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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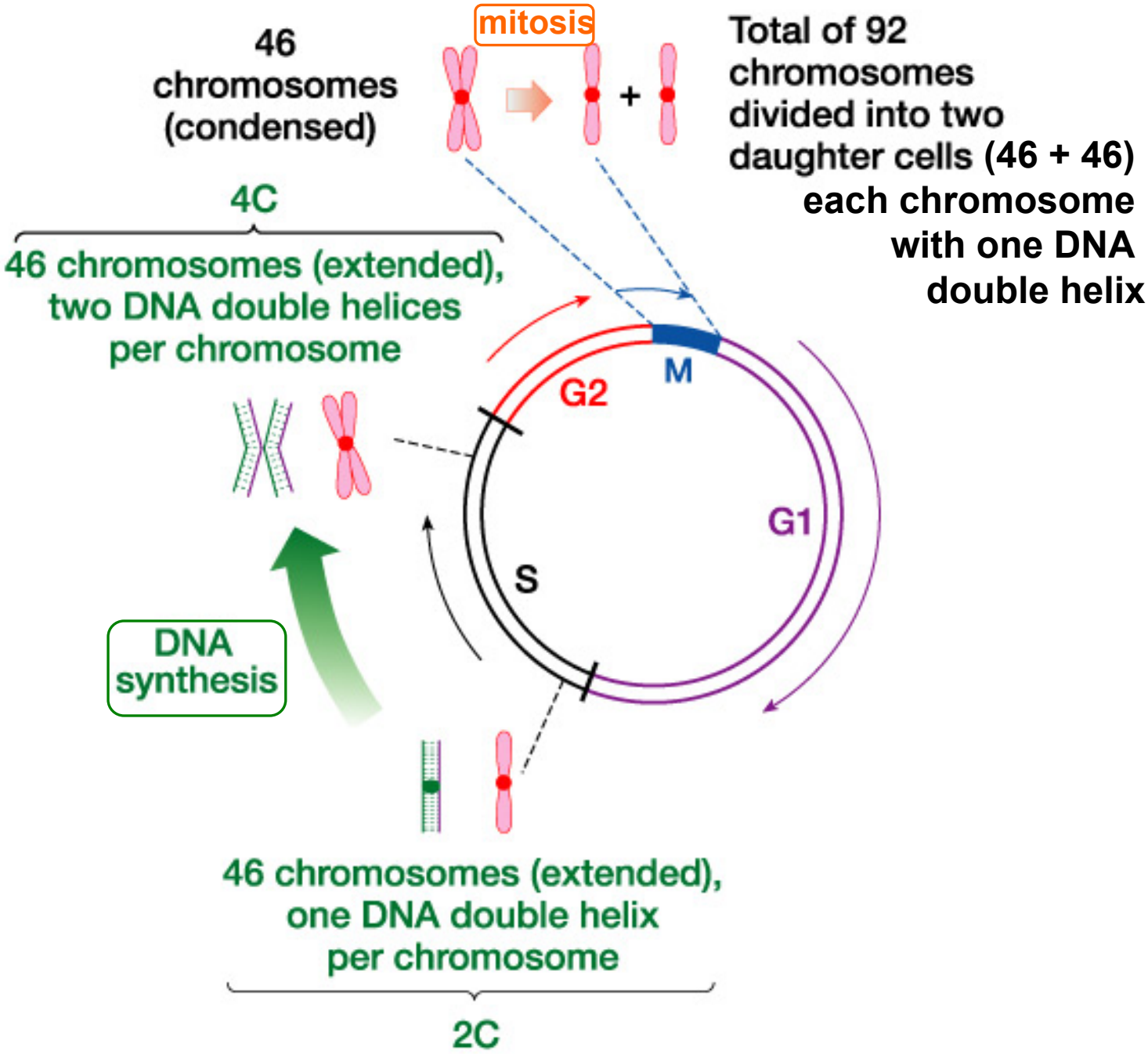
CELL CYCLE



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MITOSIS

INTERPHASE

- Nuclear envelope intact
- No chromosomes visible

Nucleolus

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

Pole

Pole

Equatorial plane = [metaphase plate

Metaphase

- Chromosomes fully condensed and located at metaphase plate

Anaphase

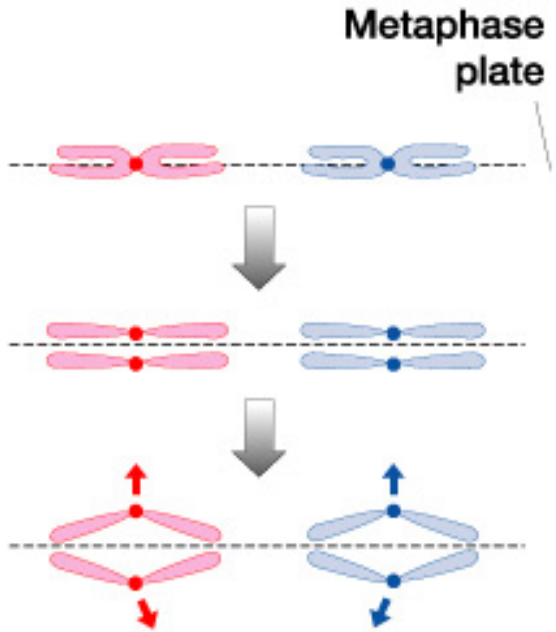
- Each centromere splits
- The two chromatids of each chromosome are pulled to opposite poles

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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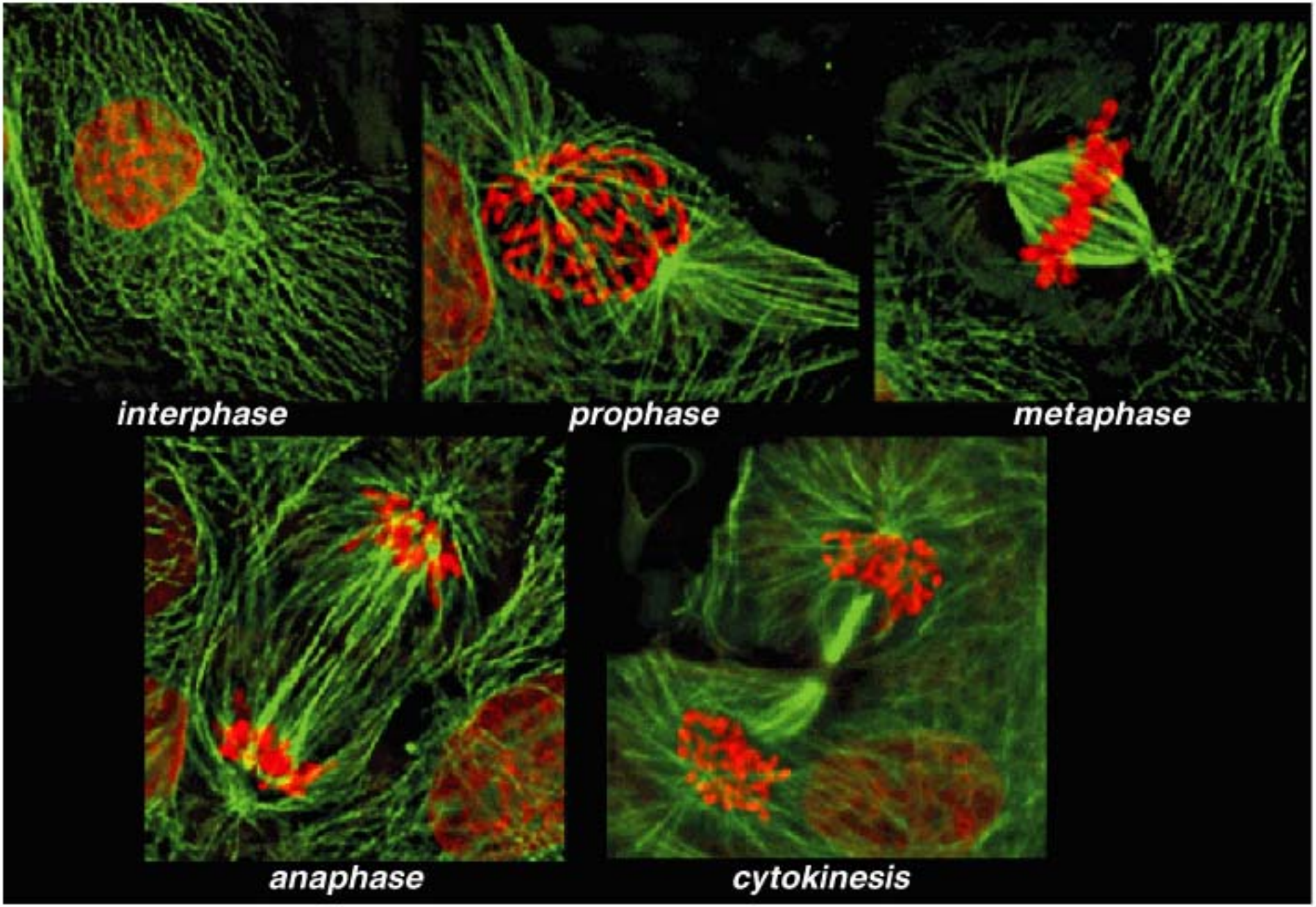
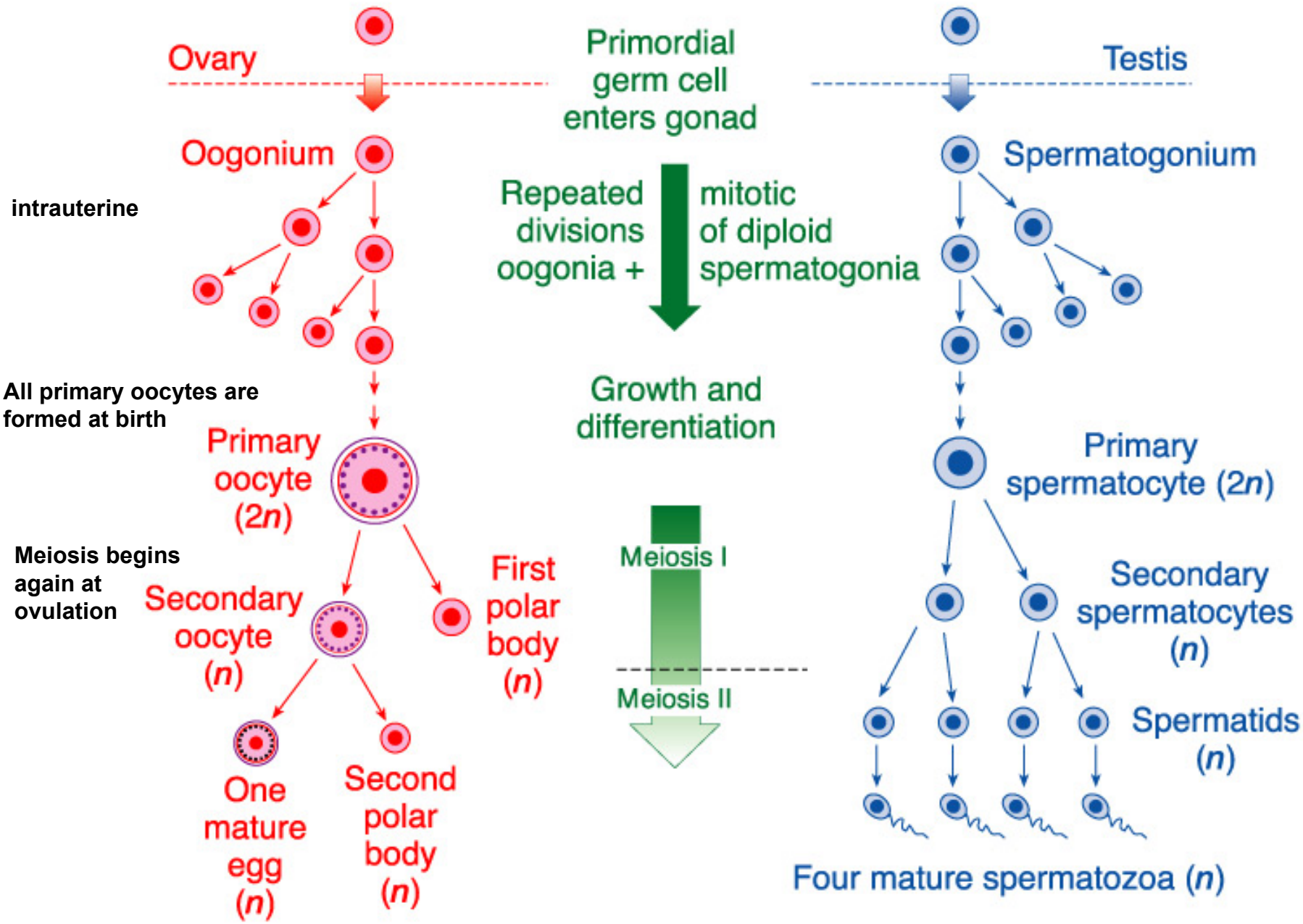

interphase
prophase
metaphase
anaphase
cytokinesis

MEIOSIS (gametogenesis)



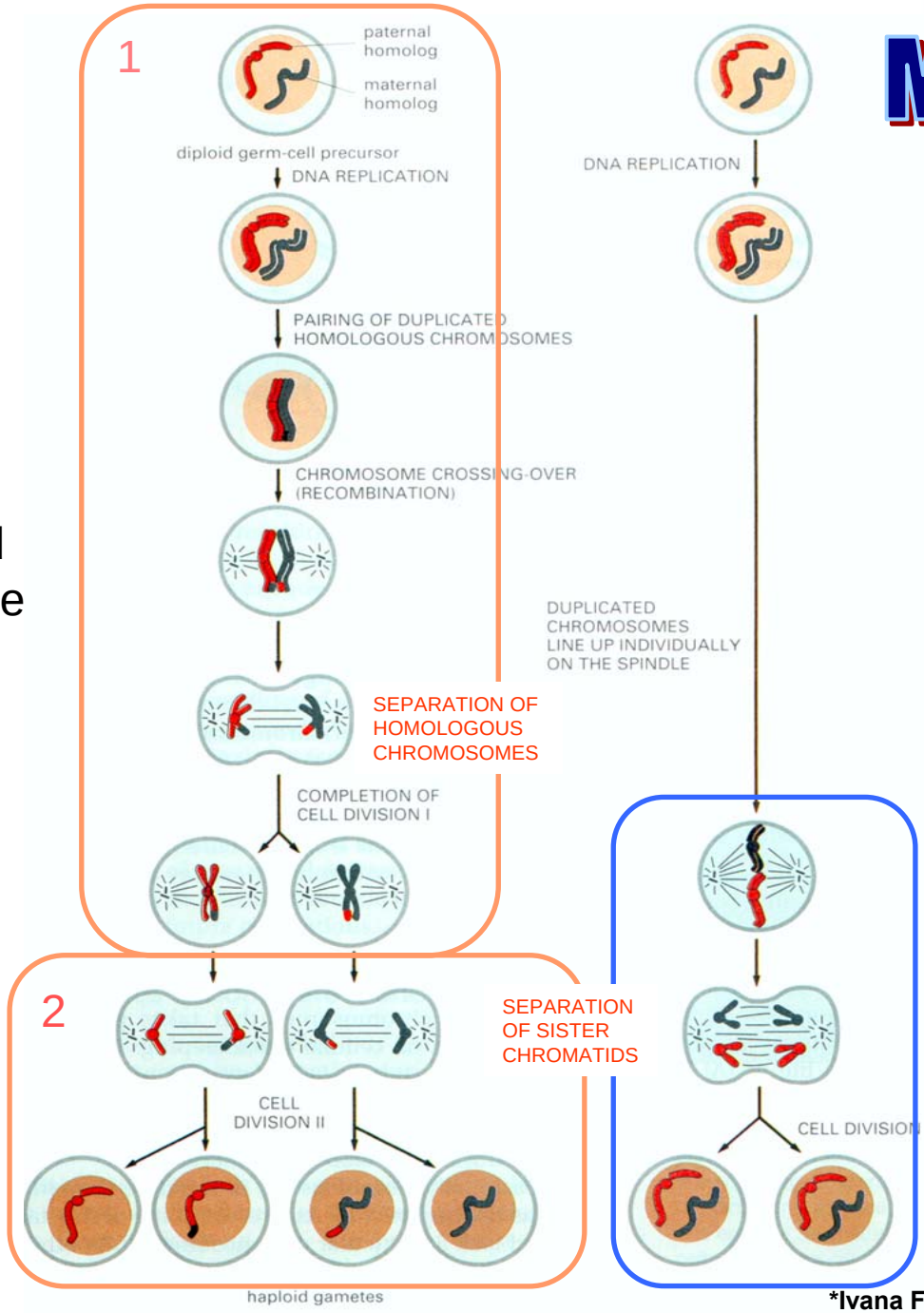
MEIOSIS

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

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

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

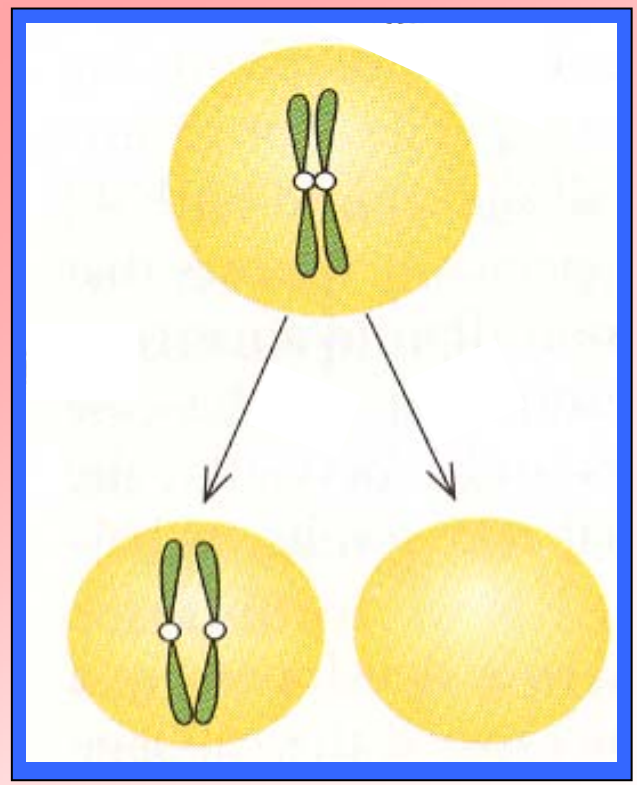
MIXPLOIDY:

organism with two or more genetically different cell linages

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

NON-DISJUNCTION

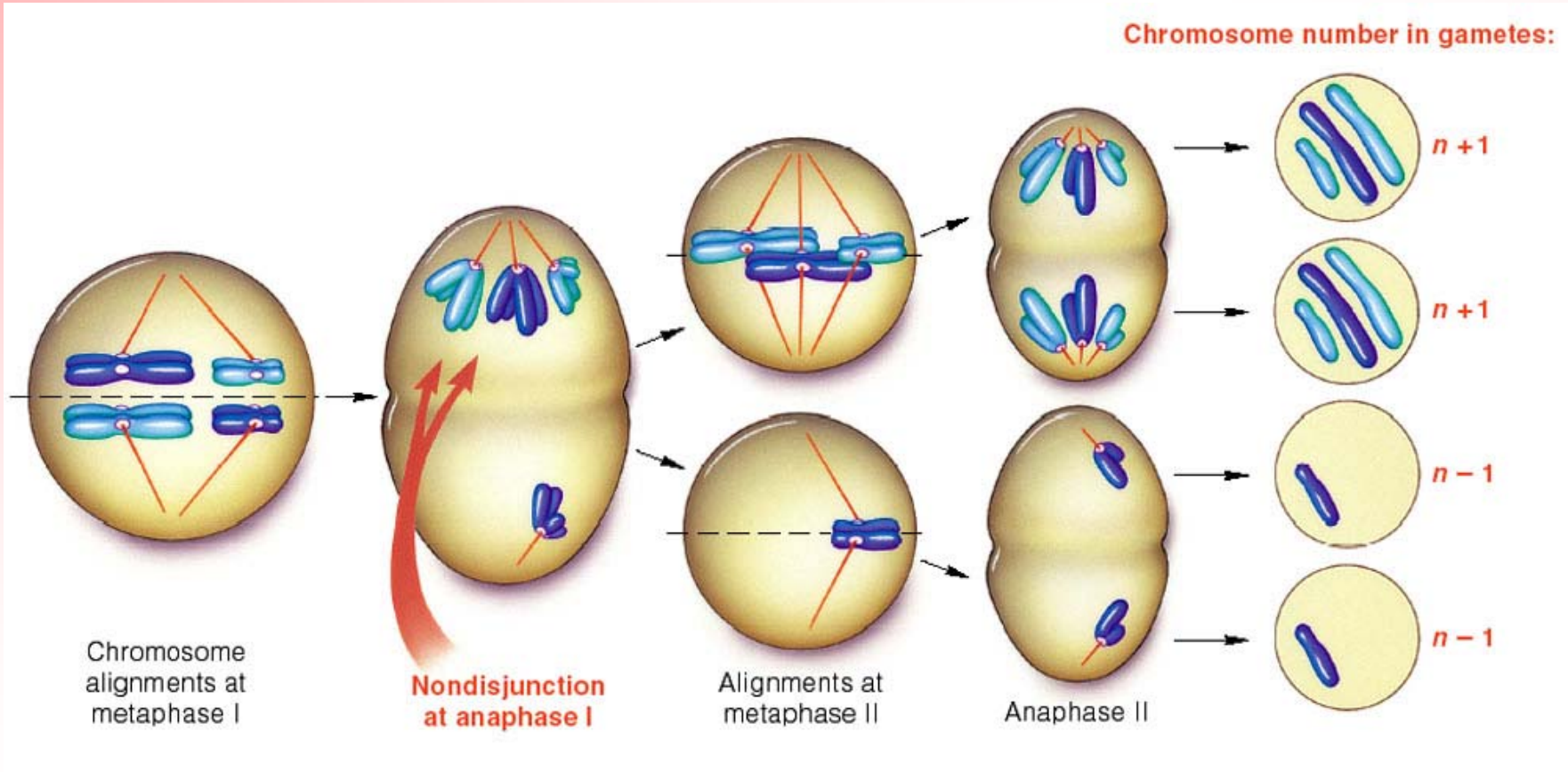
= process when homologues chromosomes or sister chromatids fail to disjoin [do not separate] into two daughter cells during cell division



Depends on when nondisjunction take place:

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

Non-disjunction



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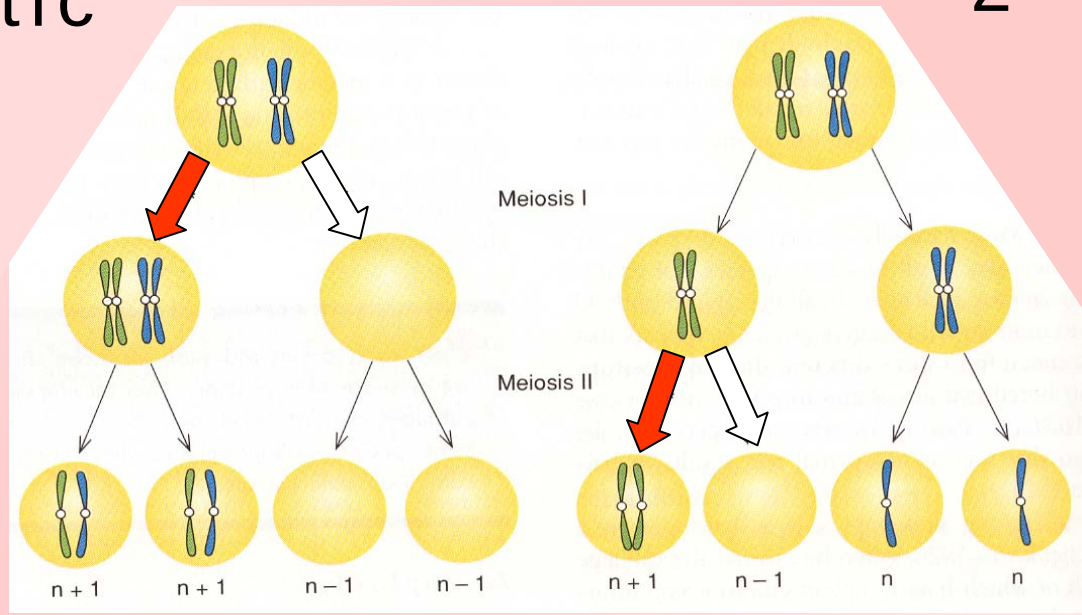
MEIOTIC non-disjunction

1st meiotic division

2nd meiotic division

Homologues chromosomes do not separate properly



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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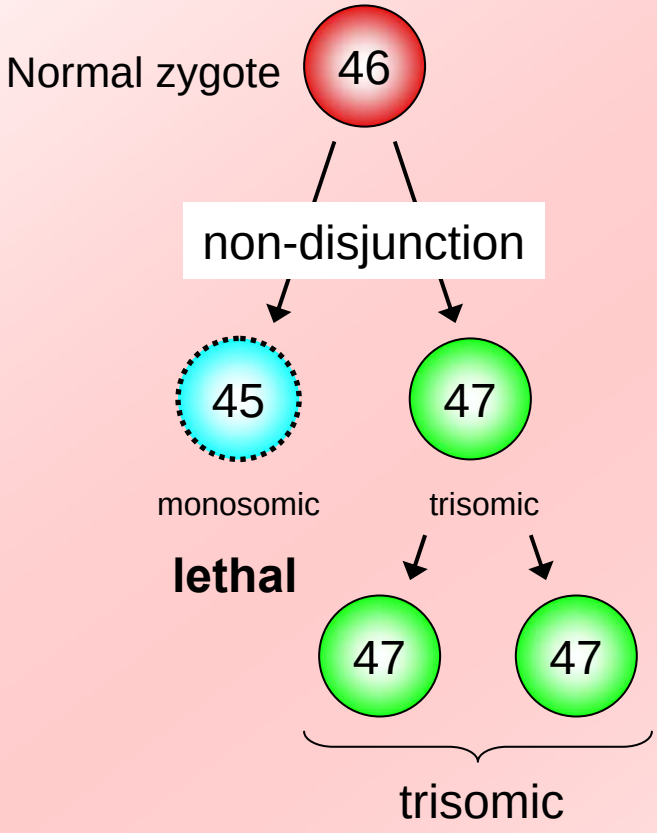
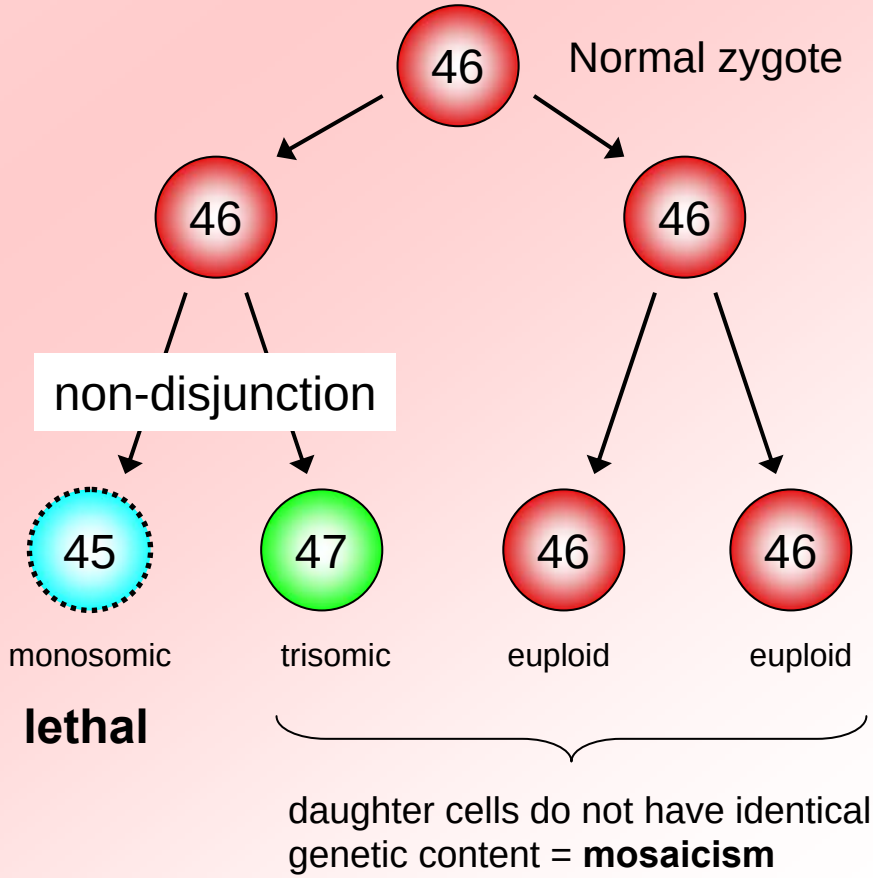
MITOTIC non-disjunction

during the 1st division of zygote



during the 2nd division of zygote



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.

---

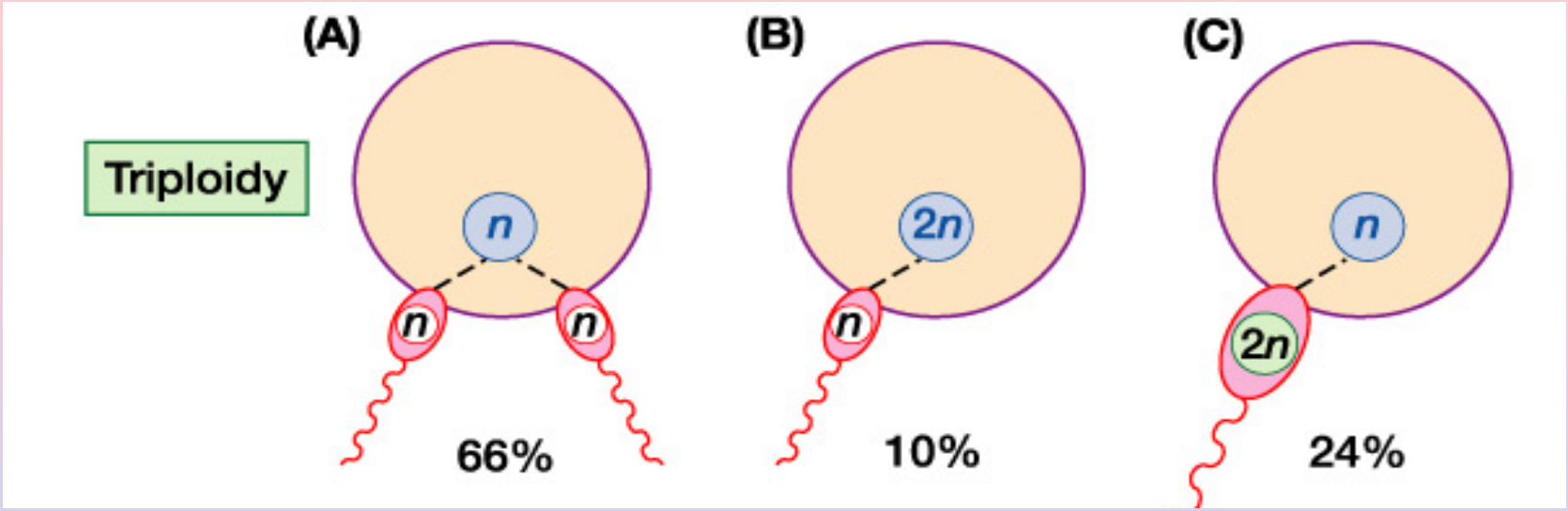
3 sets = triploidy 3n (69 XXX, 69 XXY, 69 XYY)
4 sets = tetraploidy 4n

How polyploidy arise?

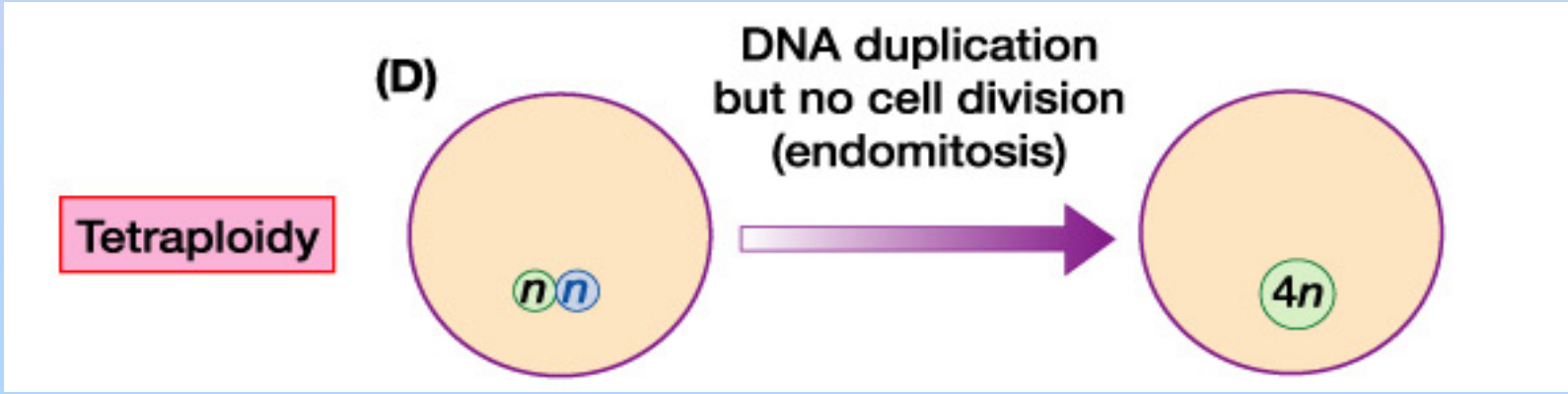
1. Multiple fertilization (polyspermy): two sperm fertilize an egg
2. Errors in meiosis : producing unreduced diploid gametes
3. Errors in mitosis that cause a somatic doubling of the chromosome number

[A] Multiple fertilization

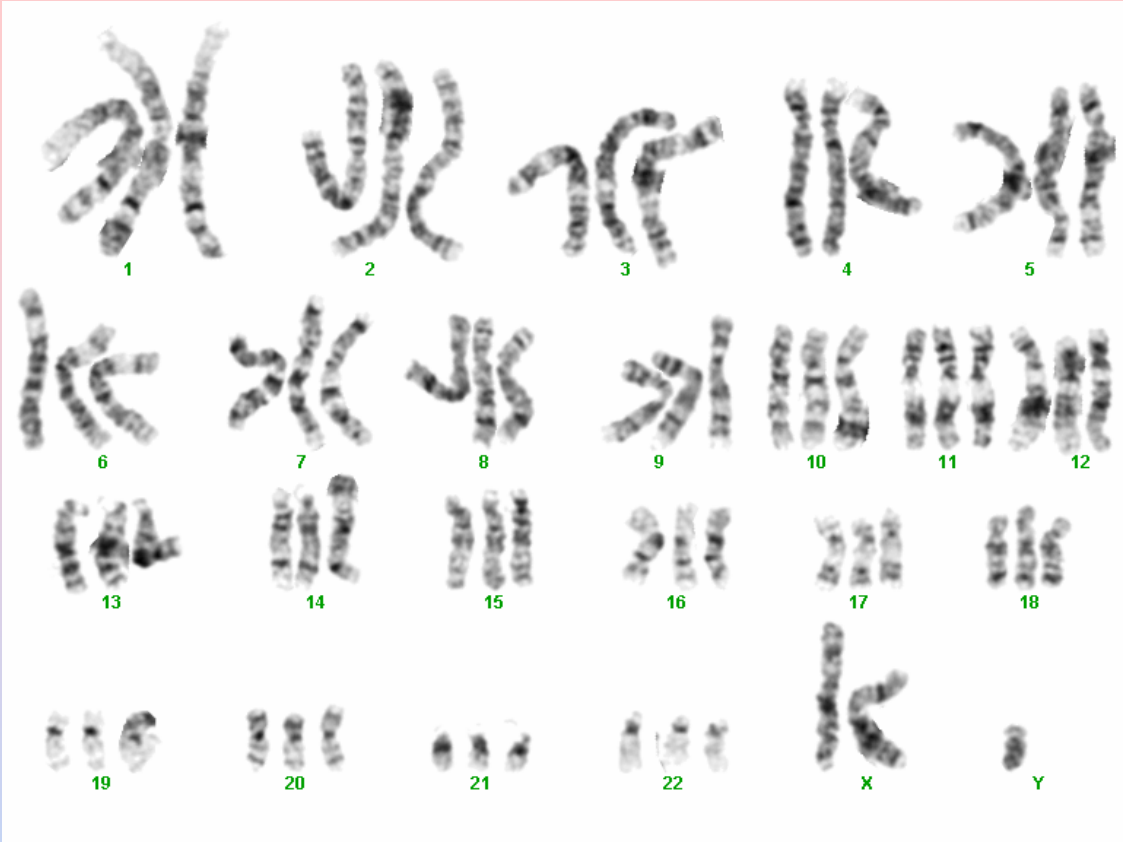
[B,C] Error in meiosis
Producing unreduced diploid gametes



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



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.

MOSAICISM

Genetically different cell population arise from one zygote

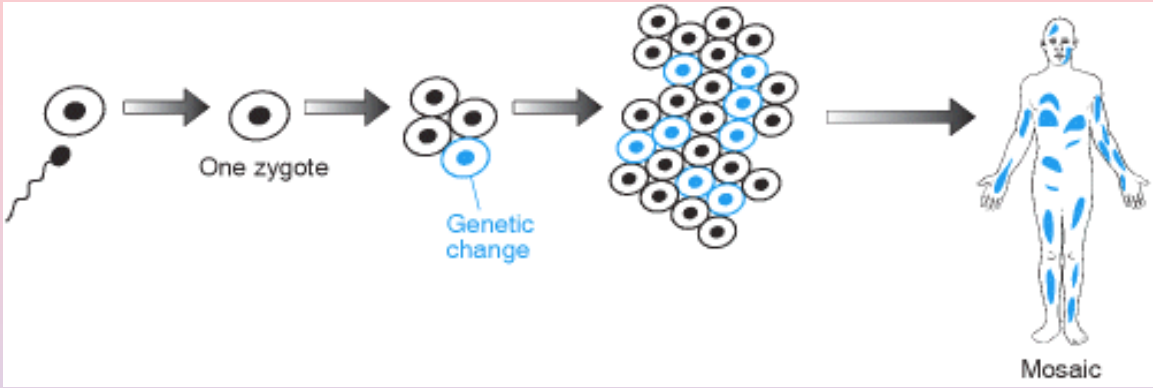
- Aneuploid mosaics (e.g. 2n/2n+1 are common) due to non-disjunction or chromosome lag in early mitotic division of zygote

- 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.

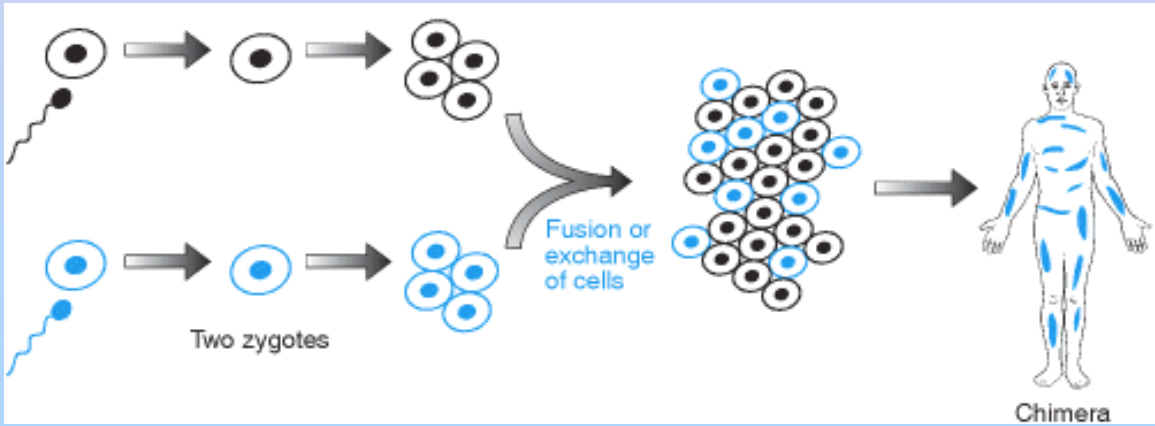
MOSAIC



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

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

AUTOSOMAL aneuploidy

Autosomal MONOSOMY - lethal condition

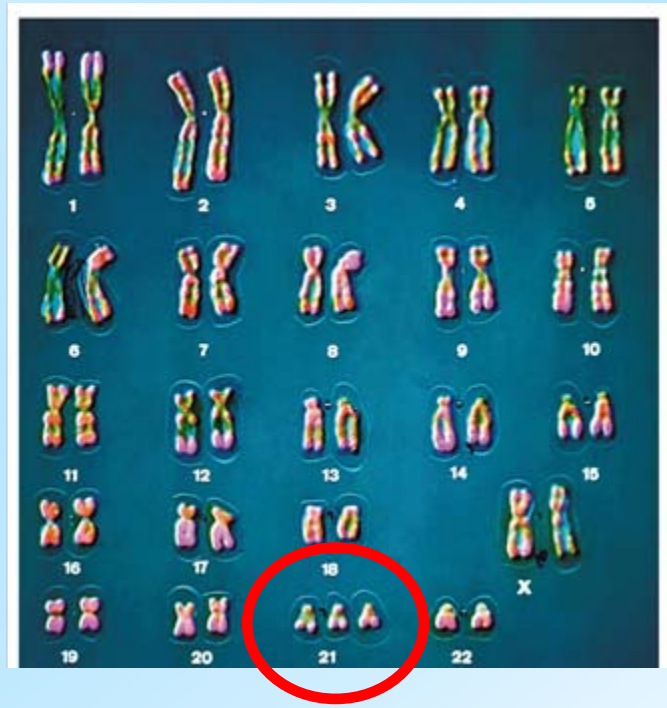
Autosomal TRISOMY - most are lethal; few exception:

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

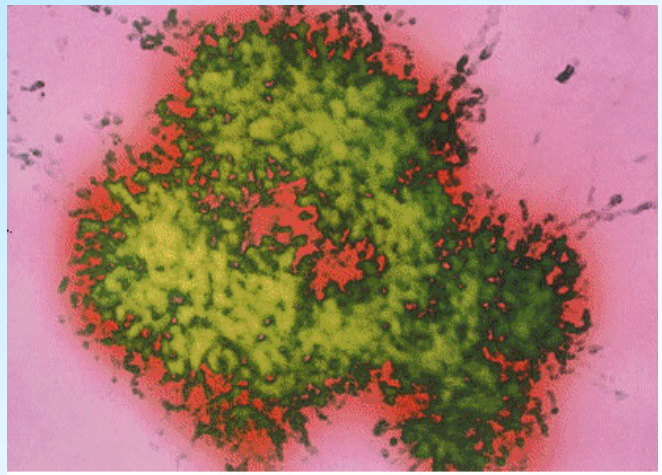
DOWN syndrome:

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

First chromosomal abnormality Discoverd in humans (1959)



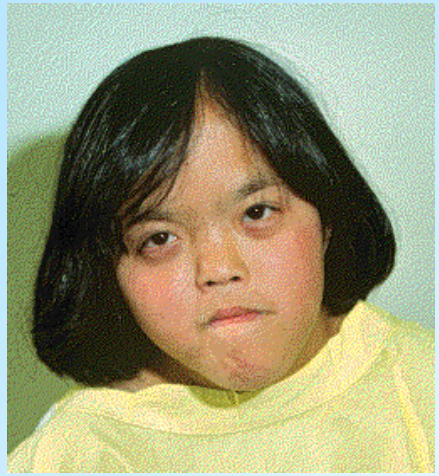
Trisomy 21



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



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:

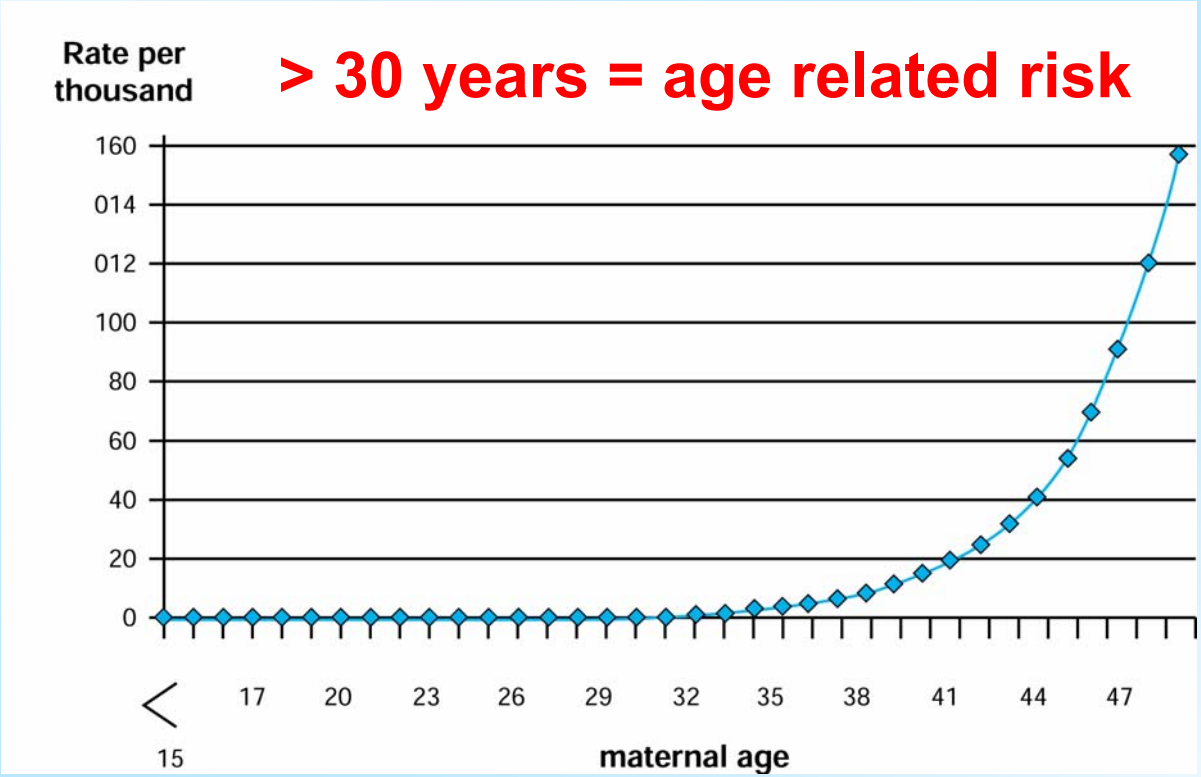
KARYOTYPE: 46/47,+21

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

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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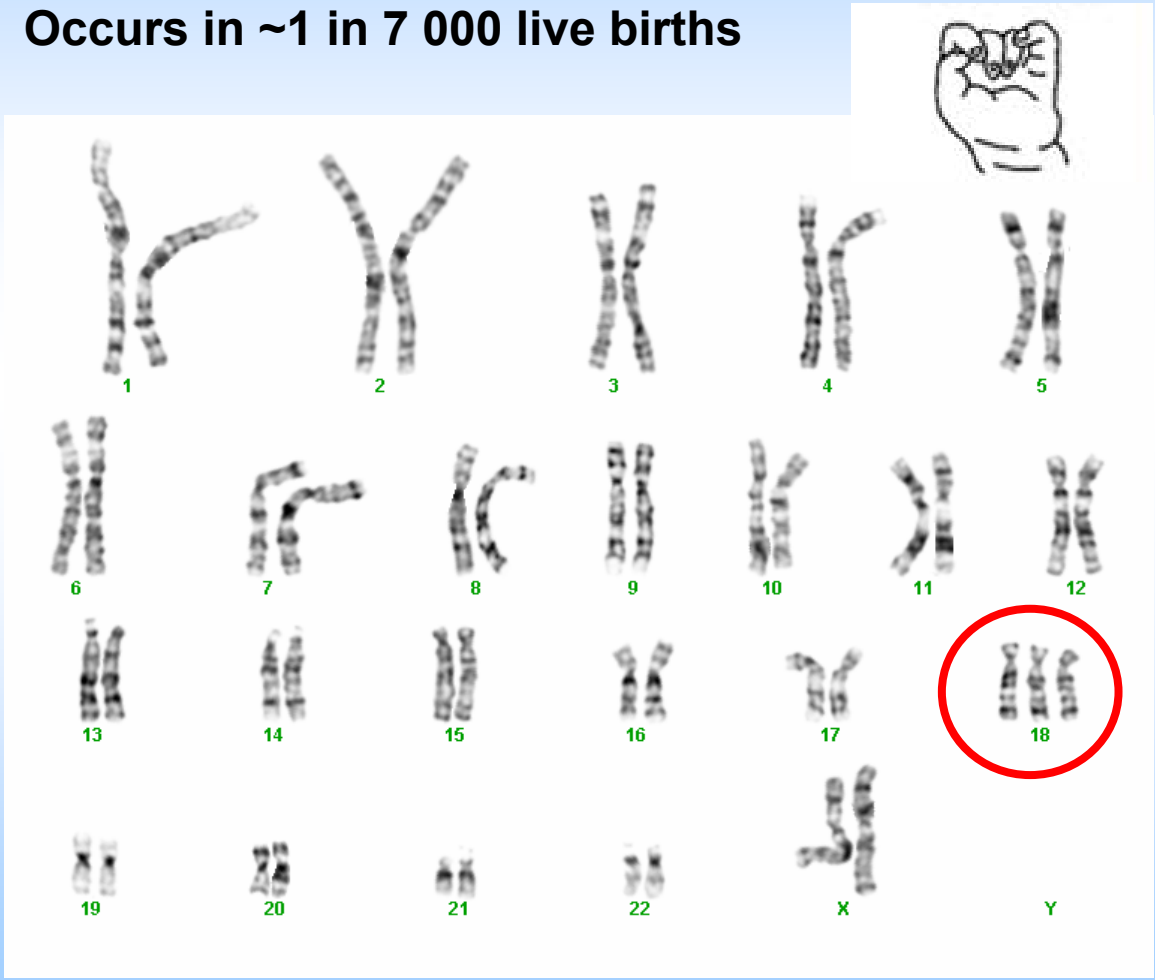
Edwards syndrome

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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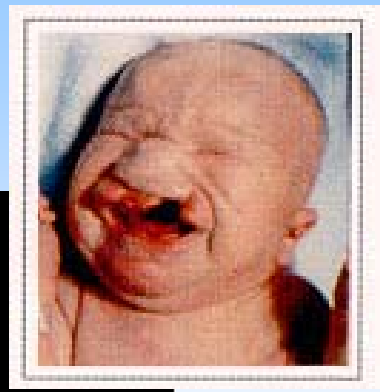
Patau syndrome

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

More tolerated than somatic aneuploidy

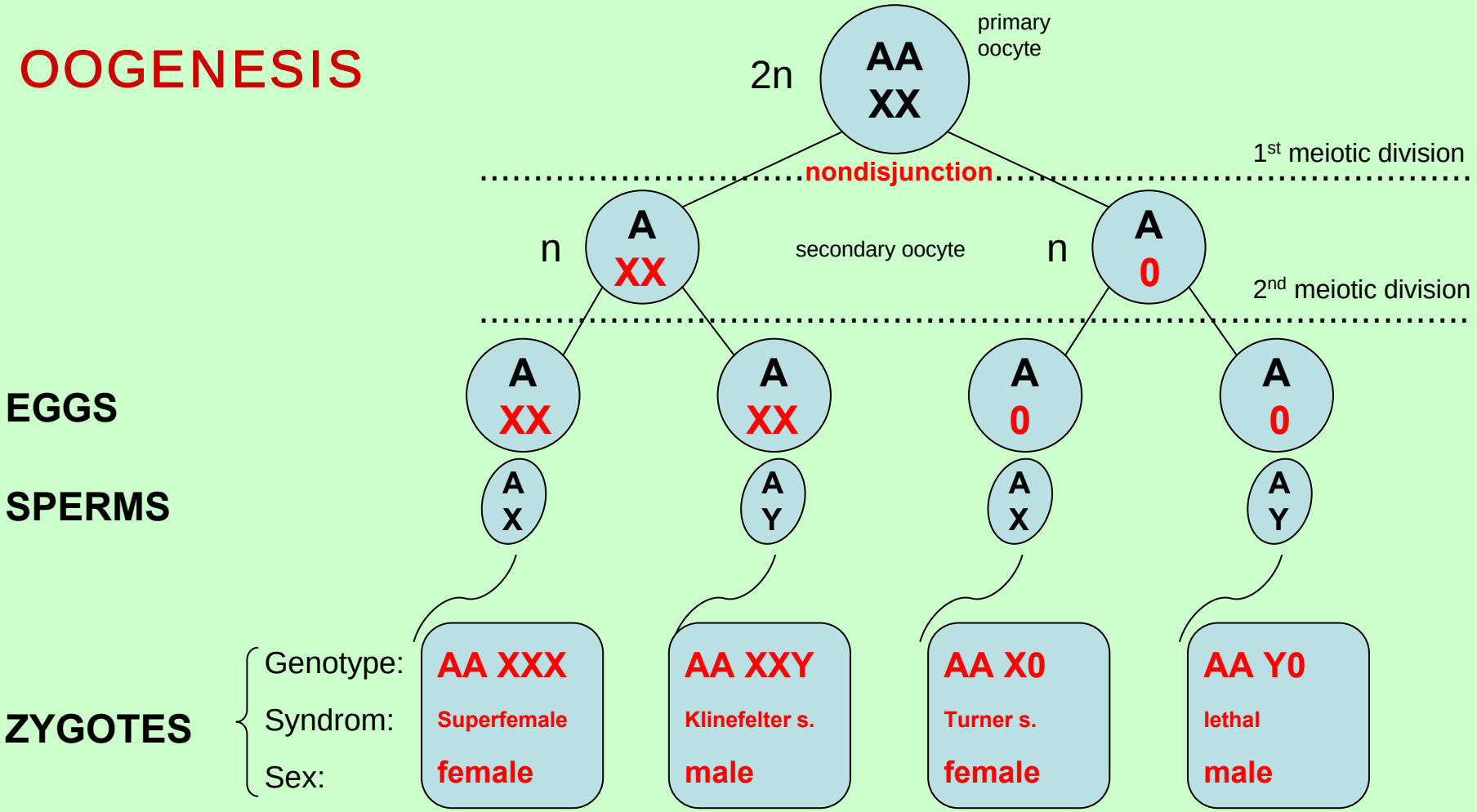
SEX CHROMOSOME aneuploidy

- 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

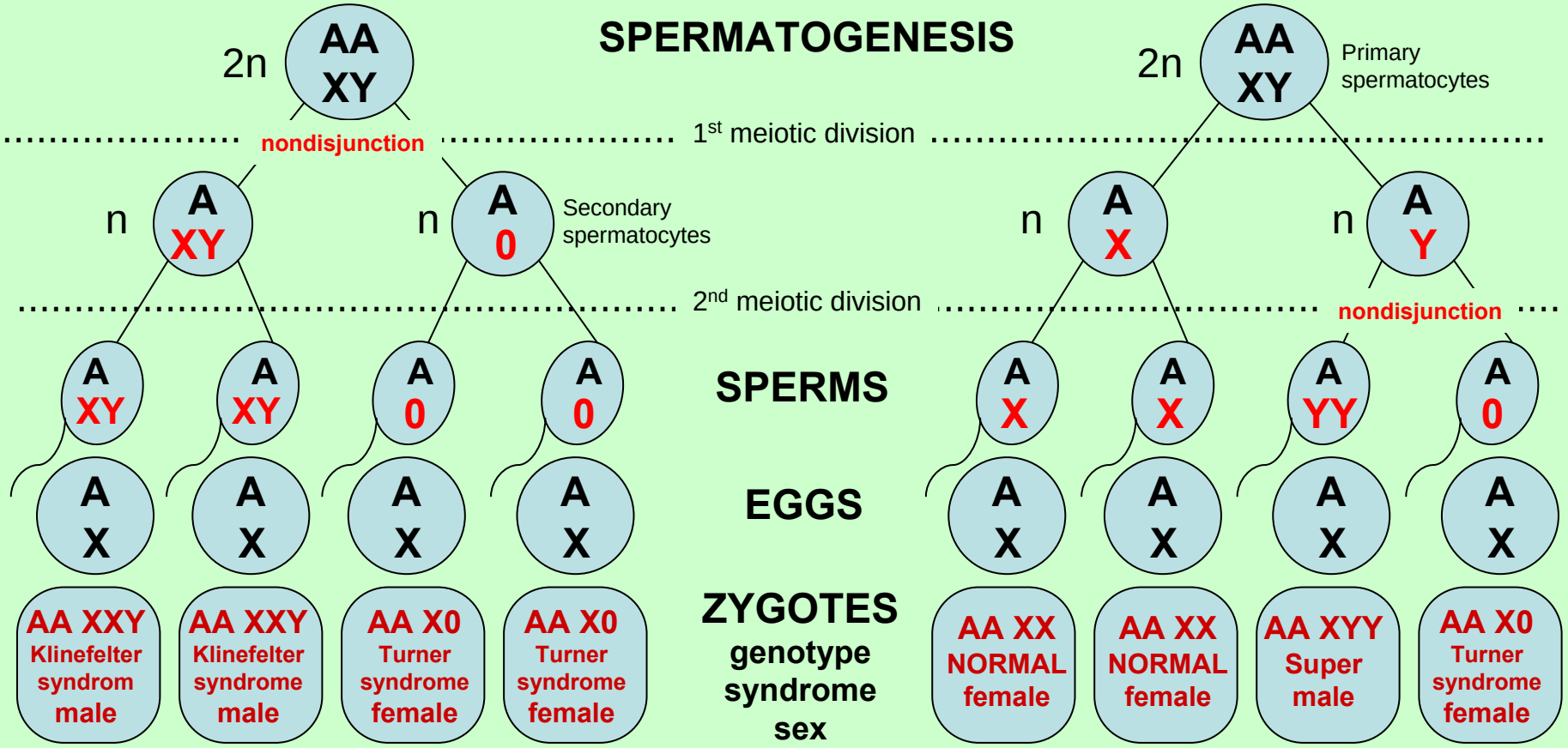
How sex-chromosome aneuploidy arise ?

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



How sex-chromosome aneuploidy arise ?

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



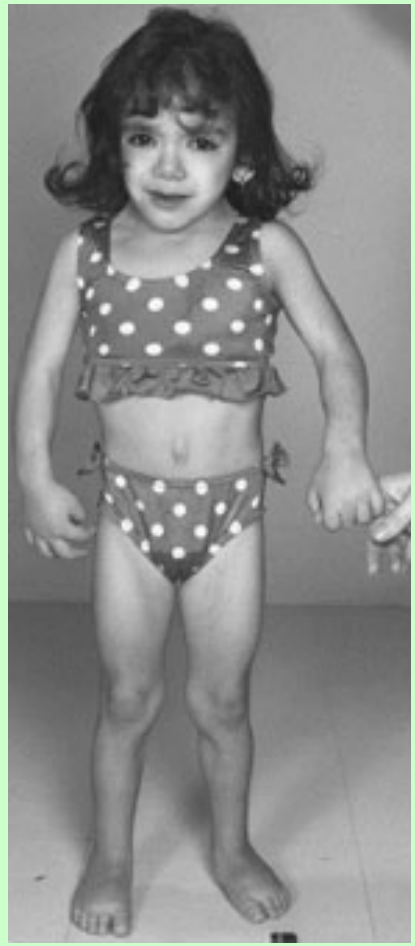
TURNER syndrome

XO

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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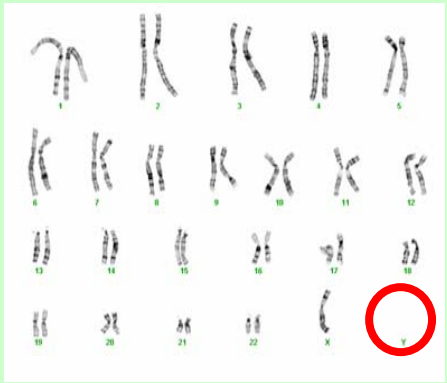
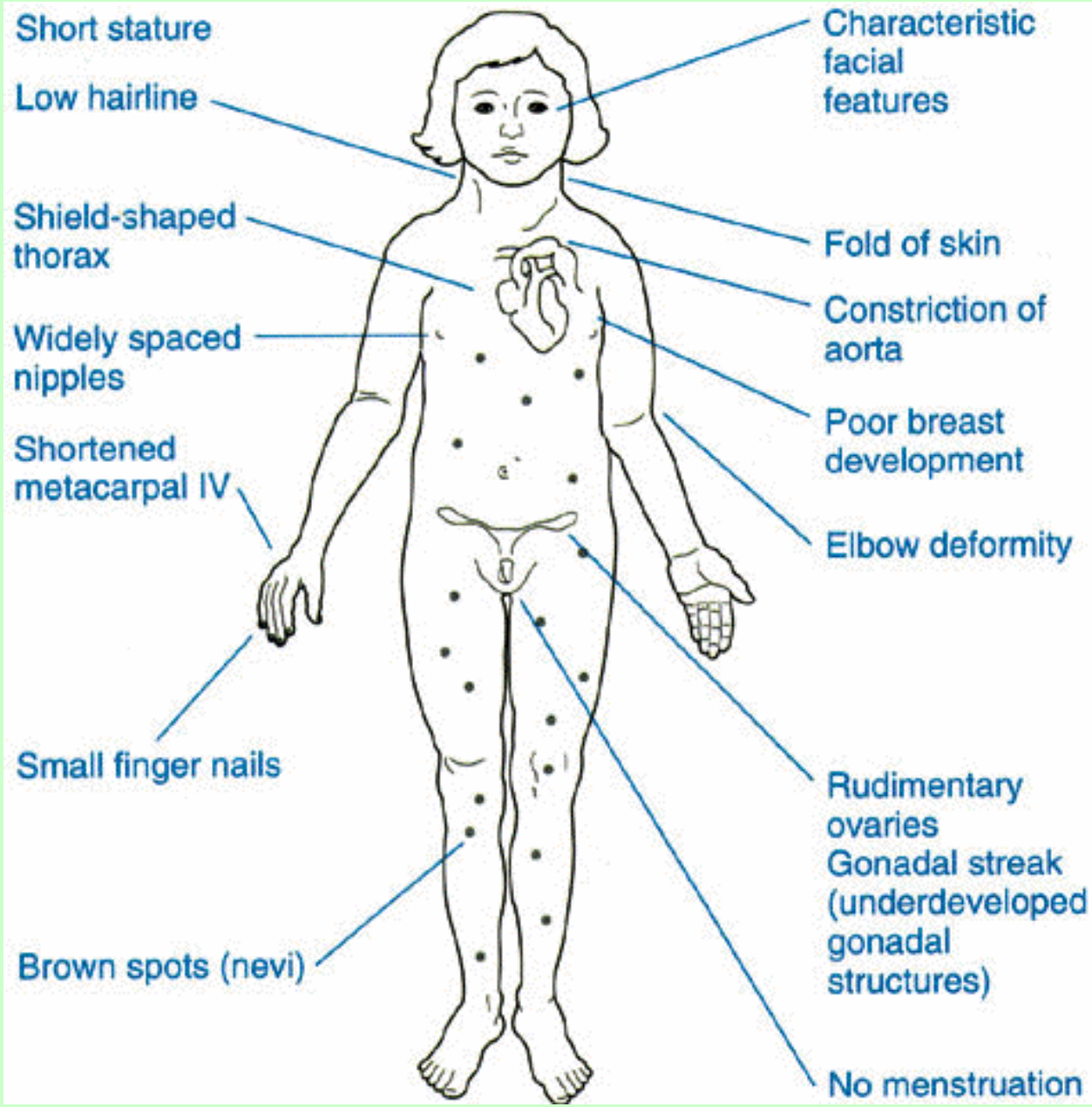
Turner Syndrome

XO (45, X)





Cytogenetic cause of

TURNER syndrome

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

"SUPERFEMALE"

Females With Multiple X Chromosomes

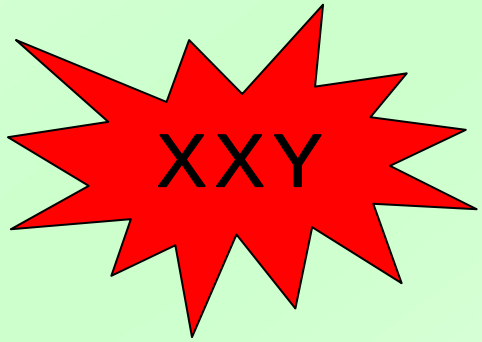
47, XXX – Mostly normal females.

48, XXXX

49, XXXXX

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

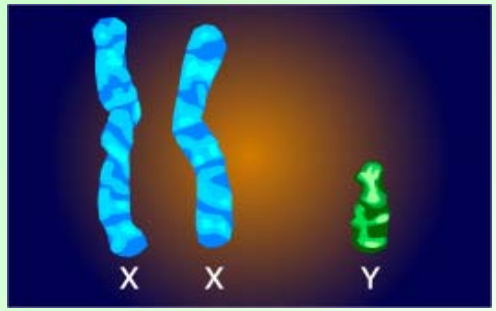
Klinefelter Syndrome



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

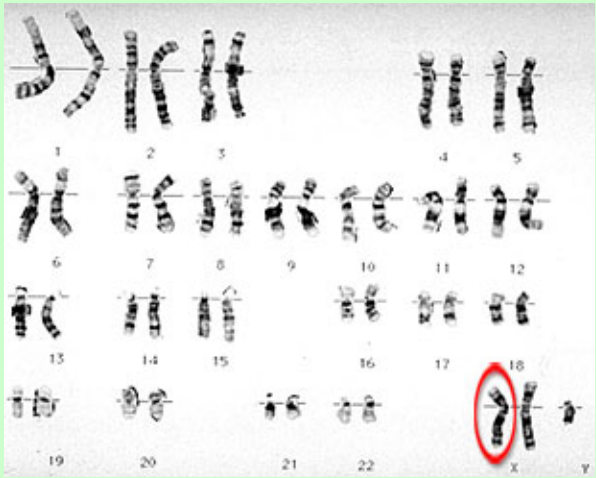
The extra chromosome X was gained either:

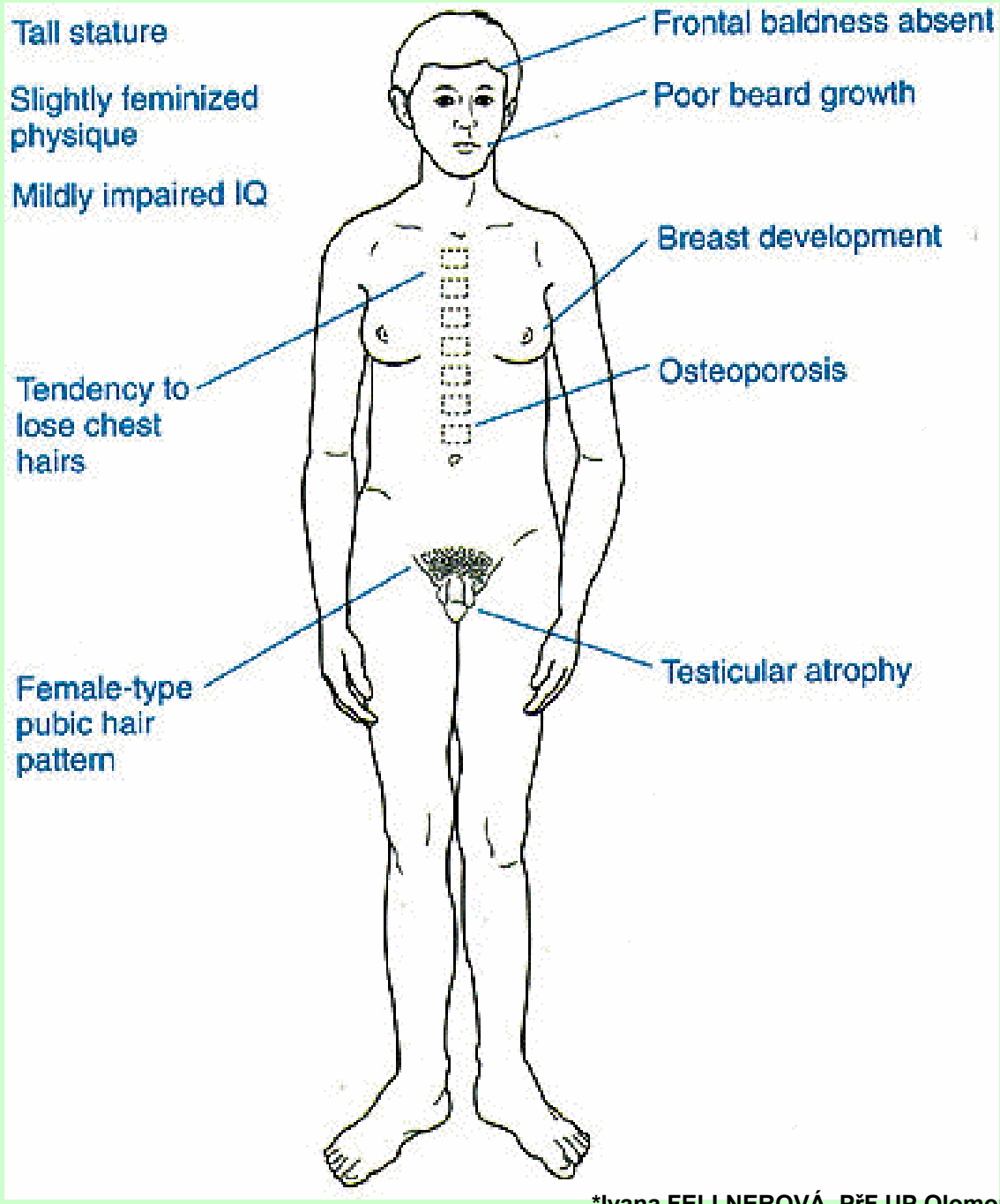
From diploid egg [XX] or sperm [XY]
[meiotic nondisjunction]
or
during early fetal development
[mitotic nondisjunction]



Klinefelter Syndrome

(47,XXY)





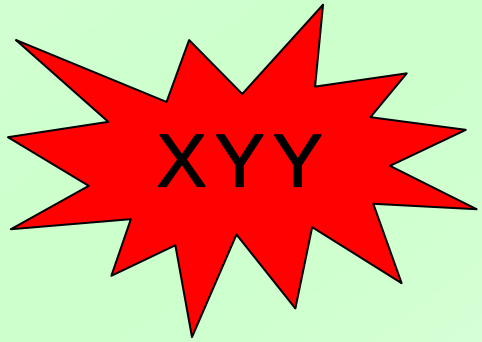
"SUPERMALE"

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.

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

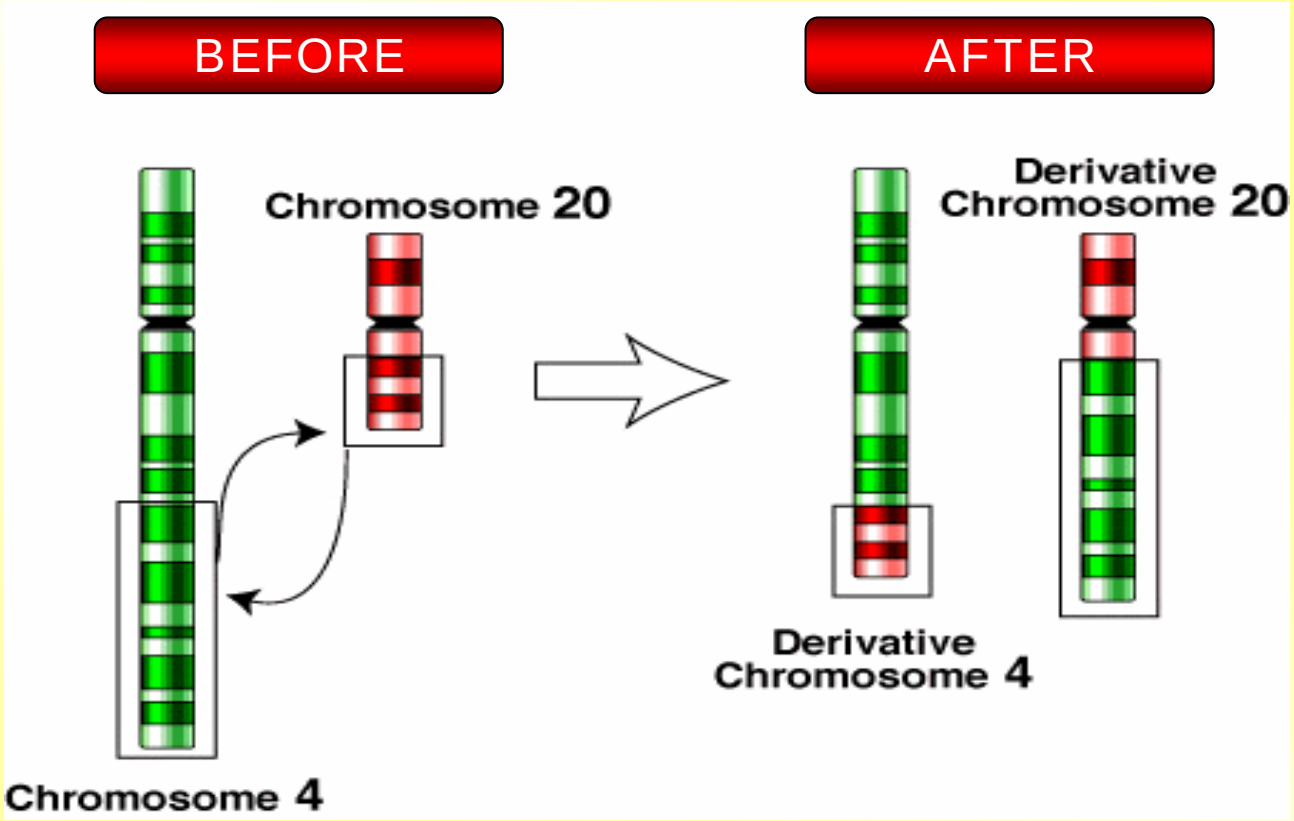
Chromosome breakage with subsequent reunion in a different configuration

- **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)

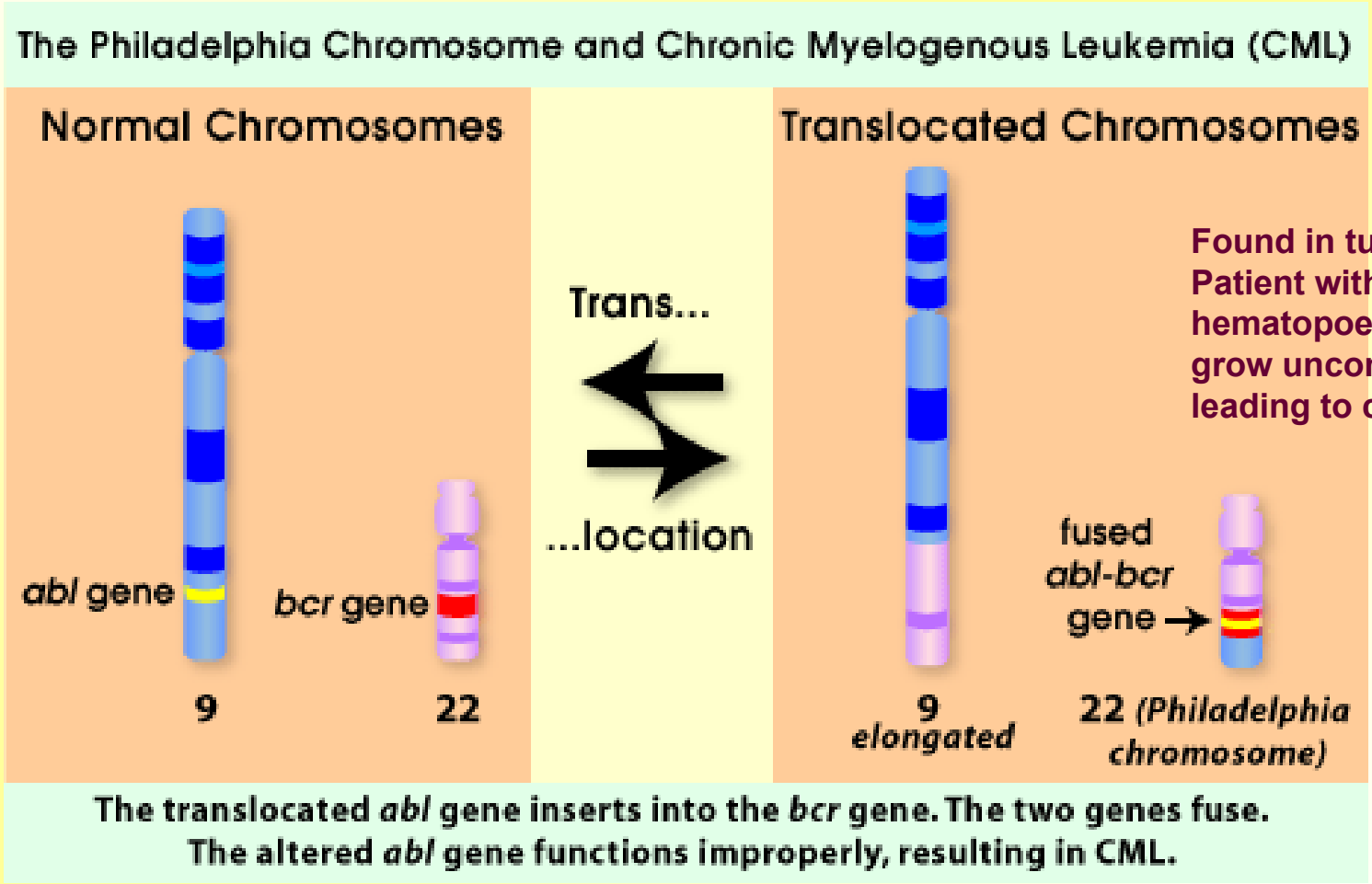
Reciprocal Translocation

- 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

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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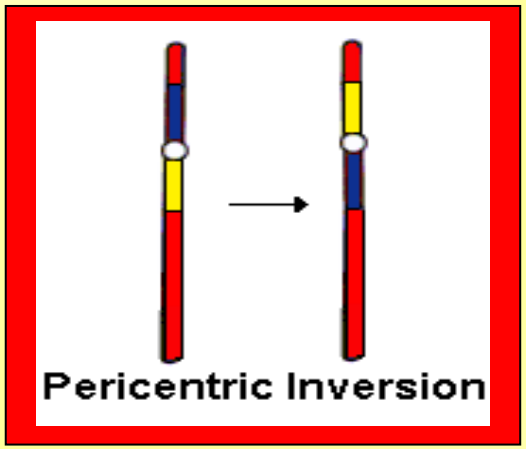
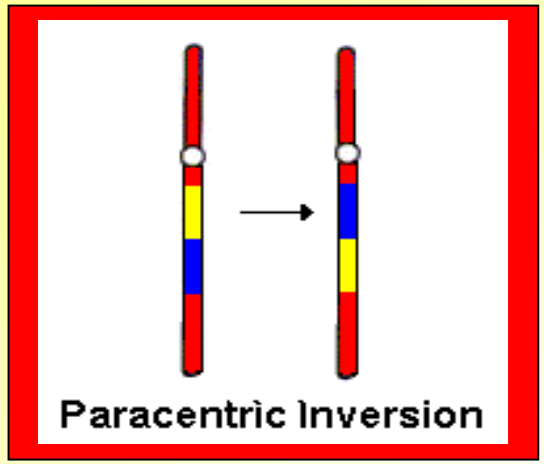
Ivnersion

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



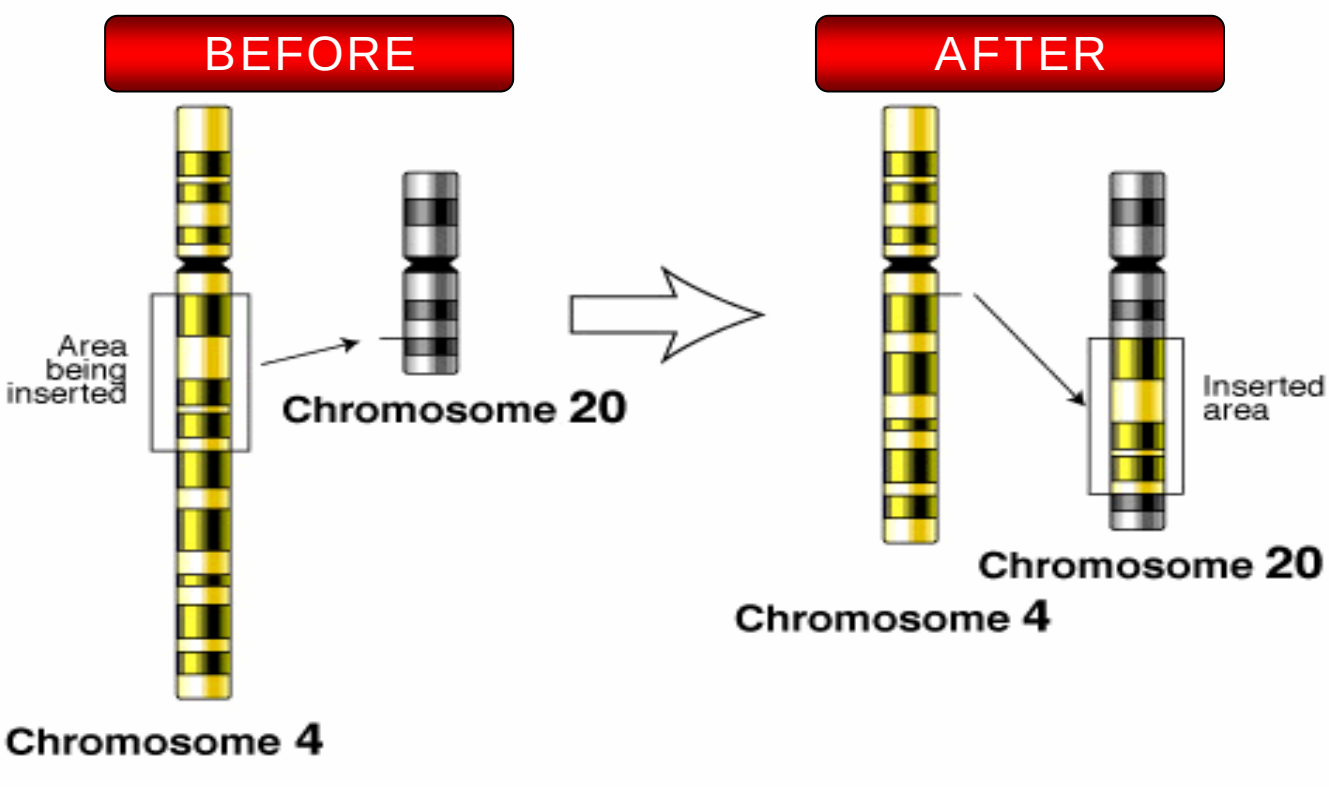
inverted area
includes the centromere



inverted area
excludes the centromere

Insertion

BALANCED



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

Unbalanced rearrangements

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

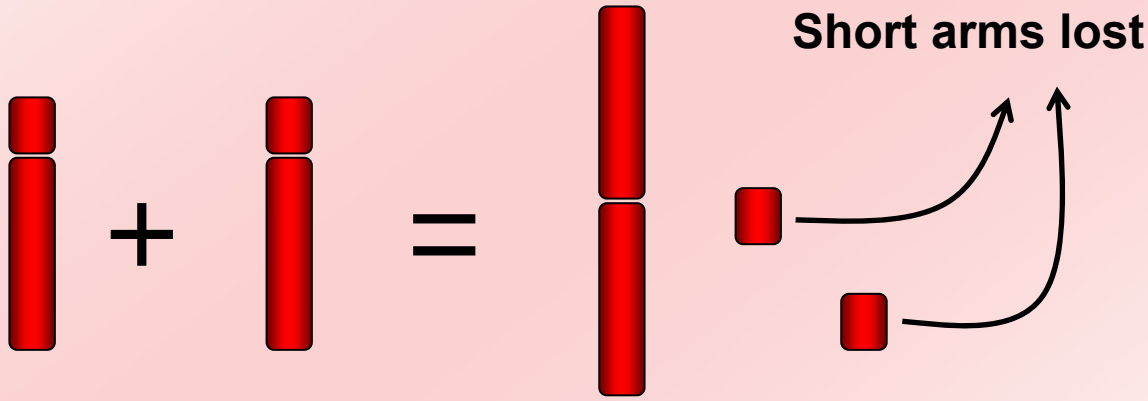
Robertsonian Translocation

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

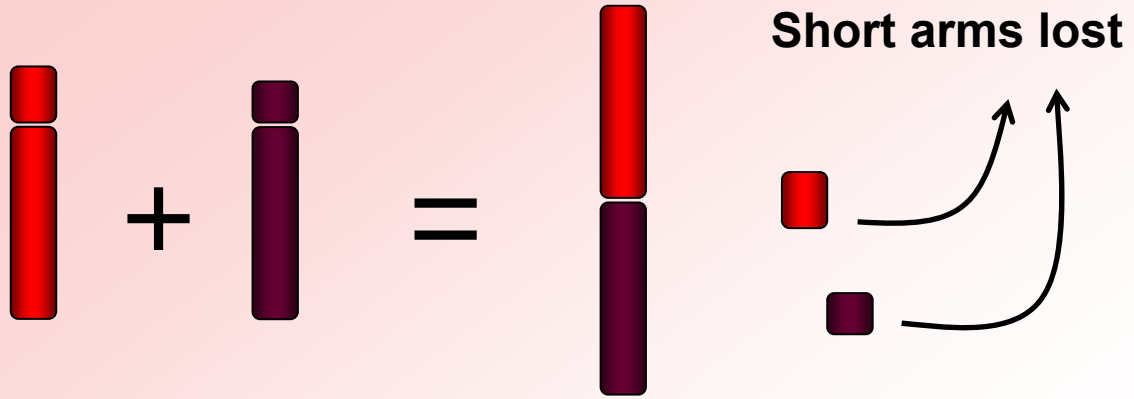
  Frequency = 1/1000 livebirths
- A special case of „almoust balanced“ translocations involves any of two **acrocentric** chromosomes: 13, 14, 15, 21 and 22
- Two types of Robertsonian translocation
  - **Homologous acrocentrics involved**
  - **Non-homologous acrocentrics involved**

Robertsonian Translocation

Homologous
acrocentric,
chromosome
i.e. 14

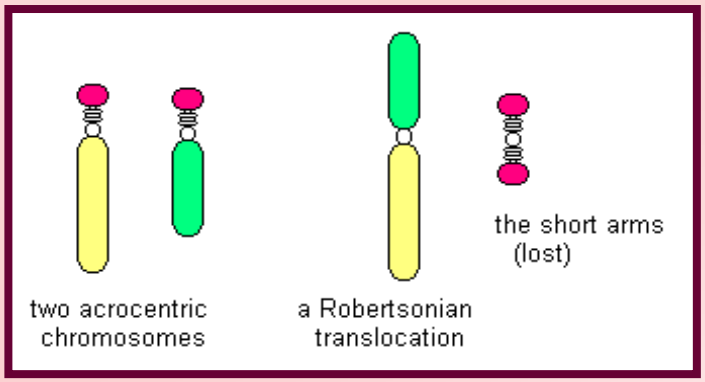


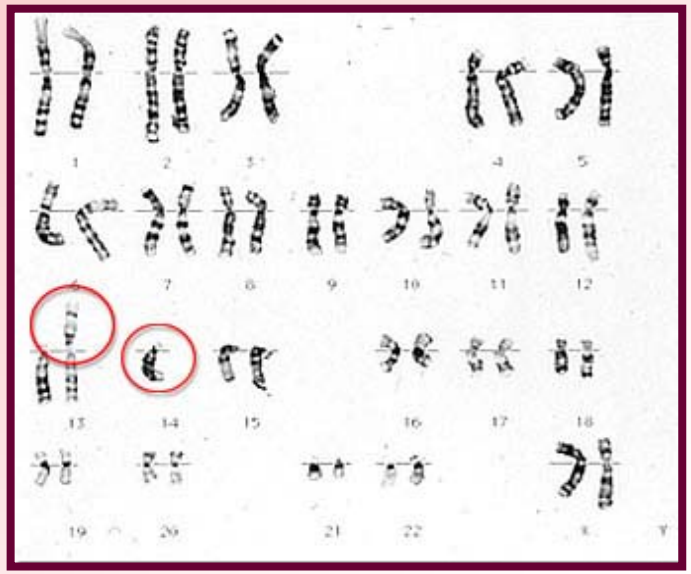
Non-Homologous
acrocentric
chromosome
i.e. 14 & 21



Robertsonian Translocation

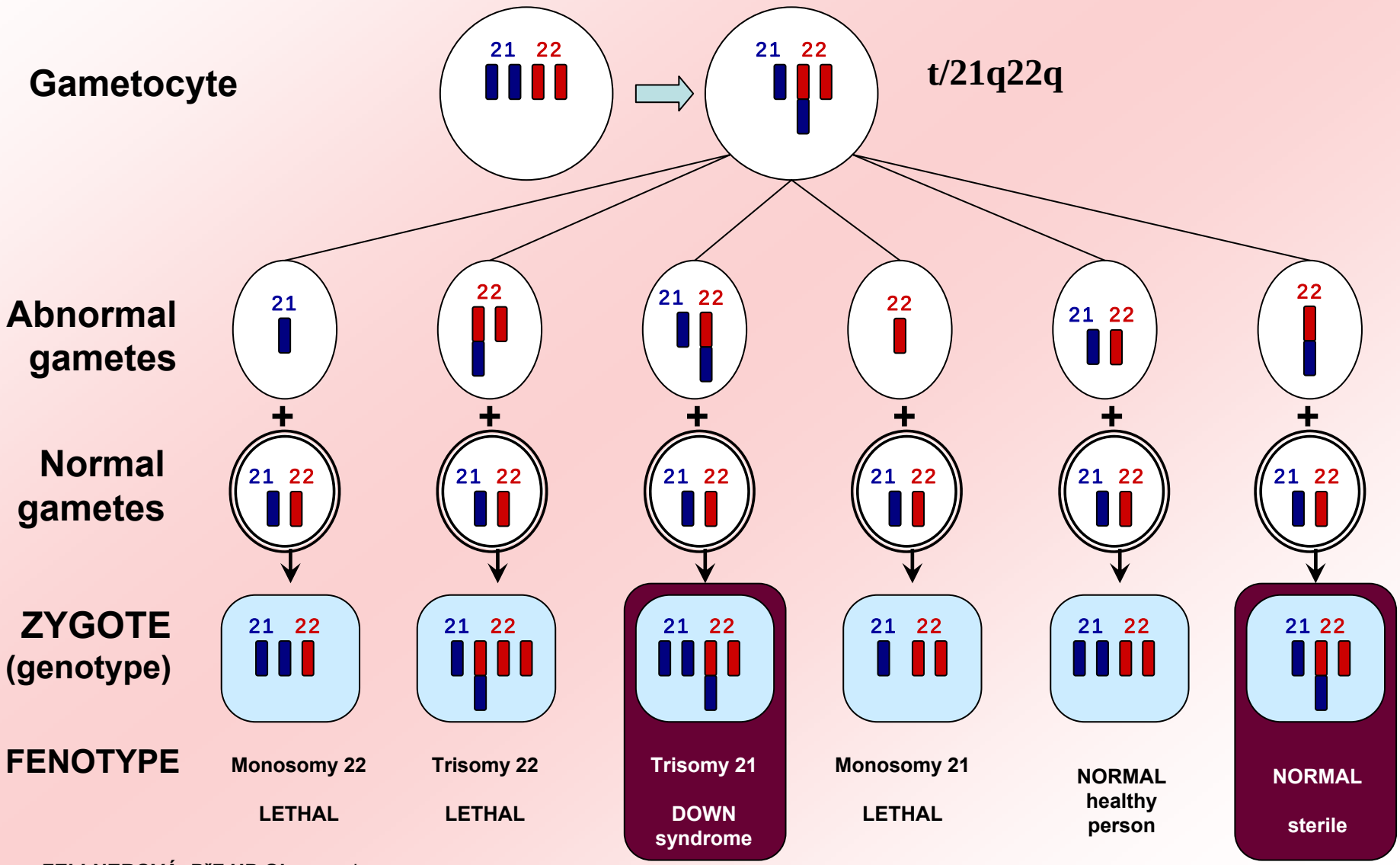
- a fusion between the centromeres of two acrocentric chromosomes forming a single derivate chromosome
- The short arms (p) are lost withouth phenotype efect (loss of the short arms does not matter – contain few, if any, genes)
- Carriers have difficulties at meiosis (modal chromosome number 45)





Case of Robertsonian Translocation

Fusion of q arm of acrocentric chromosomes # 21 and 22



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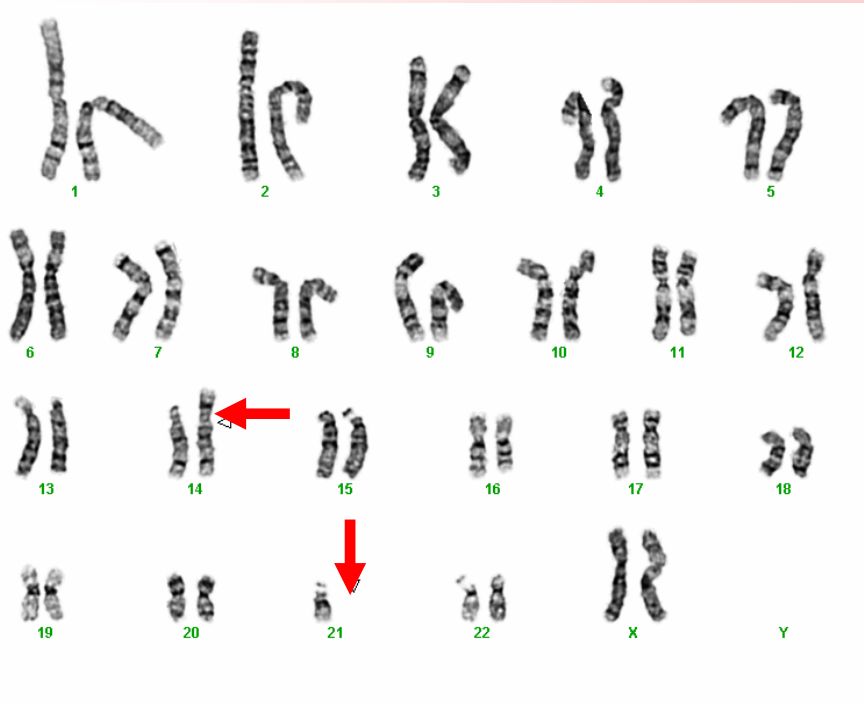
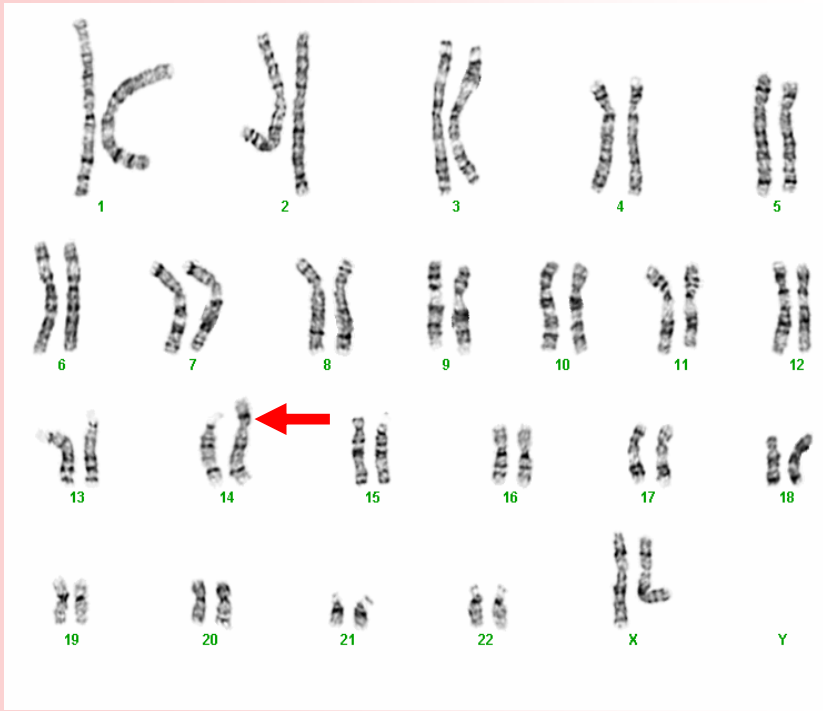
Karyotype of Robertsonian Translocation

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

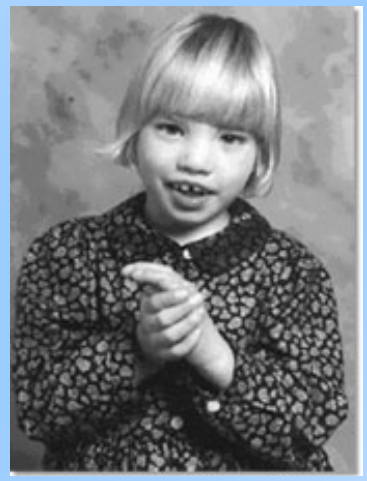
Cri-du-chat syndrom

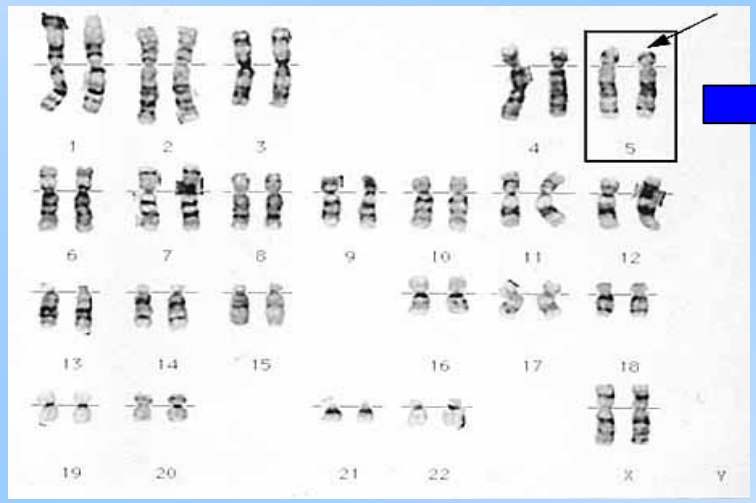
Chromosome 5 terminal deletion

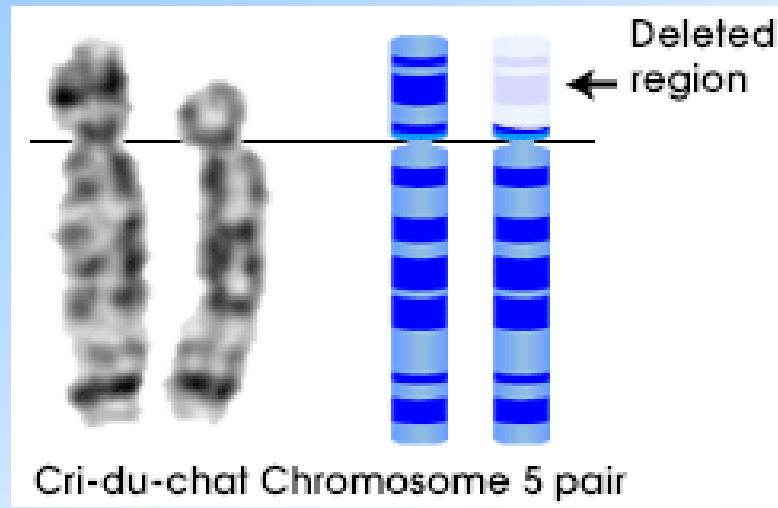
French for cry-of-the-cat
[refers to the distinctive cry of children caused by abnormal larynx]

~ 1 in 50.000 live births

Most common deletion syndrome
In humans







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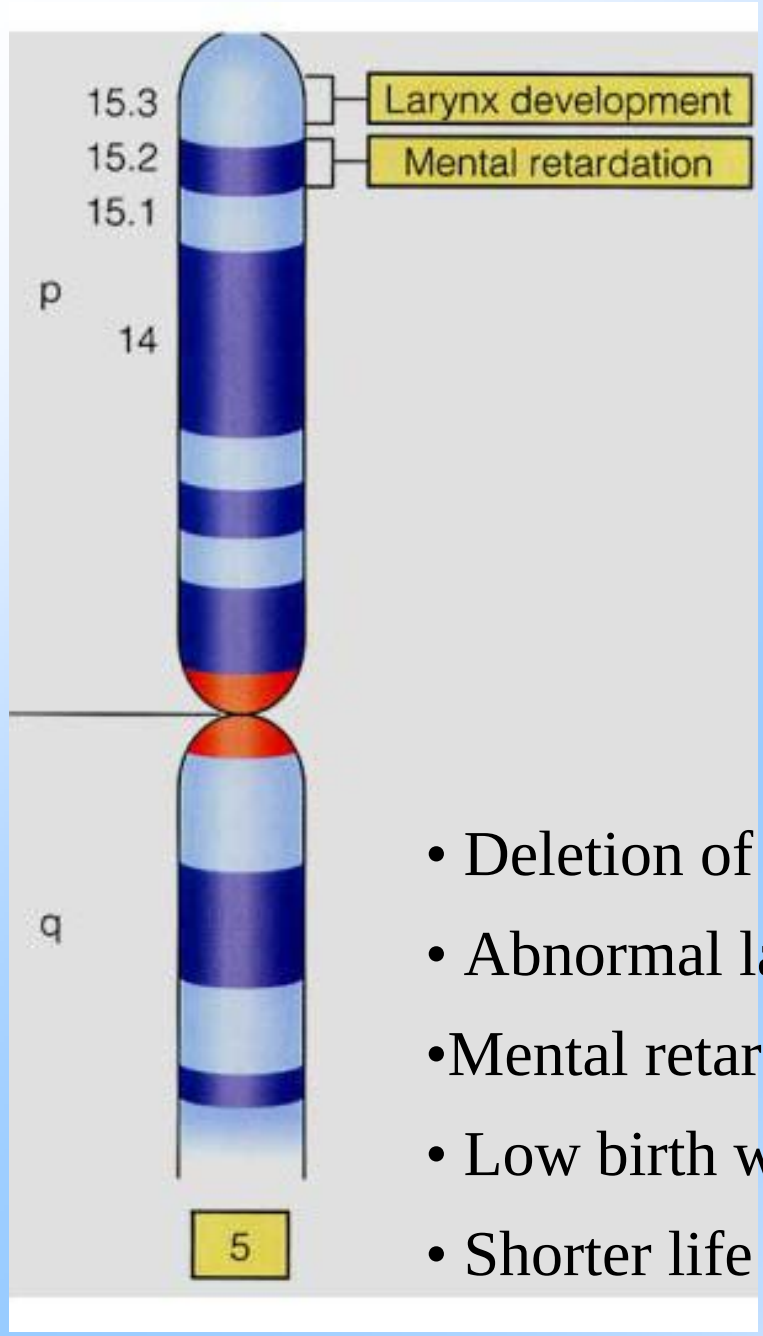
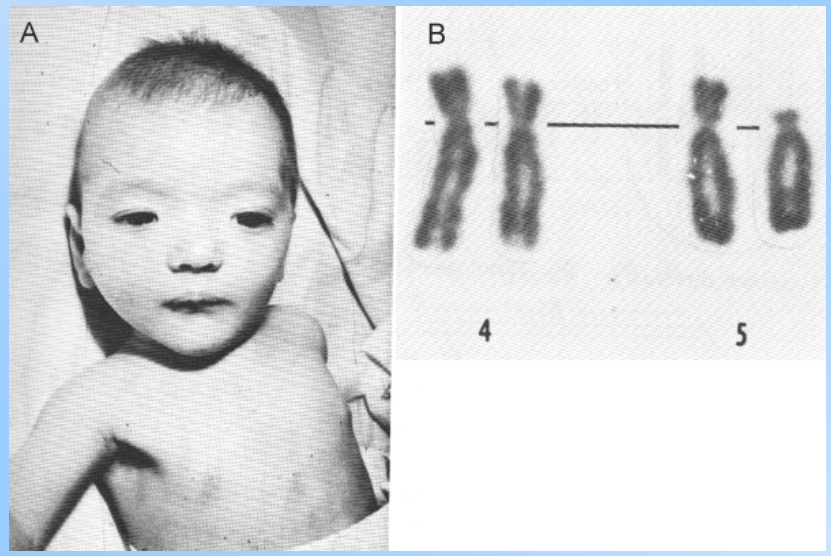
Cri du Chat Syndrome

("Cry of the Cat" in French)



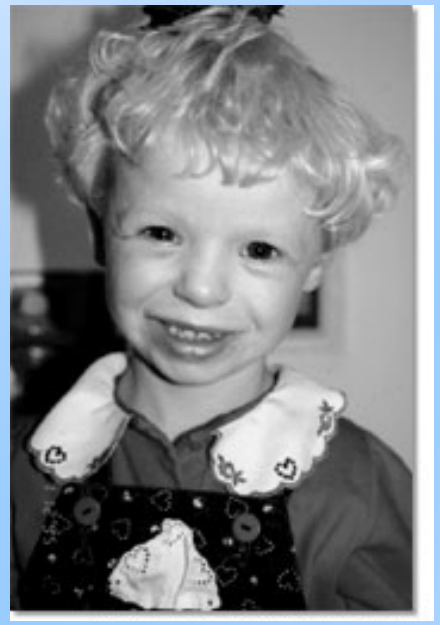


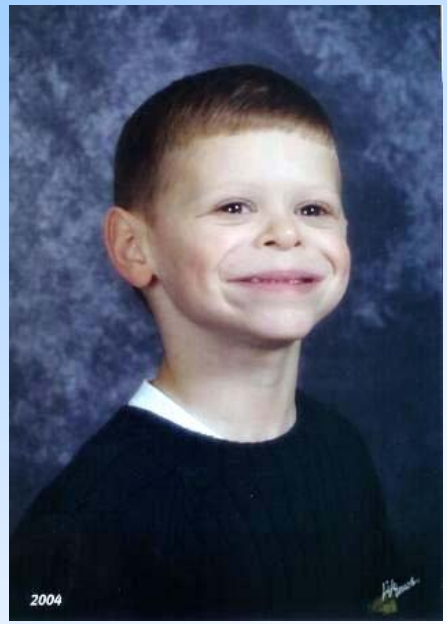
- Deletion of part of short arm of chromosome 5
- Abnormal larynx development
- Mental retardation, learning disability
- Low birth weight
- Shorter life span but most normally life expectancy

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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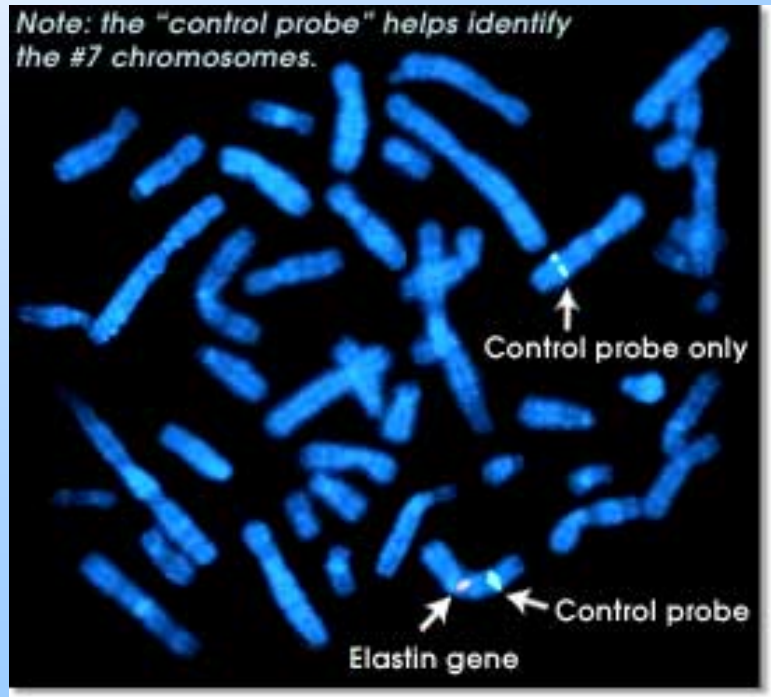
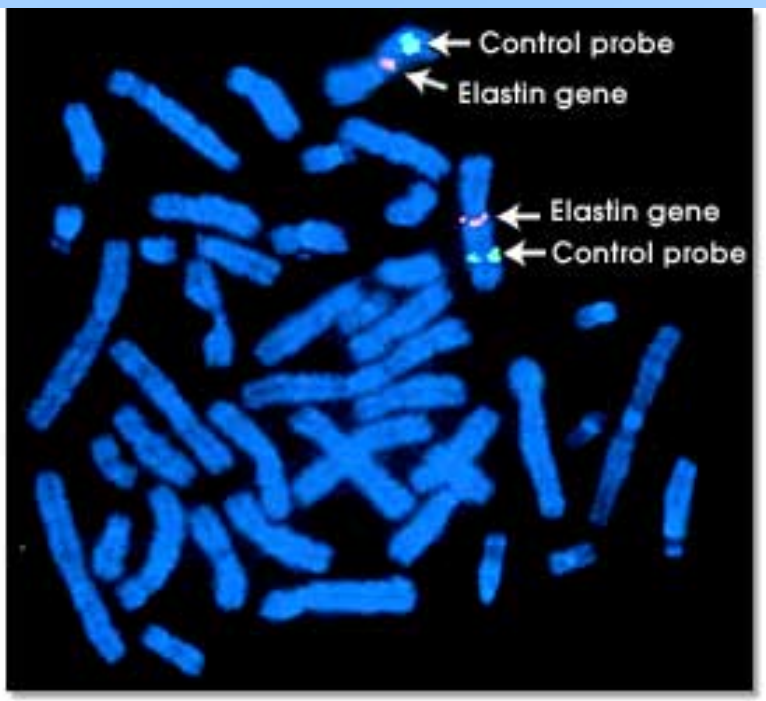
Williams syndrome

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.

FISH

Fluorescent **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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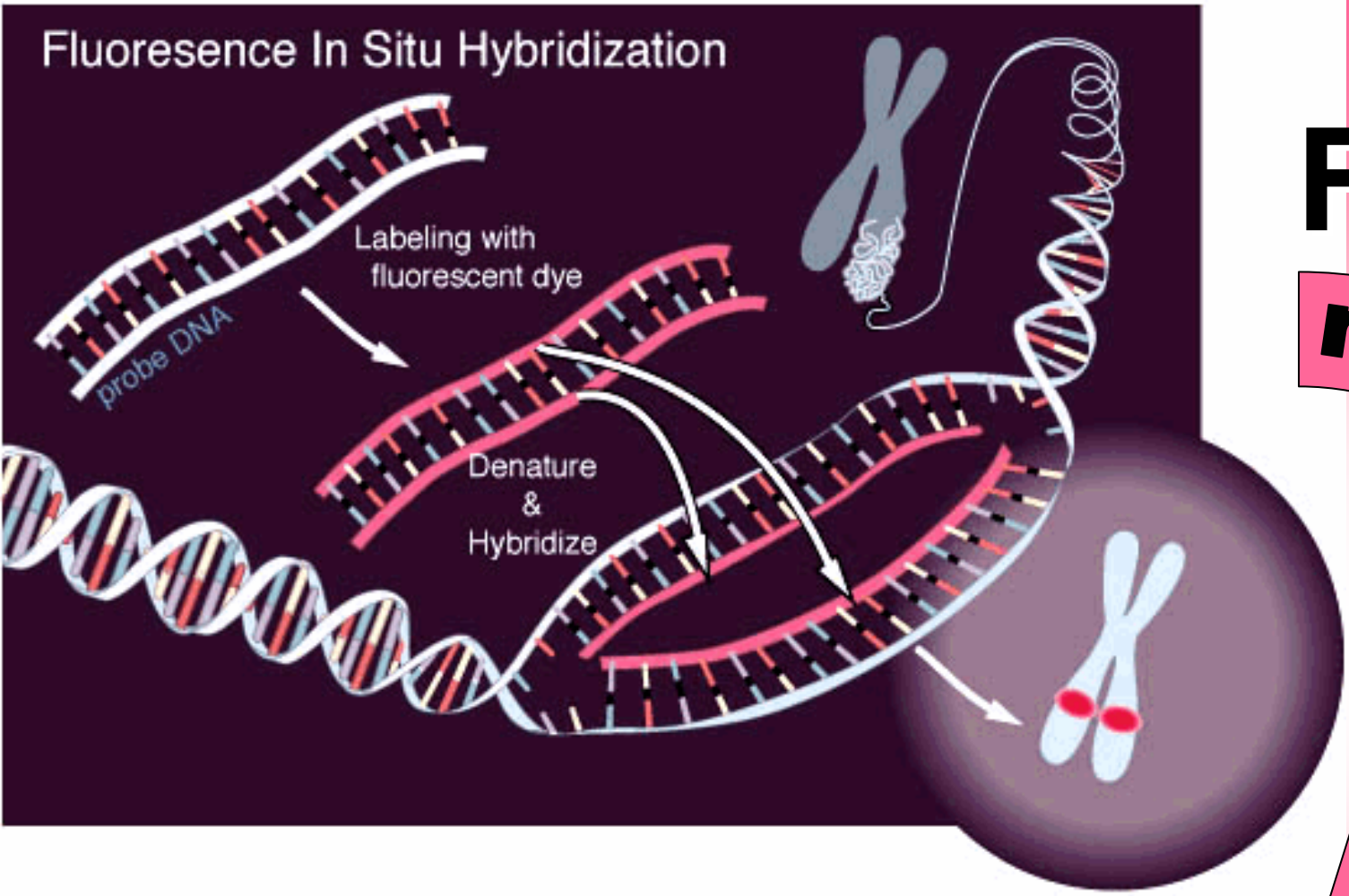

FISH

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

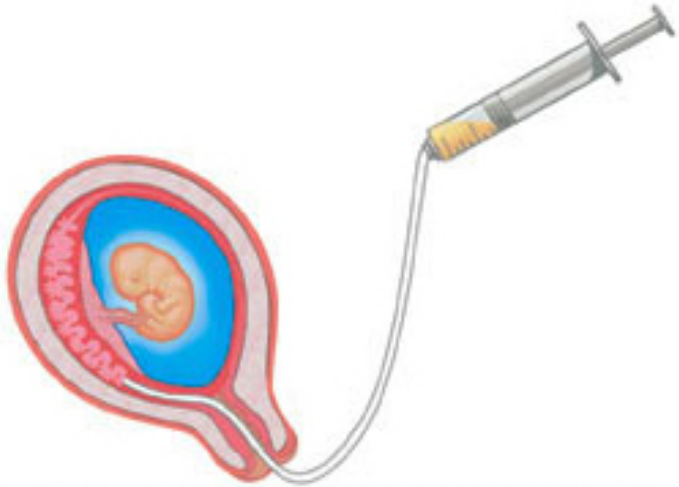
- Advanced maternal age (>35)
- Previous child with chromosomal aberration
- Parent with chromosomal rearrangement
- X-linked biochemical disorder carrier

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.

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

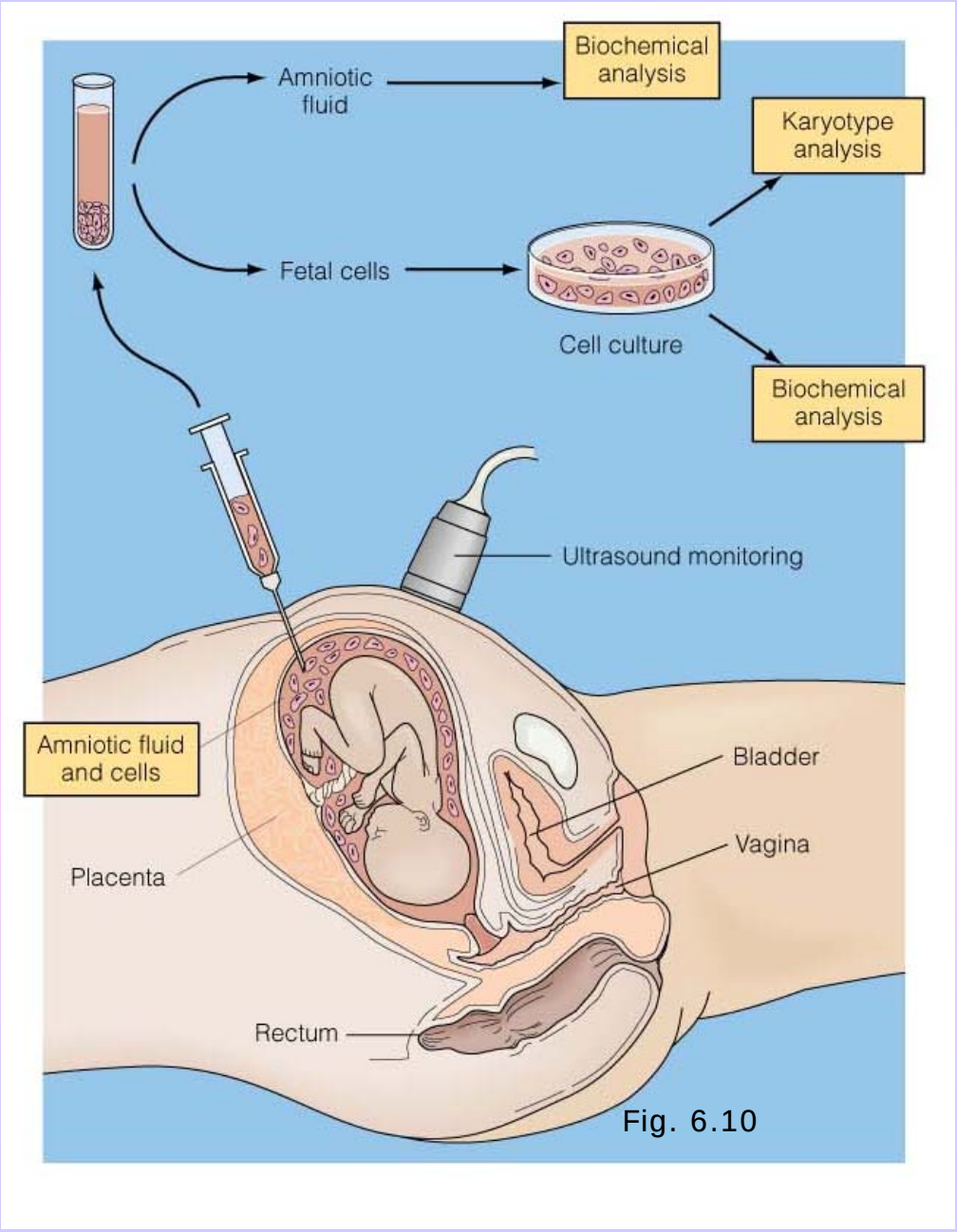
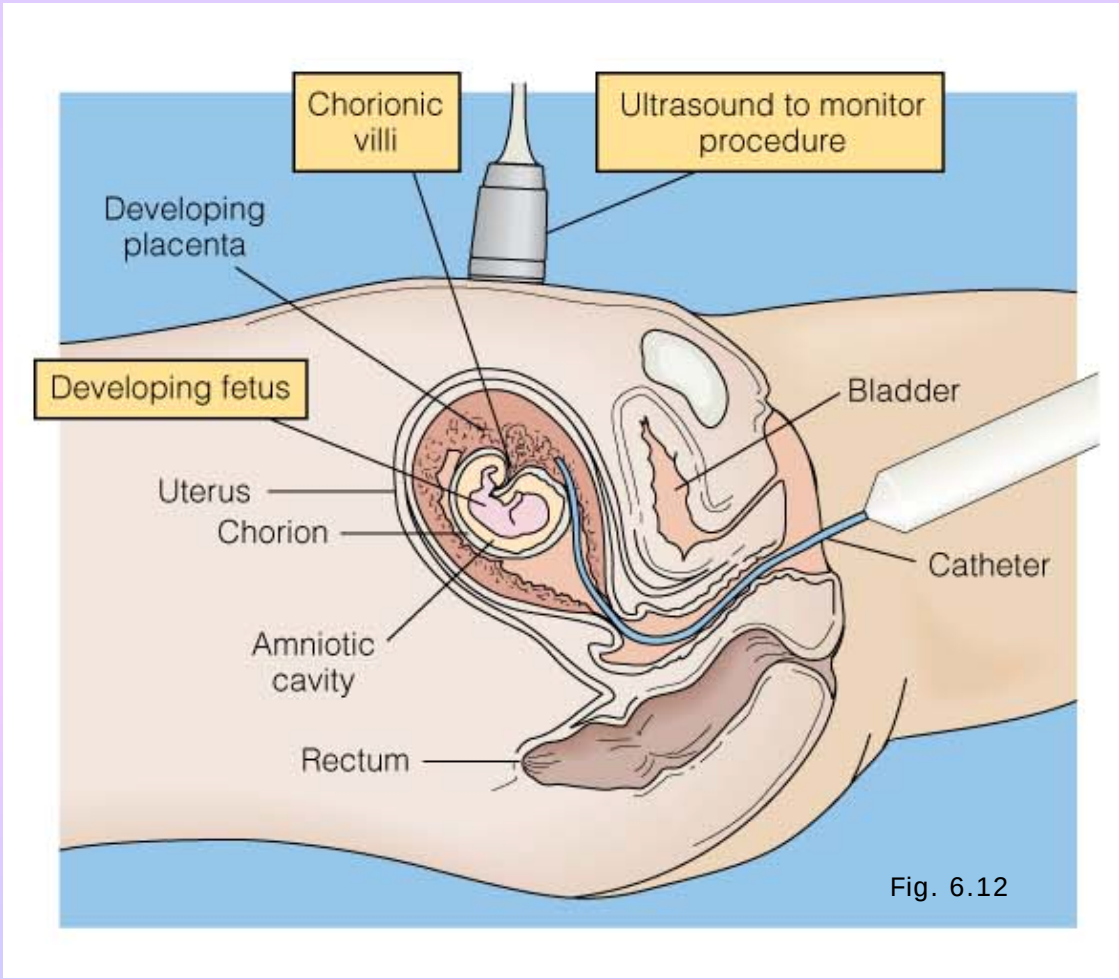


Fig. 6.10

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



ISCN

INTERNATIONAL SYSTEM for HUMAN CYTOGENETIC NOMENCLATURE

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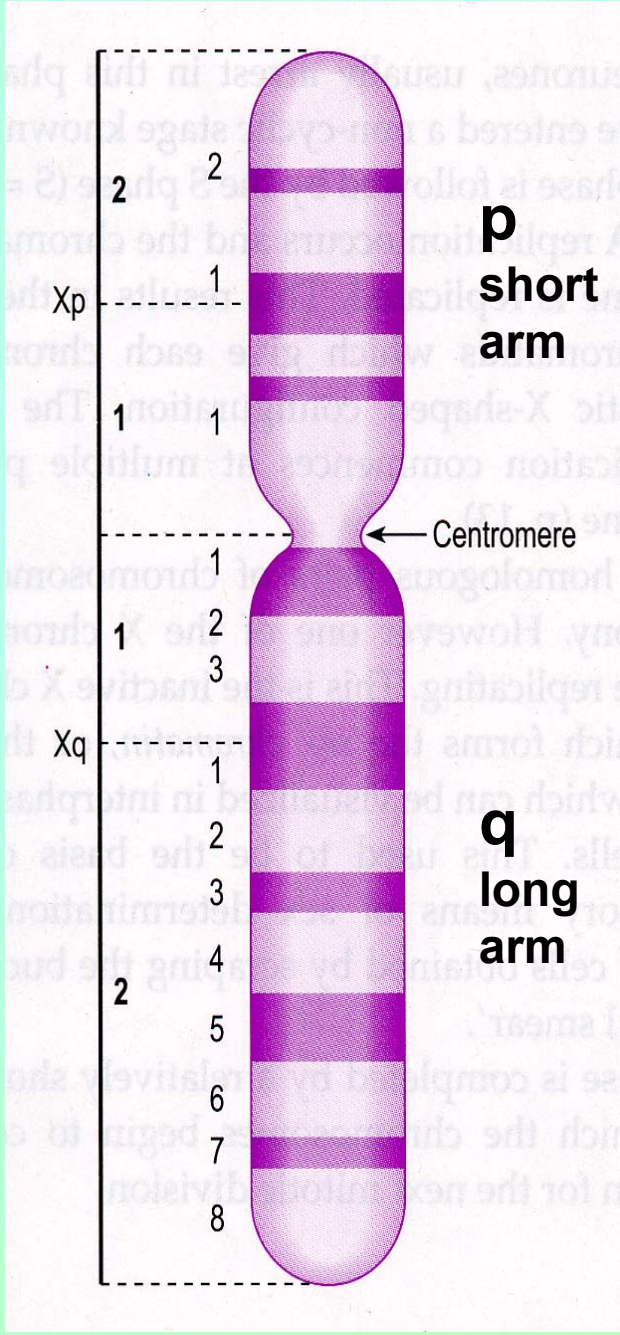
ISCN

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**

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)

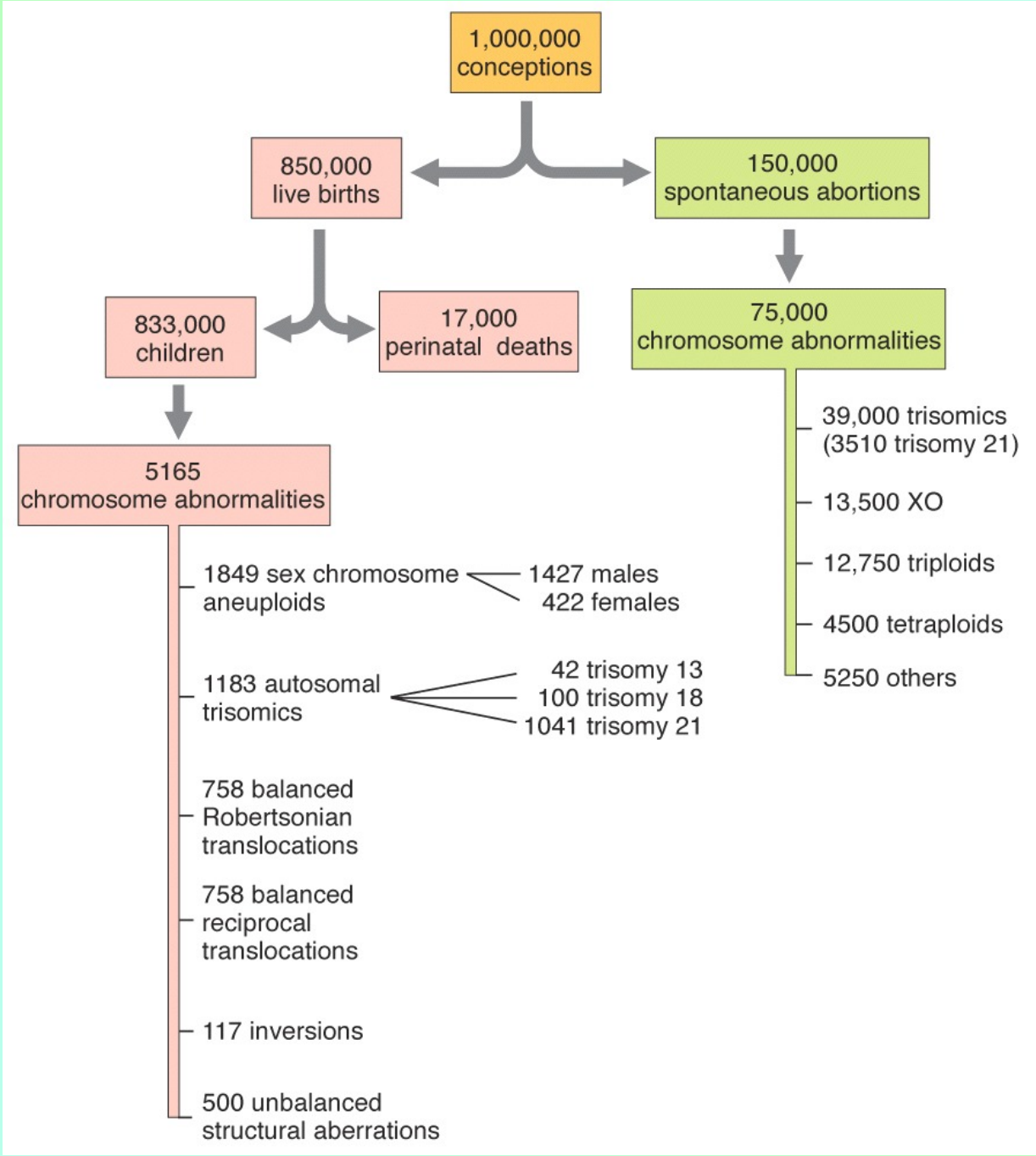
Female with 46 chromosomes with a 7 chromosome ring. The end of the short arm (p22) has fused to the end of the long arm (q36) forming a circle or 'ring'

47,XY,+21

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

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


1,000,000 conceptions
850,000 live births
150,000 spontaneous abortions
833,000 children
17,000 perinatal deaths
75,000 chromosome abnormalities
39,000 trisomics (3510 trisomy 21)
13,500 XO
12,750 triploids
4500 tetraploids
5250 others
5165 chromosome abnormalities
1849 sex chromosome aneuploids
1427 males
422 females
1183 autosomal trisomics
42 trisomy 13
100 trisomy 18
1041 trisomy 21
758 balanced Robertsonian translocations
758 balanced reciprocal translocations
117 inversions
500 unbalanced structural aberrations