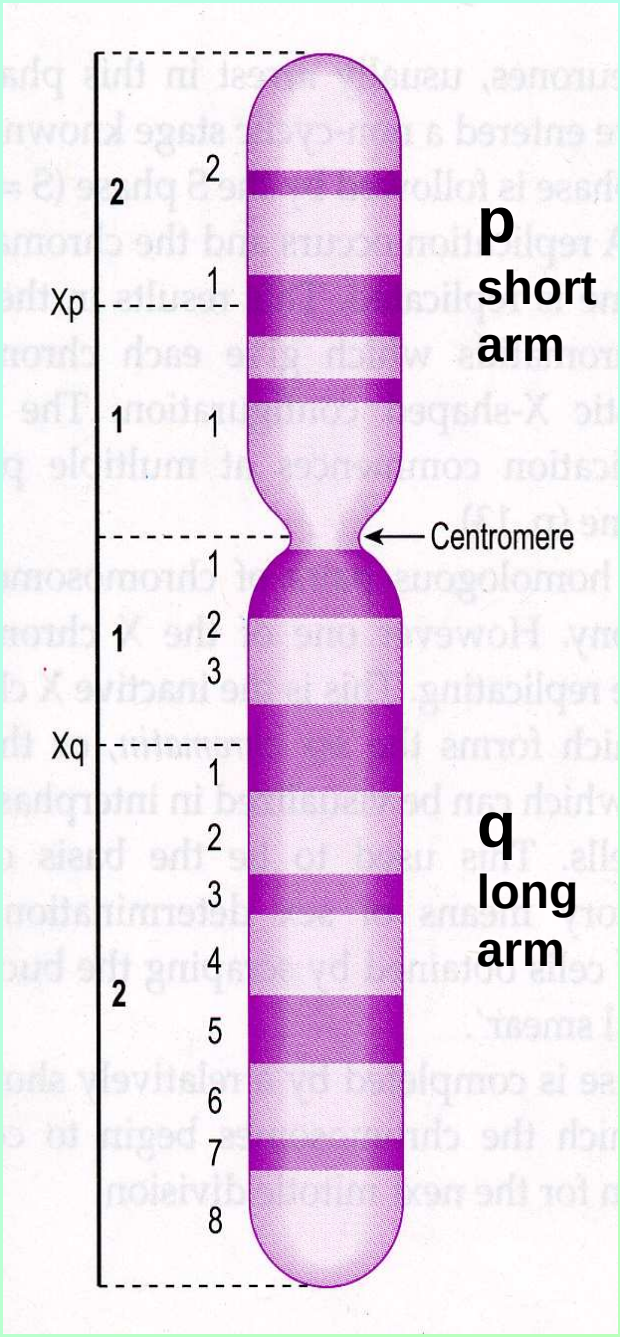
# ISCN

## International System for Human Cytogenetic Nomenclature

- each area of chromosome get the number
- Lowest number closest (proximal) to centromere
- highest number at tips (distal) to centromere

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# ISCN:

## Abreviation used for particular abnormalities

- dup = duplication
- i = Isochromosome
- ins = insertion
- inv = inversion
- r = ring
- t = translocation
- del = deletion

# ISCN:

## Diacritics used for describtion of abnormalities

46,XX,del(5p)

**Comma , separates:**
- **chromosome numbers**
- **sex chromosomes**
- **chromosome abnormalities**

46,XY,t(2;4)(q21;q21)

**Semicolon ; separates:**
- **altered chromosomes**
- **break points in structural rearrangements involving more than 1 chromosome**

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# How are chromosome abnormality labeled?

**46,XX,del(14)(q23)**

Female with 46 chromosomes with a deletion of chromosome 14 on the long arm (q) at band 23.

**46,XY,dup(14)(q22q25)**

Male with 46 chromosomes with a duplication of chromosome 14 on the long arm (q) involving bands 22 to 25.

**46,XX,r(7)(p22q36)**

Female with 46 chromosomes with a 7 chromosome ring. The end of the short arm (p22) has fused to the end of the long arm (q36) forming a circle or 'ring'

**47,XY,+21**

Male with 47 instead of 46 chromosomes and the extra chromosome is a 21. (Down Syndrome)

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# Chromosomal shorthand

| Abbreviation | What it means |
|---|---|
| 46, XY | Normal male |
| 46, XX | Normal female |
| 45, X | Turner syndrome female |
| 47, XXY | Klinefelter syndrome male |
| 47, XYY | Jacobs syndrome male |
| 46, XY del (7q) | Male missing part of long arm of chromosome 7 |
| 47, XX+21 | Female with trisomy 21 |
| 46, XY t (7;9) (p21.1;q34.1) | Male with translocation between short arm of chromosome 7 band 21.1 and long arm of chromosome 9 band 34.1 |

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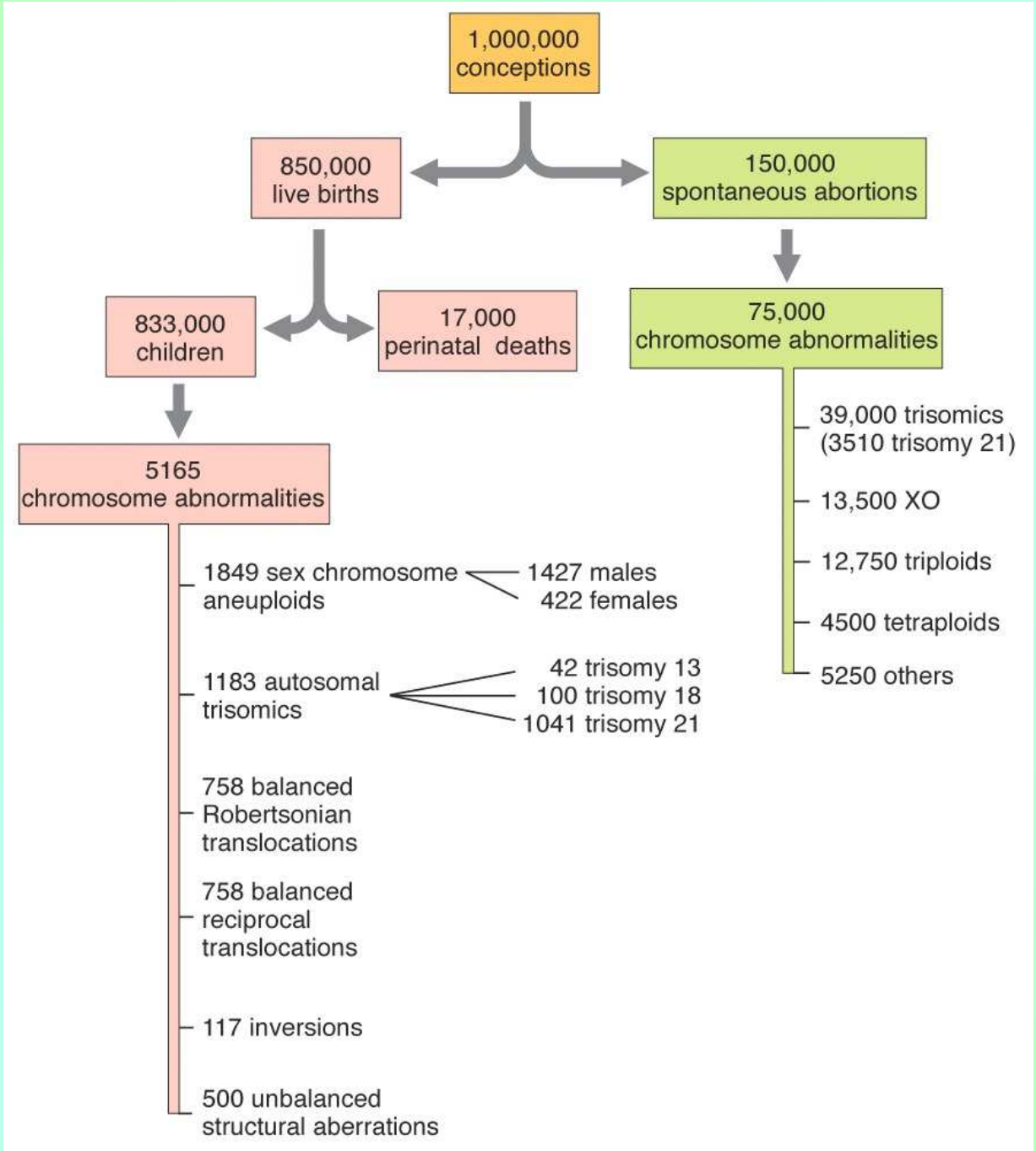


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