# Medical genetics I

# Chromosomal aberrations

**AUTOSOMAL**

a) Structural

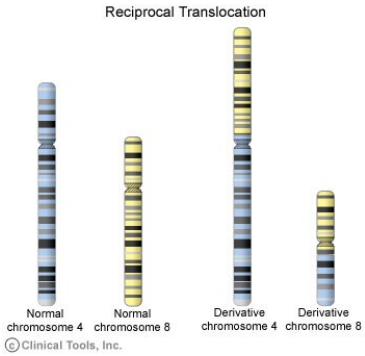
- *Polymorphysms*
  - different length of chromosomes in homologous pair
  - no phenotype effect
- *Inversions*
  - pericenric – including centromere
  - paracentric – does not include centromere
  - usually has no phenotype effect
- *Ring chromosomes*
  - breaks on both chromatids and their connection
  - mental and physical retardation
  - always newly created
  - sometimes redundant

# Chromosomal aberrations

- *Deletion*
  - terminal – one break
  - intersticial – two breaks
  - deletion syndromes:
  - Wolf-hirschhorn syndrome; 4p deletion
  - Cri-Du-Chat syndrome; 5p deletion
- *Microdeletion syndromes*:
  - Prader-Willi syndrome; 15q11-12 deletion
  - DiGeorge syndrome; 22q13 deletion
  - Angelman syndrome; 15q11-13 deletion
  - Williams-Beuren syndrome; 7q11.23 deletion
- *Insertion*
  - inserted part can be in the same or inverted position

# Chromosomal aberrations

- *Translocation*
  - reciprocal
    - mutual exchange between two or more nonhomologic chromosomes
    - balanced - no phenotype effect
    - genetic risics of unbalanced genom gamets formation
  - robertsonian
    - between two acrocentric chromosomes
    - breaks in the area of centromeres and deletion of short arms
    - centric fusion of the remaining arms
    - balanced – normal phenotype
  - tandem
    - deletion of part of an acrocentric chromosome
    - fusion of the remaining part with another chromosome

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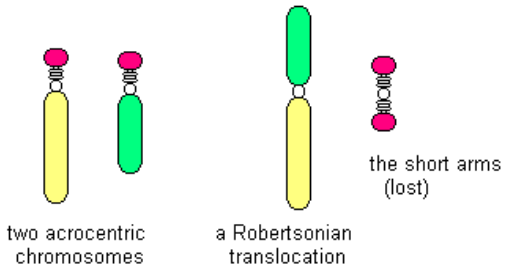



http://drugline.org/medic/term/robertsonian-translocation/

# Chromosomal aberrations

**b) Numerical**

- Trisomy
  - 21 chromosome trisomy – Down syndrome
  - 18 chromosome trisomy – Edwards syndrome
  - 13 chromosome trisomy – Patau syndrome

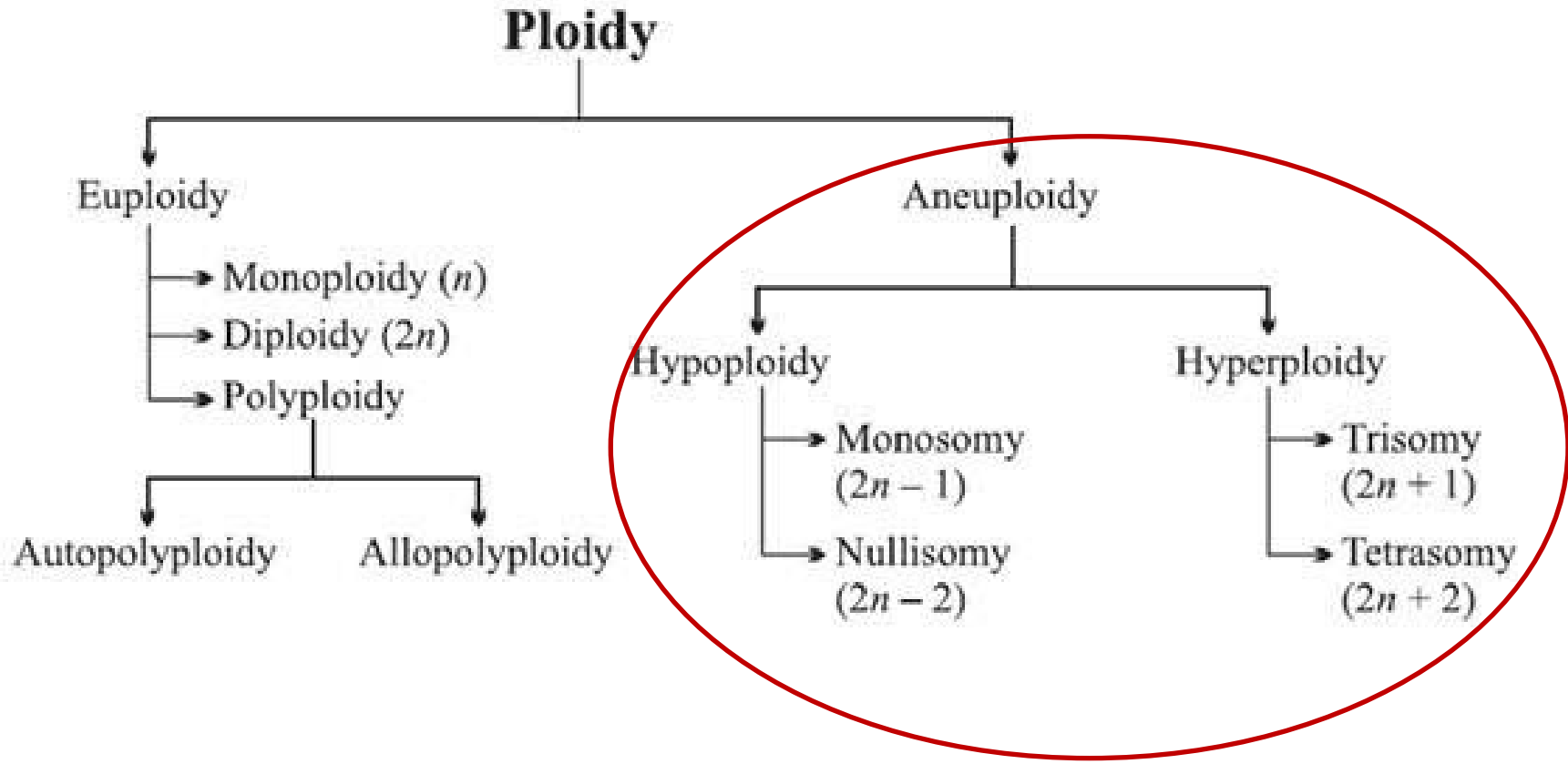
- Triploidy
  - 69,XXX; 69,XXY
  - nonviable
  - mosaic triploidy – mental retardation, syndactyly, abnormal genitals, lateral asymetry

# Chromosomal aberrations

**2. GONOSOMIC**

- *Chromosome Y*
  - structural aberrations – very rare
  - numerical aberrations
    - 47,XYY – supermale syndrom
- *Chromosome X (male)*
  - Numerical aberration
    - 47,XXY – Klinefelter syndrom
- *Chromosome X (female)*
  - numerical aberrations
    - 45,X – Turner syndrom
    - 47,XXX – XXX syndrom
- *Fragile X – fraX*
  - the most common cause of mental retardation
  - nonspecific phenotype

# Numerical chromosomal changes - aneuploidy

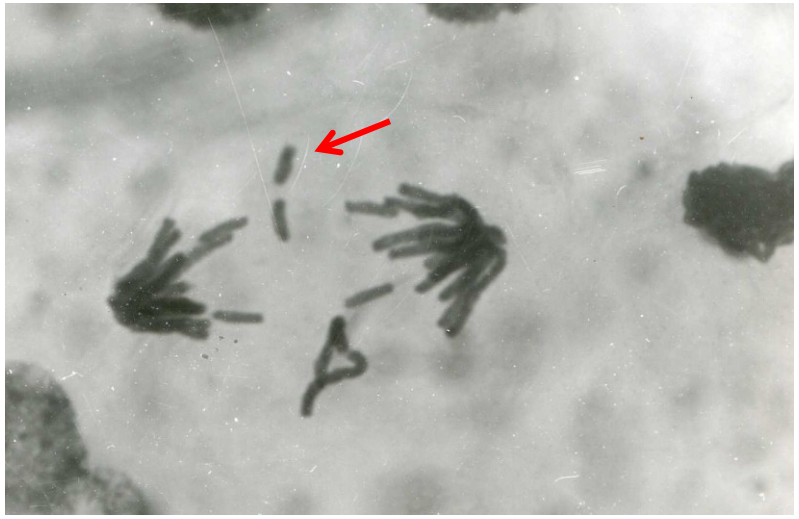


# Aneuploidy - origin

**A) Chromosome loss**
(no centromere or non-functioning kinetochore)

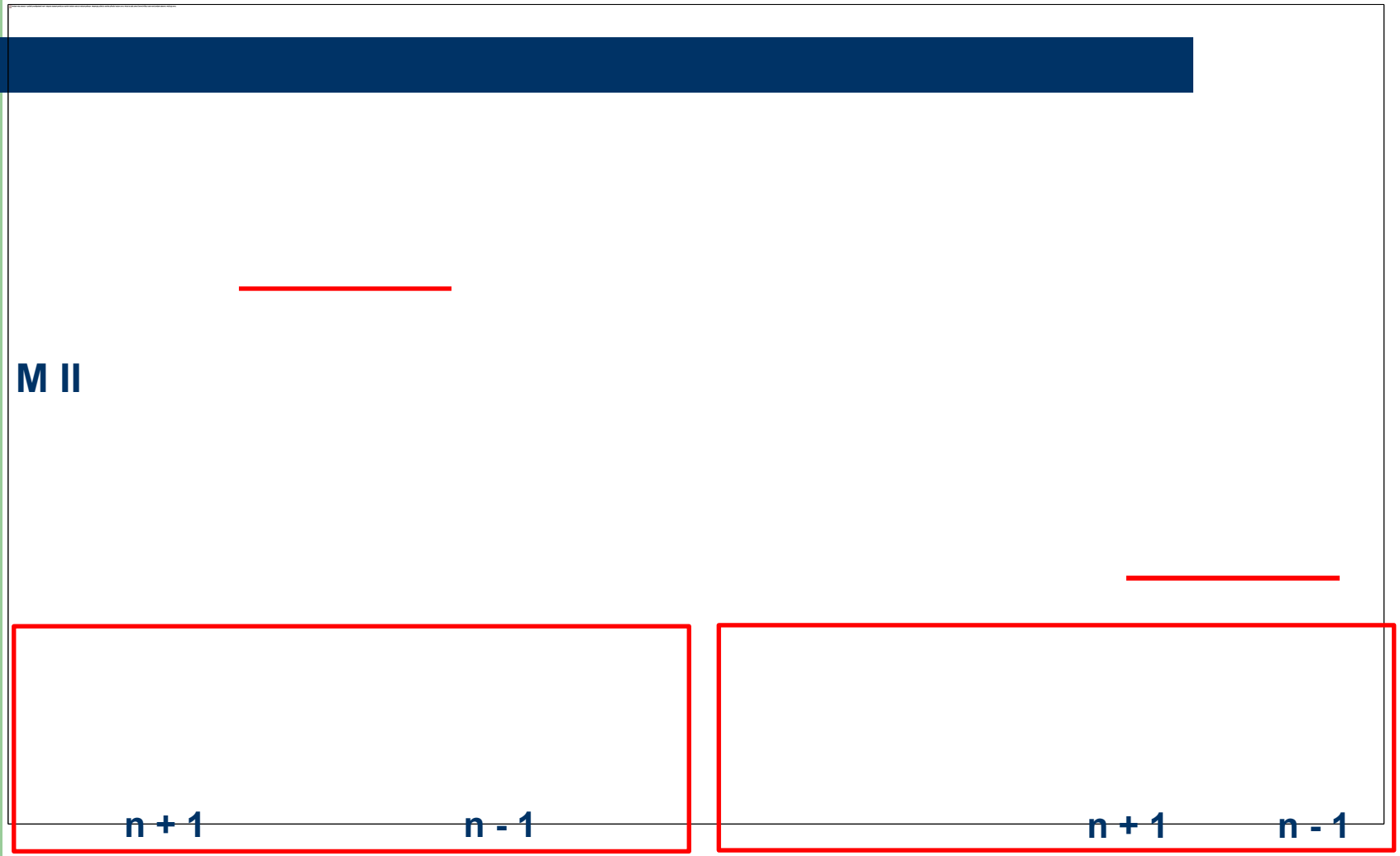
**B) Robertsonian translocations**

**Anaphase**



**C) Errors during segregation during meiosis or mitosis (Non-disjunction)**

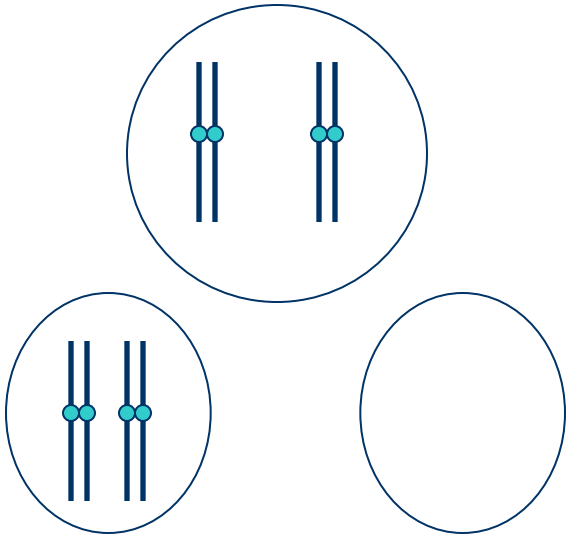
# Aneuploidy: non-disjunction during meiotic division I or II (gametes n+1 disomic, n-1 nulisomic)



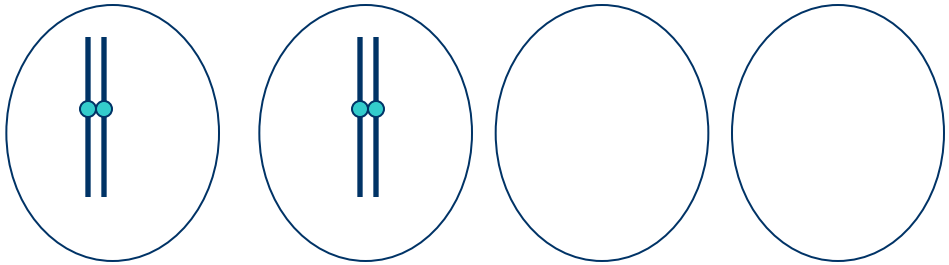
# First meiotic division

**Nondisjunction**

**First Division**

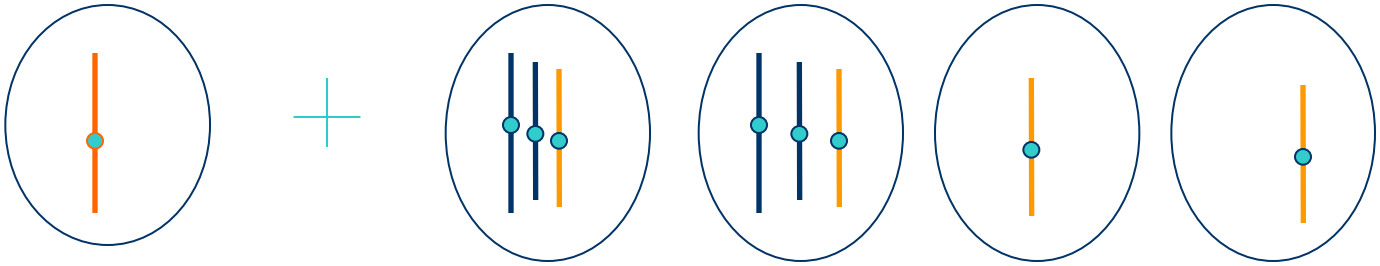


second division

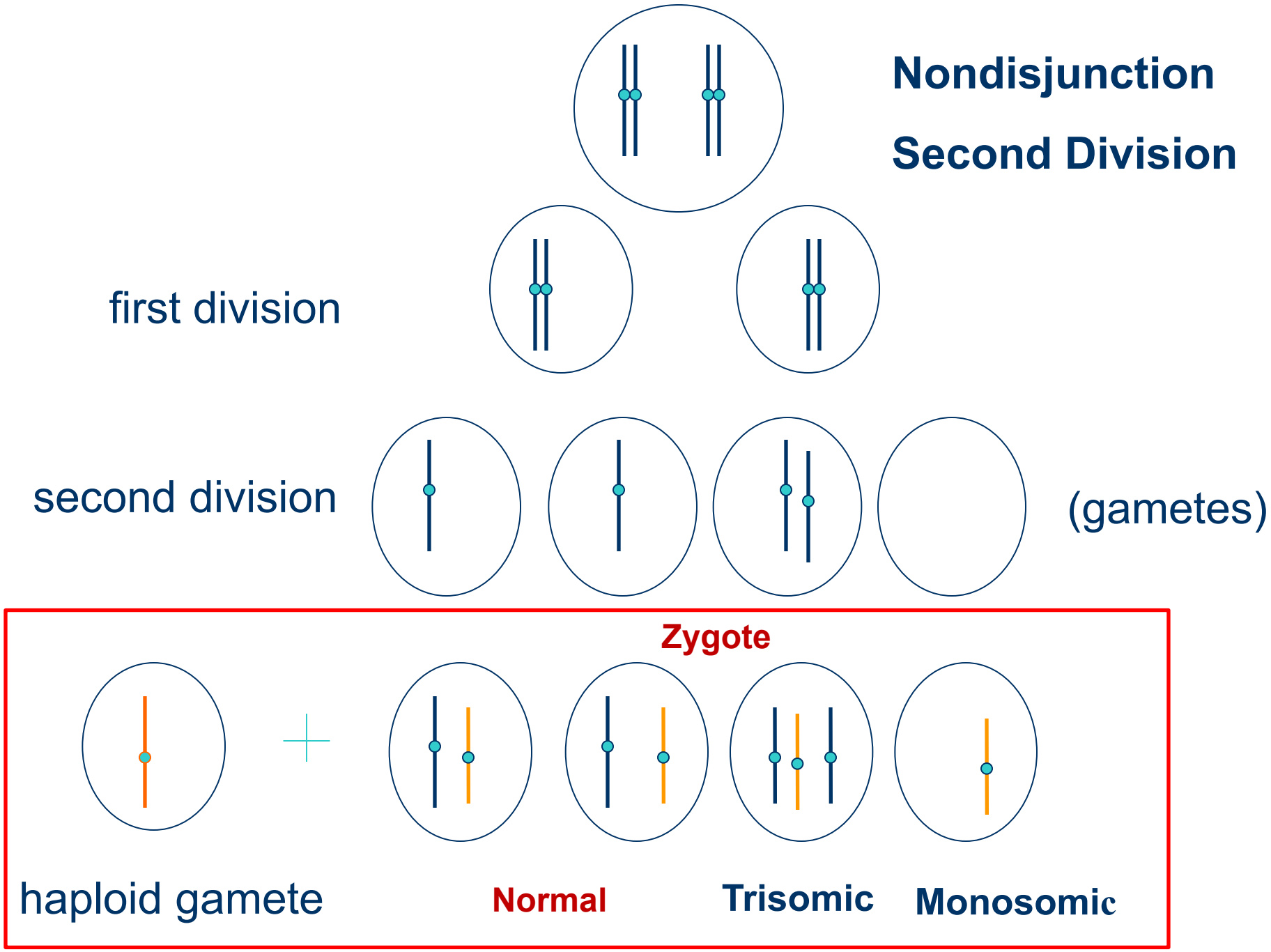


(gametes)

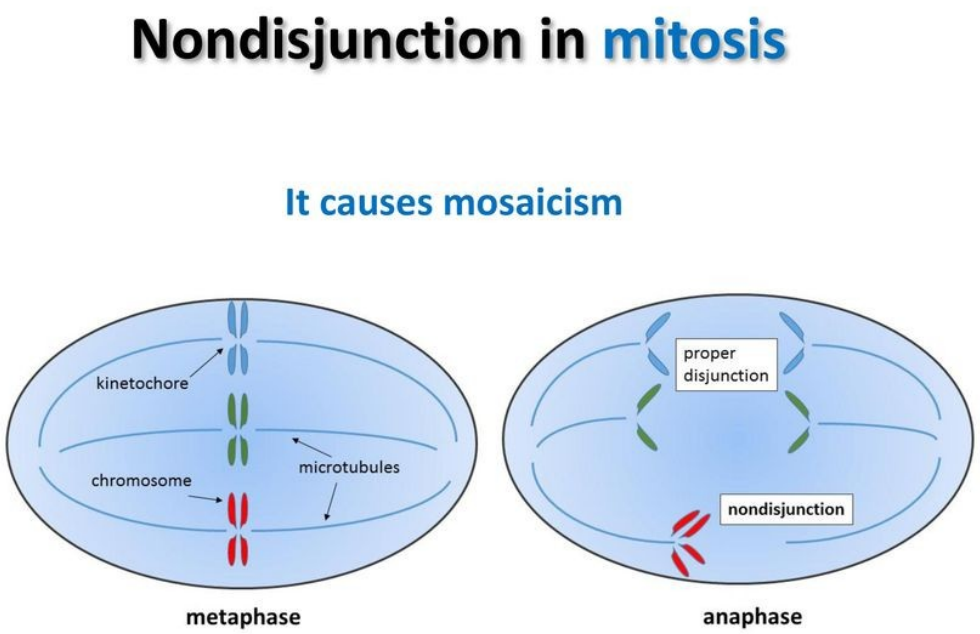
**Zygote**



haploid gamete **Trisomic** **Trisomic** Monosomic Monosomic

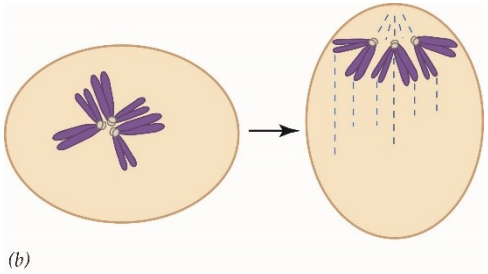

Nondisjunction
Second Division
first division
second division
(gametes)
Zygote
haploid gamete
Normal
Trisomic
Monosomic

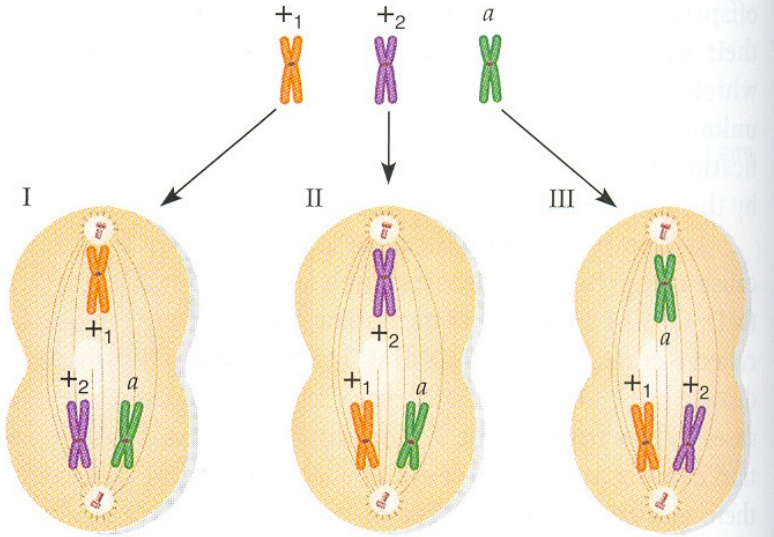
# Non-disjunction can take place not only in meiosis but also in mitosis - somatic clones (cancer)



# Trisomy - reduced vitality and fertility - trivalent formation during gamete meiosis - haploid (n) and disomic (n+1)

## Irregular spacing of chromosomes in meiosis - sterility !


Gametes produced after 2nd meiotic division

| | haploid | disomic |
|---|---|---|
| I | $+_1$ | $+_2/a$ |
| II | $+_2$ | $+_1/a$ |
| III | $a$ | $+_1/+_2$ |

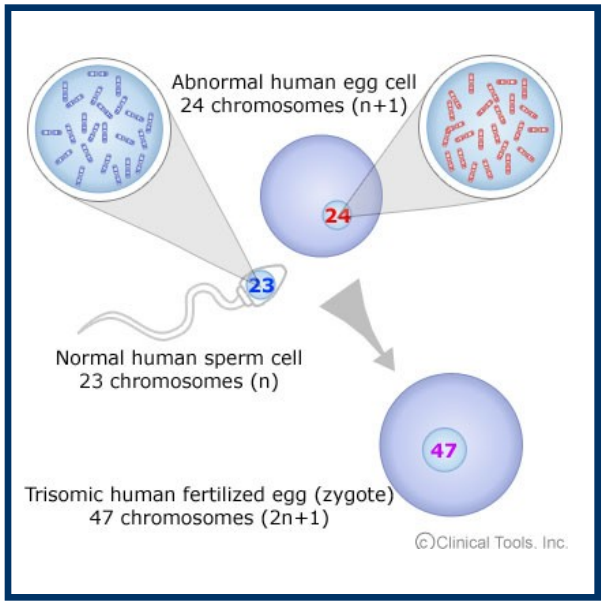
In sum: 2 +/ $a$ : 2 + : 1 + /+ : 1 $a$

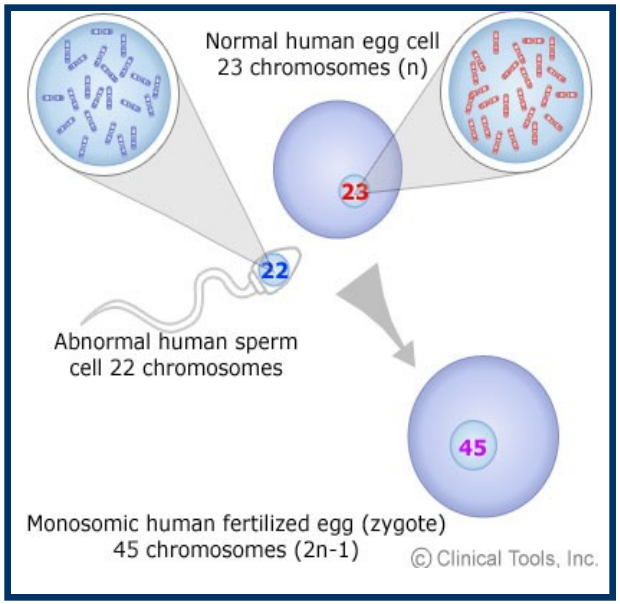
**Pairing of 3 homologous chromosomes**

**Trizom. cell: 2n + 1**

**2 Types of gametes: n a n+1**

# Origin of aneuploidy in humans



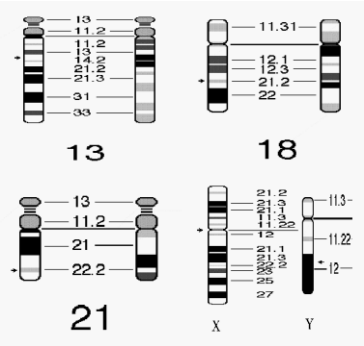

**Aneuploidy – trisomy, monozomy lethal (aborts), effect of gene dosage !!!**

# Aneuploidies in humans – trisomies

- **The most common** and clinically significant type of **congenital aberrations** !
- **10% of pregnancies** = chromosomally abnormal (consequence:NDD, abortions)
- Any chromosome can be affected by aneuploidy... **selection !**
- **Aneuploidy** - trisomy, monosomy **lethal** (abortion), gene dose effect !

## Viable aberrations

- **Down syndrome +21**
- **Edwards syndrome +18**
- **Pata's syndrome +13**
- **Klinefelter's syndrome XXY**
- **Turner syndrome X - monosomy**




➡ **Low gene count!!**

## Characteristic features of trisomies in humans

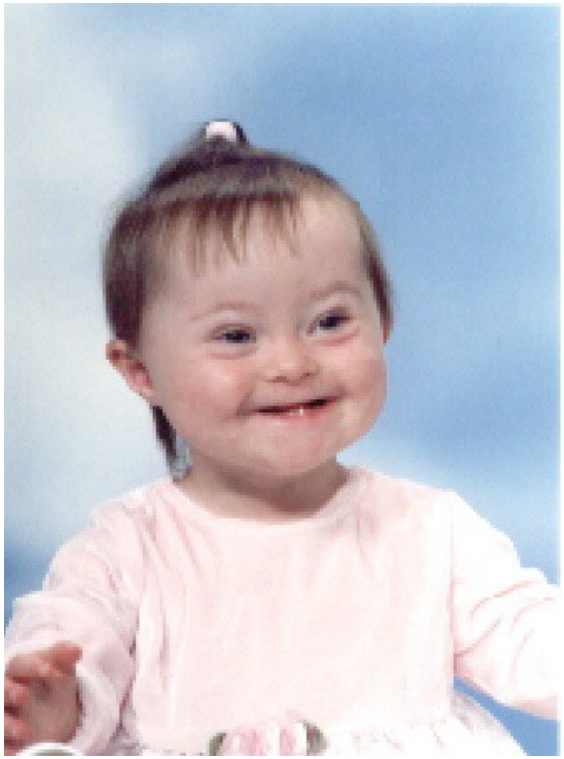
*a) the **supernumerary** chromosome is of **maternal origin (90%)***

*b) the cause is most often an **error** in **division** during meiosis I*

*c) the **frequency** of trisomies in the fetus **increases with maternal age***

# Down syndrome (47,XX or XY,+21)

- **Incidence 1:800**
- Described 1866 J.L.Down
- **IQ 25-50**
- small dumpy figur
- **round face**
- short neck
- **mongoloid eyes**
- **epicanthic fold**
- wide nose root and flattened nose
- small mouth, large tongue, small teeth
- single transverze palmar crease
- heart diseases



# Causes of Down syndrome

**A) simple trisomy**

- **47,XX or XY,+21) - de novo**
- **90% of maternal origin** - in meiosis I

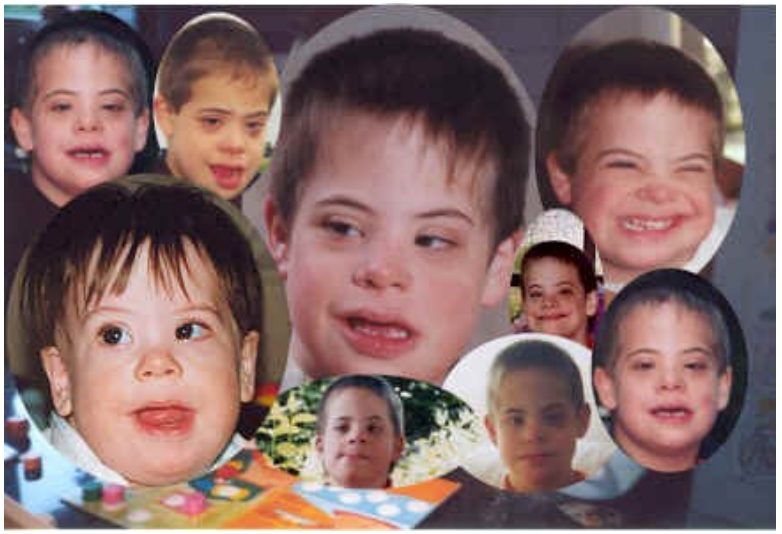
**B) translocation form**

- **Robertsonian translocation der(14;21) - hereditary form of D.S.**

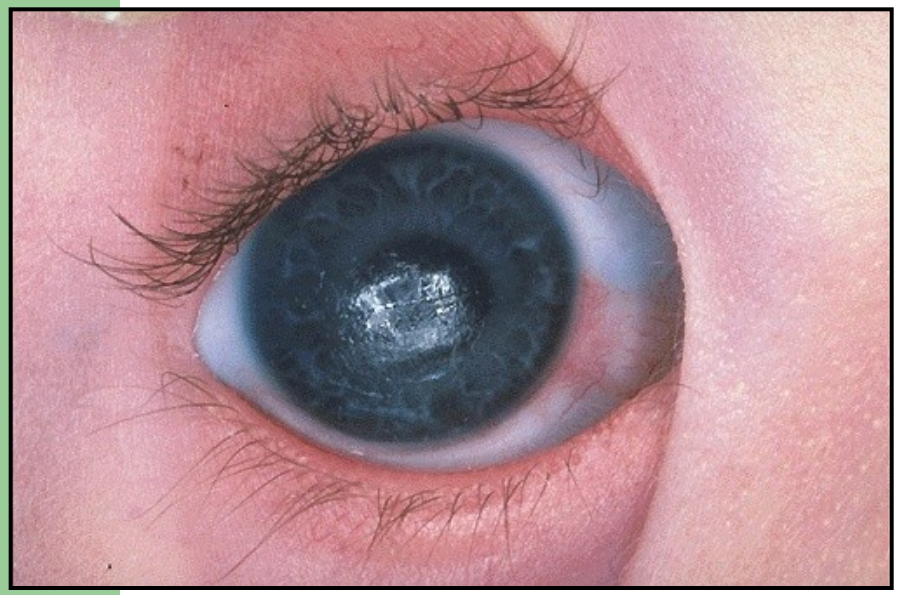
**C) partial trisomy**

**multiplied minimal critical region for DS 21q21**

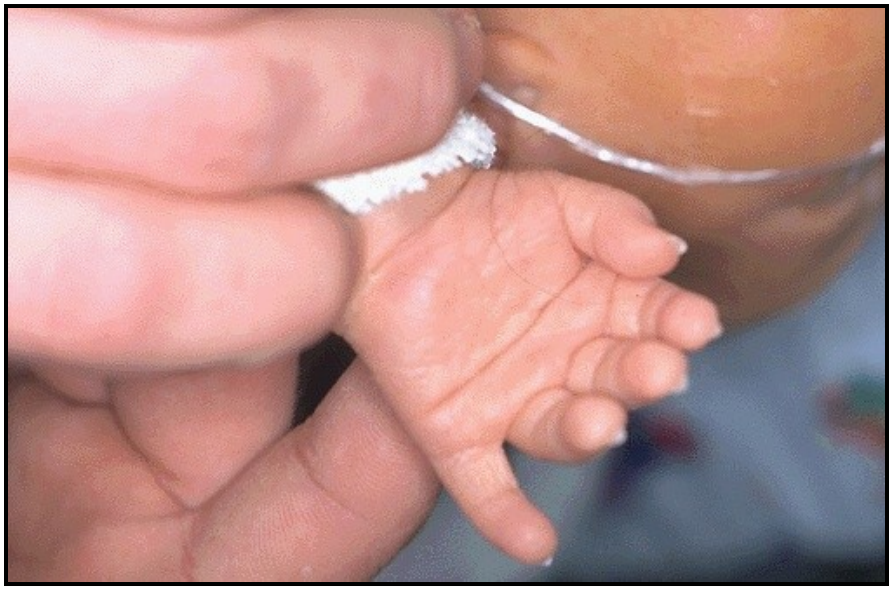
**D) mosaic 47,XX,+21/46,XX**



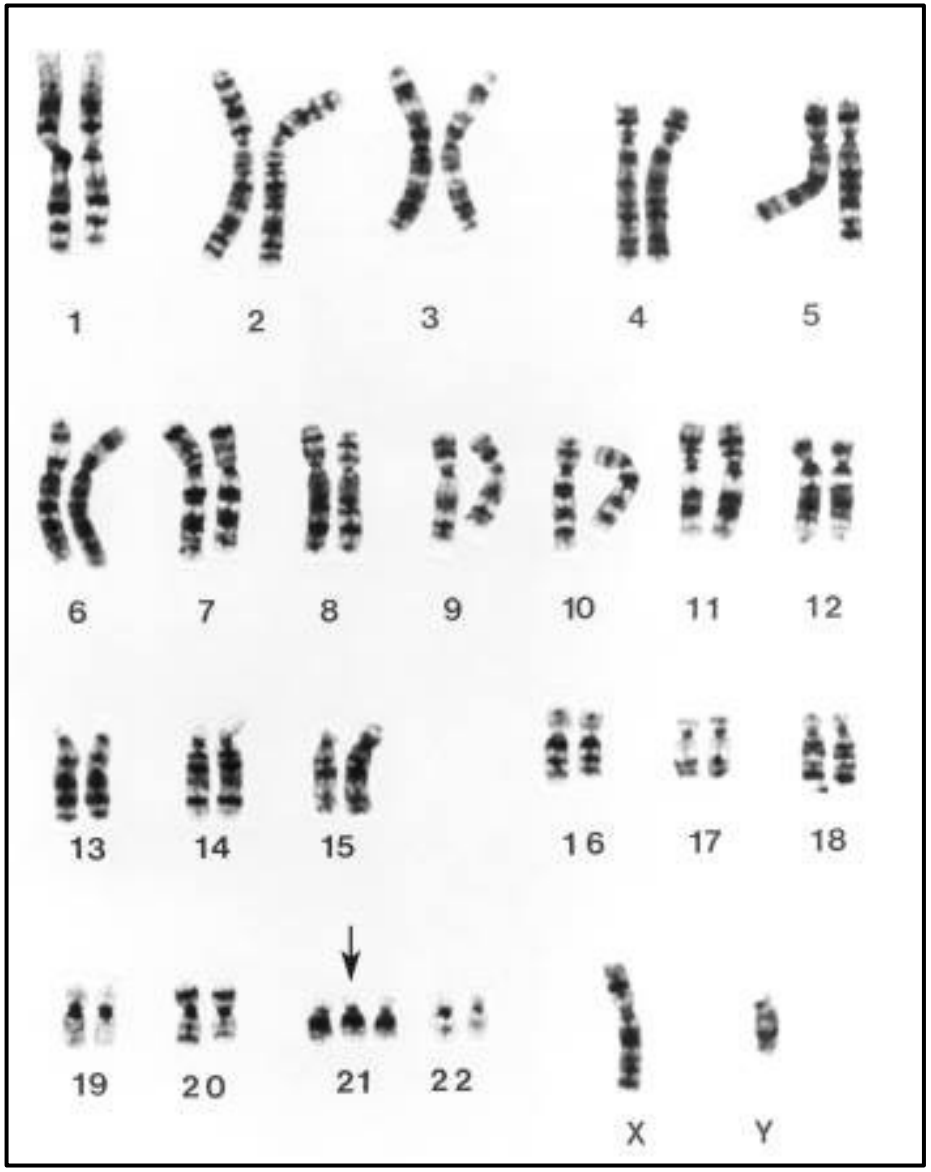
# Down syndrome

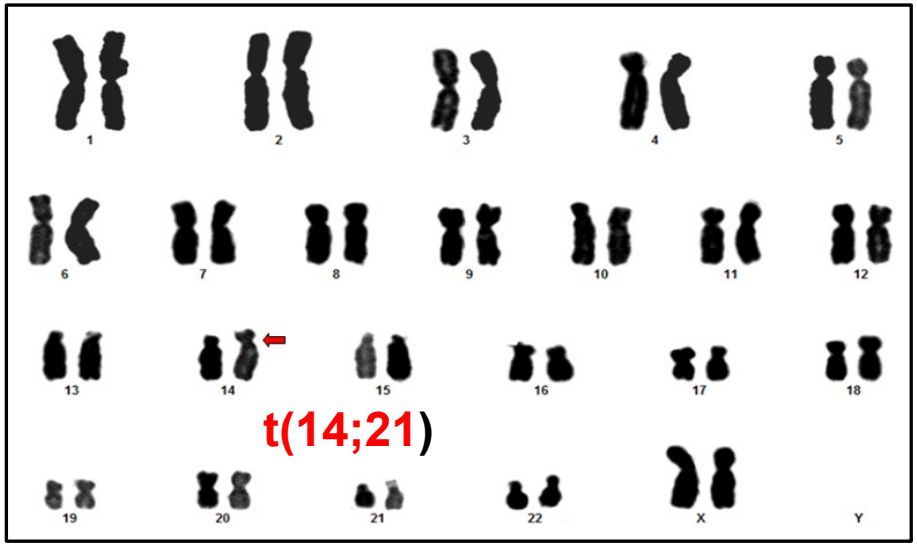


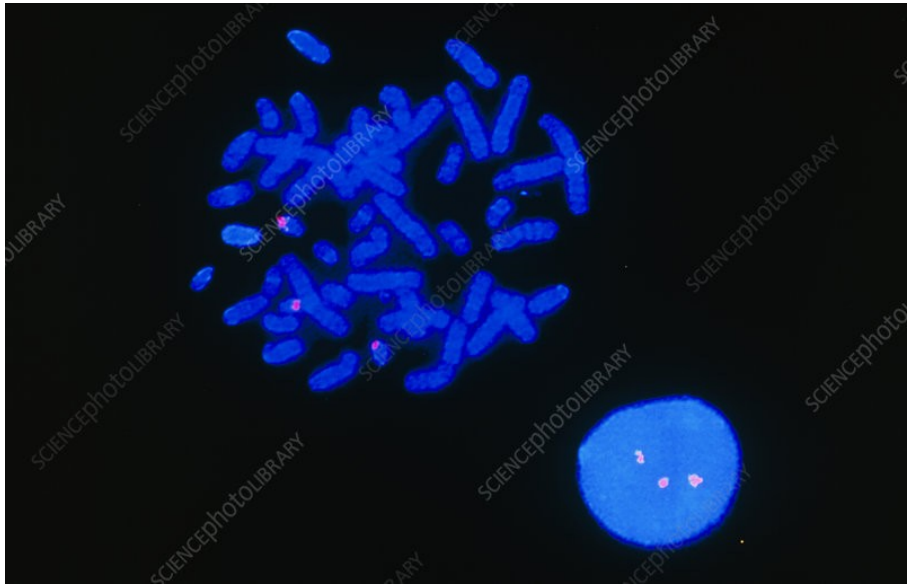
Epicanthus



palmar crease



**Examples of chromosomal aberrations responsible of Down syndrome**

# Incidence of Down syndrome is influenced by age of mother

**Cause of D.S. - in 95% nondisjunction in the course of meiosis I in the mother, i.e. two copies of chromosome 21 in the egg !**

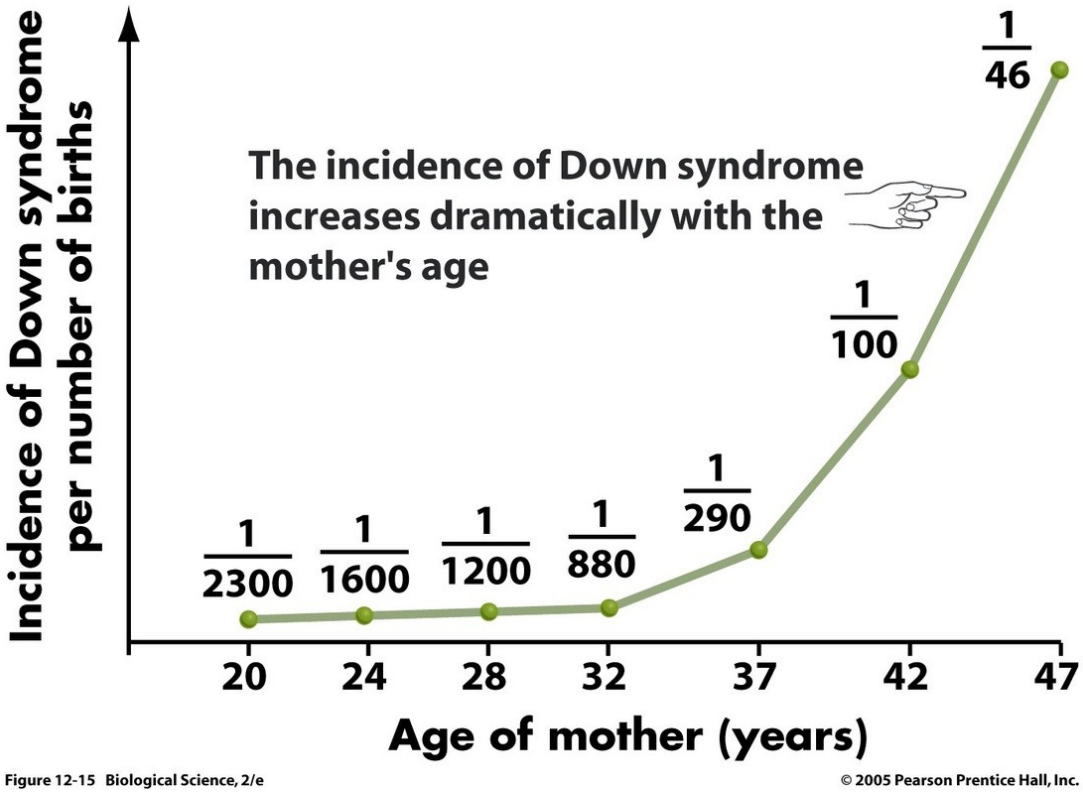
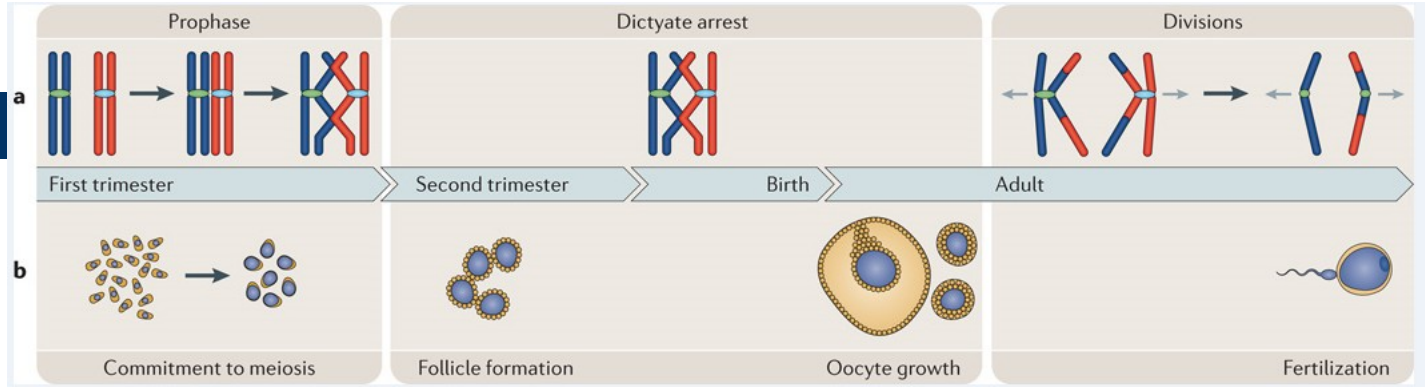


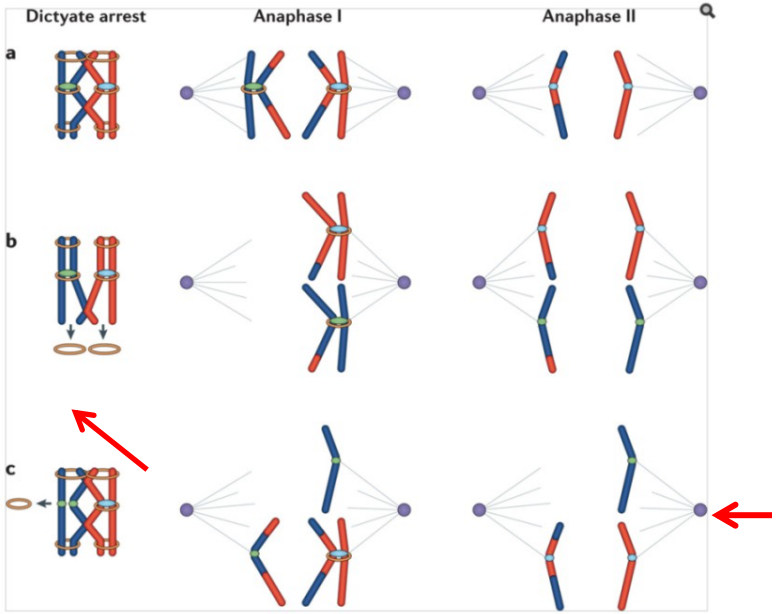

Figure 12-15 Biological Science, 2/e



http://downsyndrome2014.weebly.com/uploads/2/6/2/0/26201118/5926215_orig.jpg

# Causes of nondisjunction in oocytes and maternal age - hypotheses

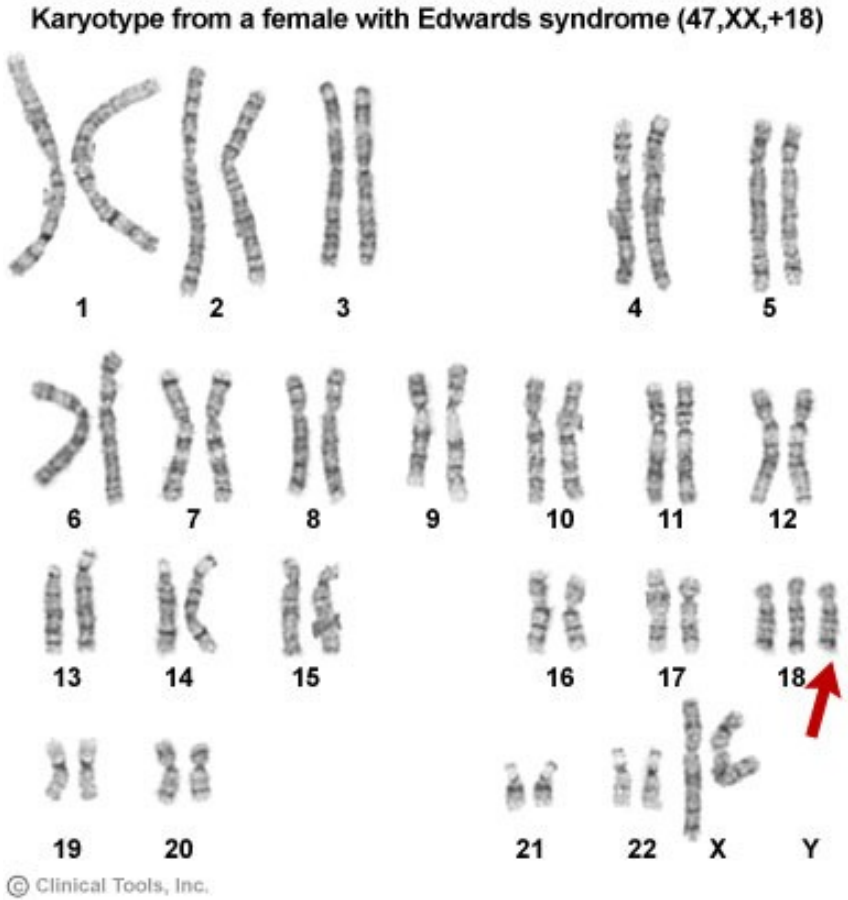


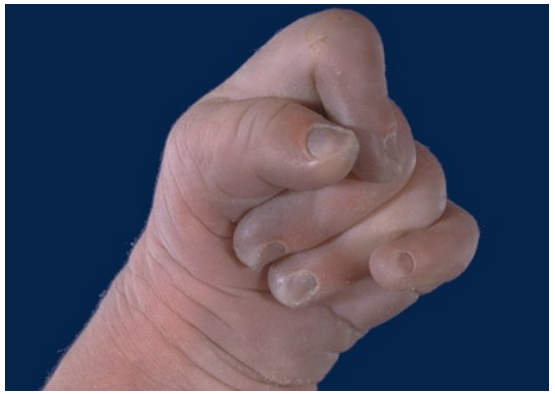




- **Meiosis** in women takes **a long time** - starts in the prenatal period in the fetal ovaries - **lasts 10 - 50 years**
- oocytes **remain in M** I prophase until s**exual maturity** - primary oocyte (about 400 at birth)
- meiosis II completed at fertilization
- Nondisjunction: multiple mechanisms !!!
- **CROSSING-OVER DISORDERS**
- **COHESIN DEGRADATION DEPENDING ON MATERNAL AGE**
- **DISORDERS OF THE DIVISION SPINDLE CONNECTION ?**

# Edwards syndrome (47,XX or XY,+18)

1/6000, John Edwards 1960



## Edwards syndrome

**Epidemiology**
Incidence: ~ 1:6.000
♀>♂

**Etiology**
presence of an extra chromosome 18

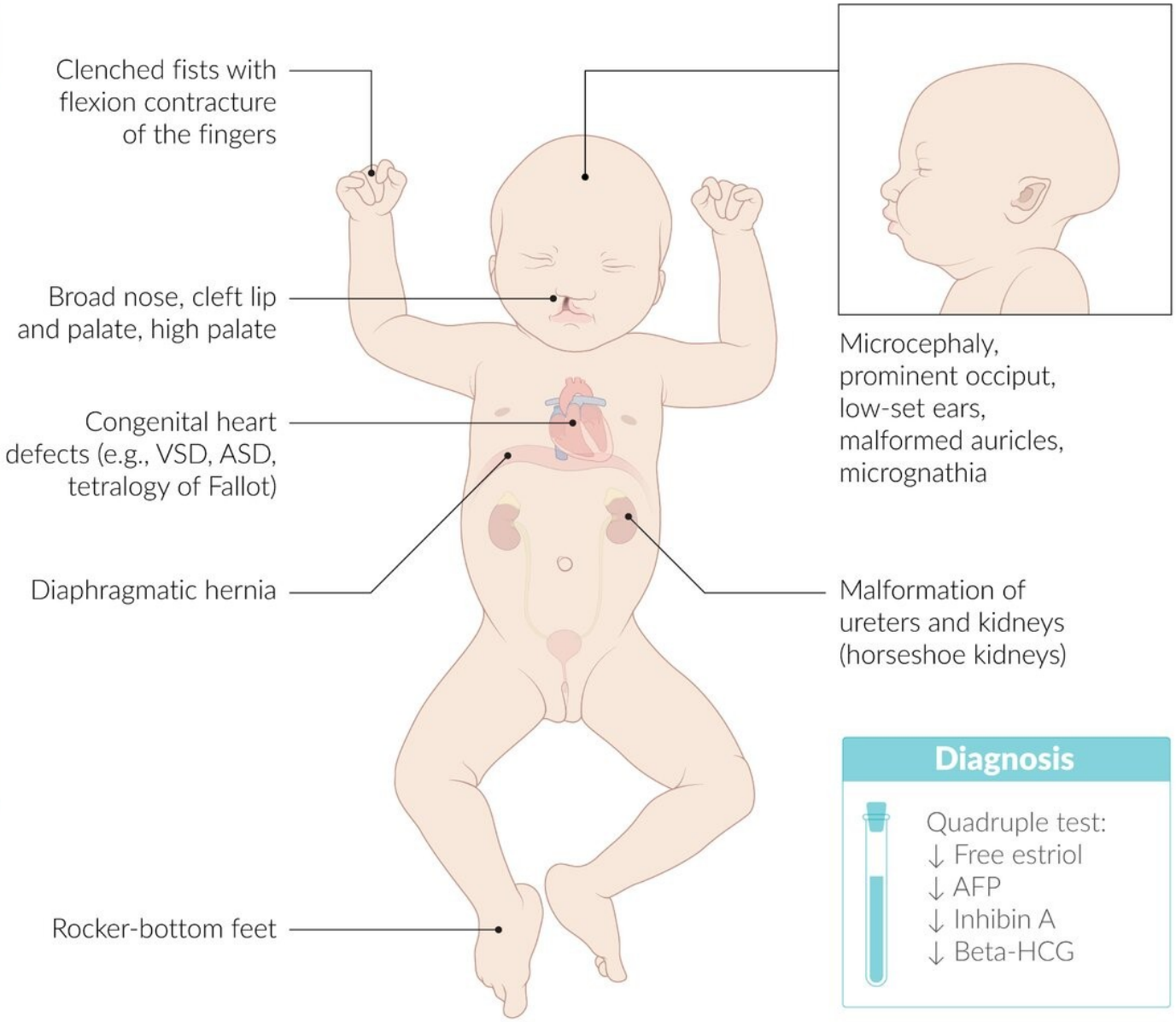
**Karyotype**
♀ : 47,XX+18
♂ : 47,XY+18

**Important**
Second most common trisomy after Down syndrome (trisomy 21); risk increases with maternal age

**Life expectancy**
Only 5–10% survive past 12 months of age

## Karyotype

+18



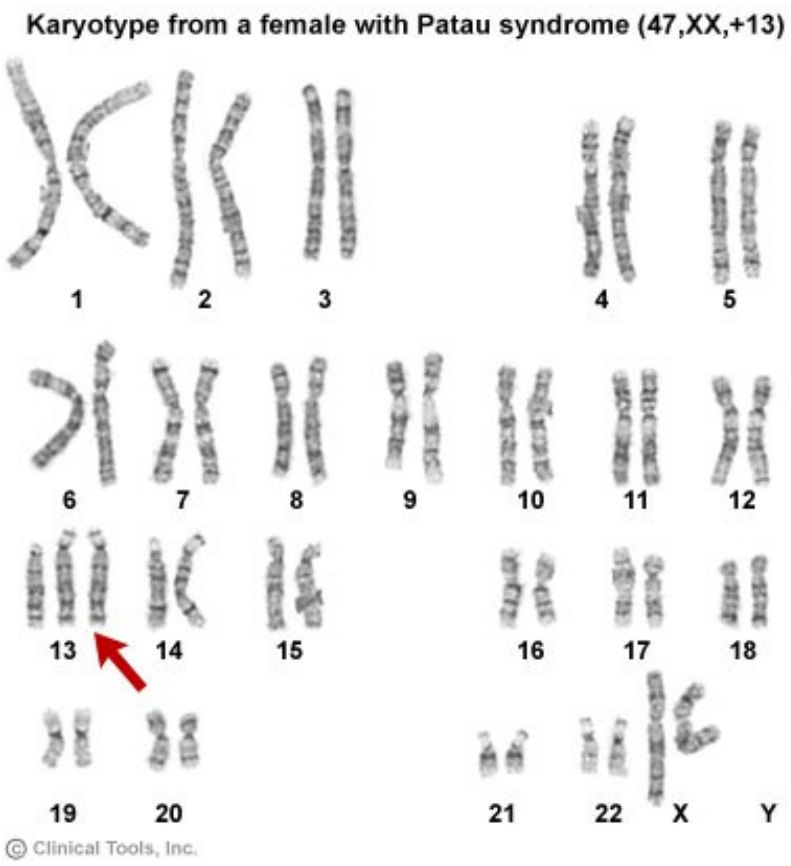

## Diagnosis

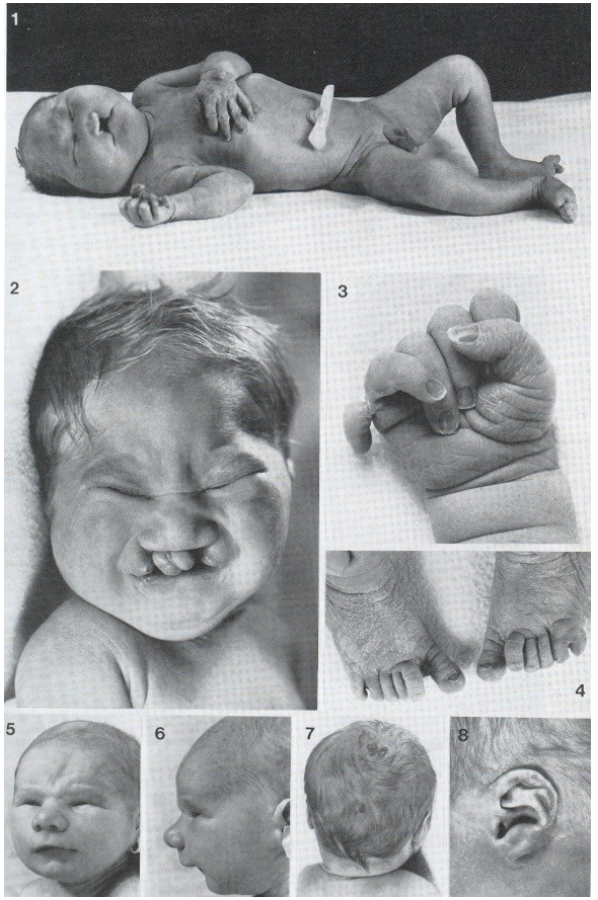


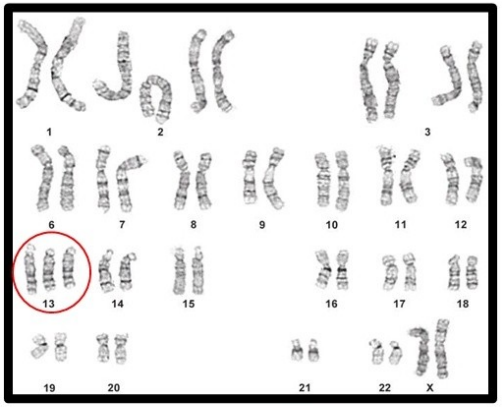
Quadruple test:
↓ Free estriol
↓ AFP
↓ Inhibin A
↓ Beta-HCG

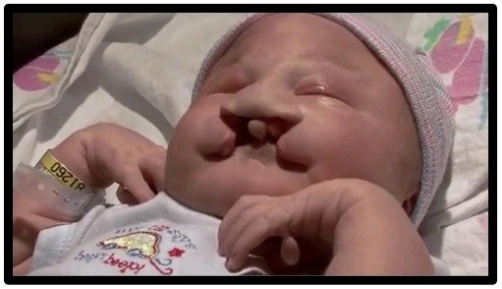
# Patau syndrome (47,XX or XY,+13)

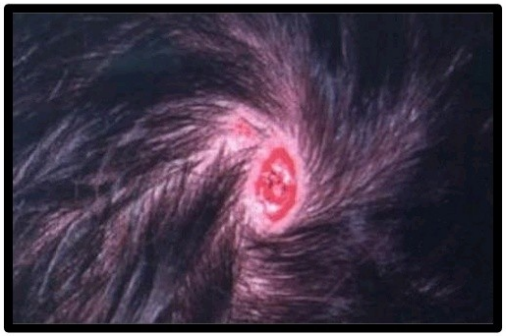
Claus Patau, 1960









# 3) Trisomy 13 (Patau syndrome)

❖ **Clinical features**
- ✓ **Midline defect**
- ✓ **Aplasia cutis congenita**
- ✓ Microphthalmia
- ✓ Microcephaly
- ✓ Postaxial polydactyly
- ✓ Hypotonia
- ✓ Holoprosencephaly
- ✓ Hypoplastic / absent ribs
- ✓ Abdominal wall defect
- ✓ Deafness
- ✓ Colobomas
- ✓ Capillary hemangioma
- ✓ Genital anomalies
- ✓ Clenched fist

**3rd most common autosomal trisomy**

❖ **Most common cardiac defect ?**
1. **Ventricular septal defect (VSD)**
2. Atrial septal defect (ASD)
3. PDA

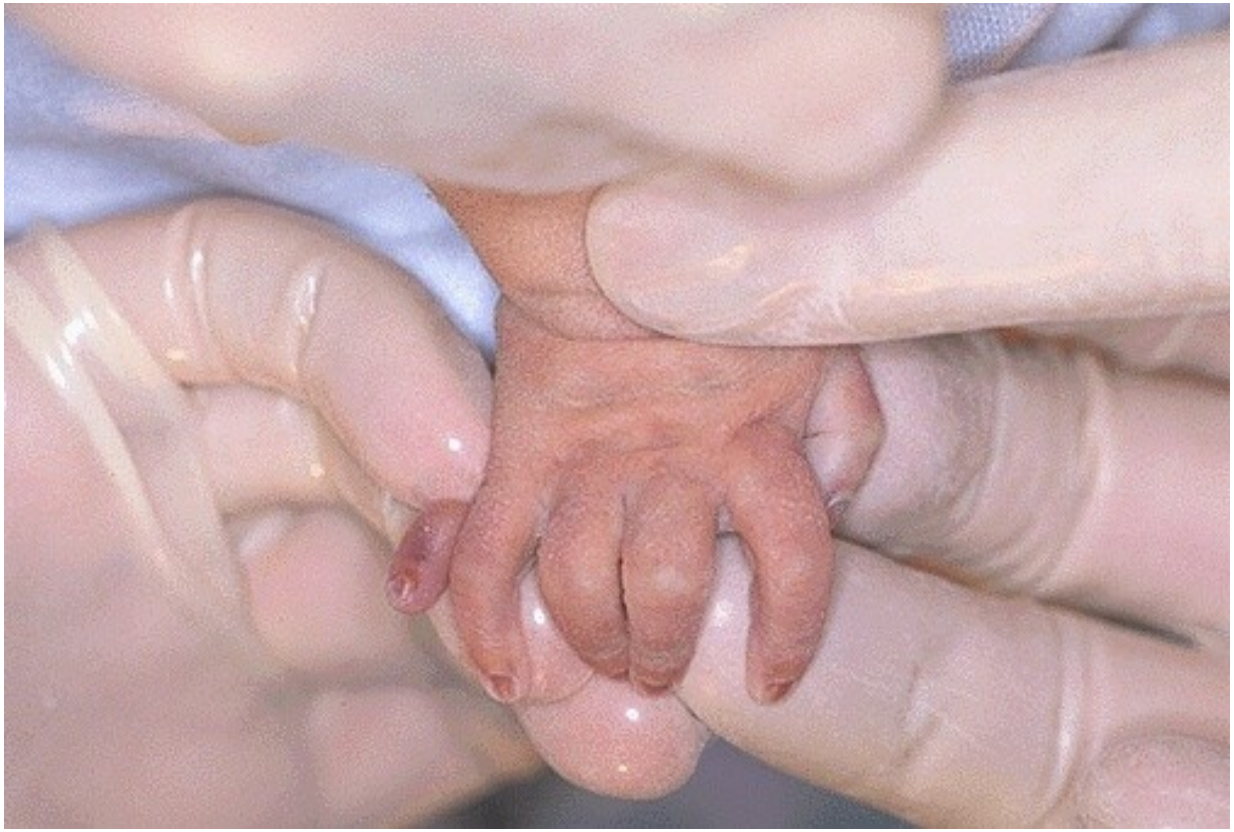
❖ **Most common cause of death?**
- ✓ Central apnea

Pediatric On Squores

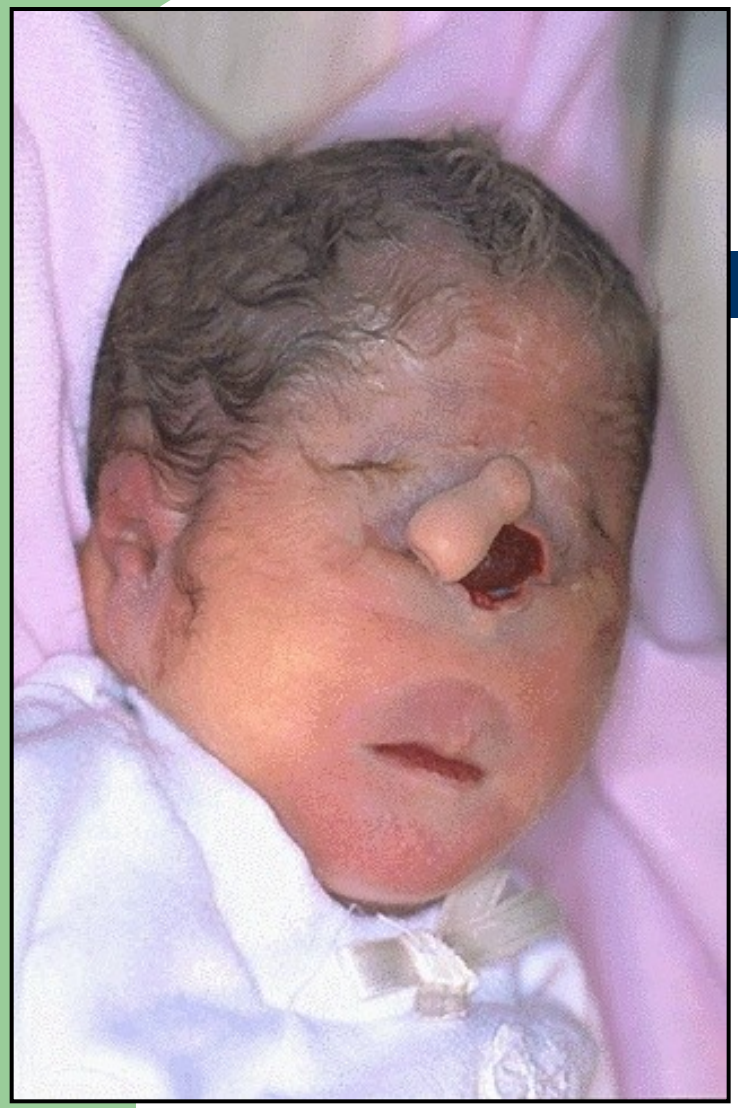
❖ **Prognosis**
- ✓ 70% die in the 1st 3 months of life
- ✓ 95% die by 3 years of age
- ✓ Rarely reach up to 10 years

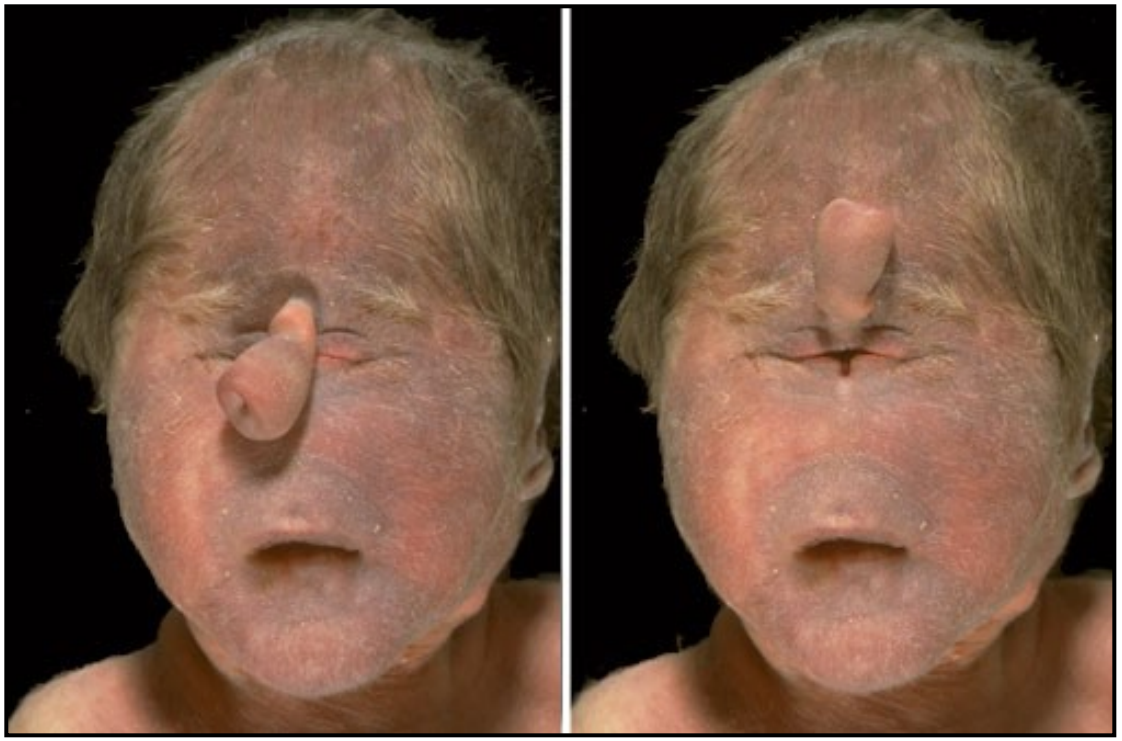
https://pbs.twimg.com/media/EXSZhKiWsAIVZbg.jpg:large

# Hexadactyly in newborn with trisomy 13



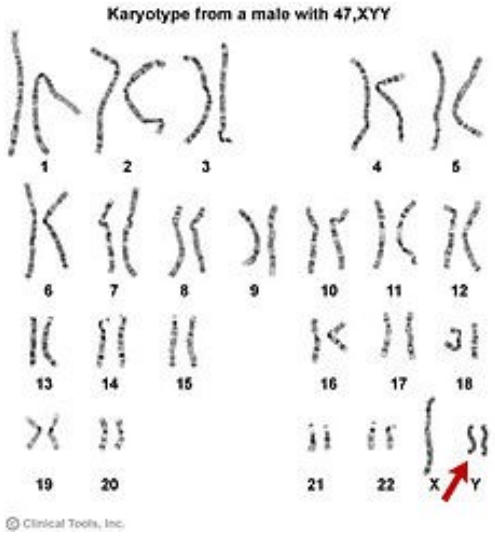
# Patau syndrome – cyclopia

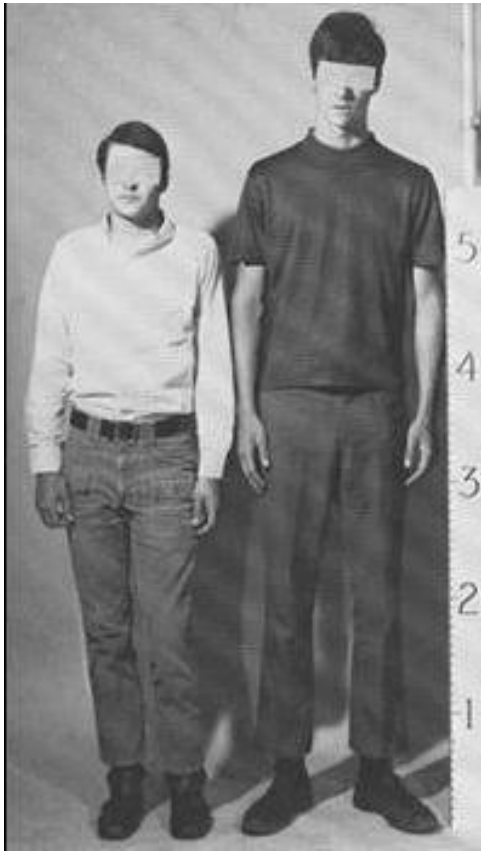




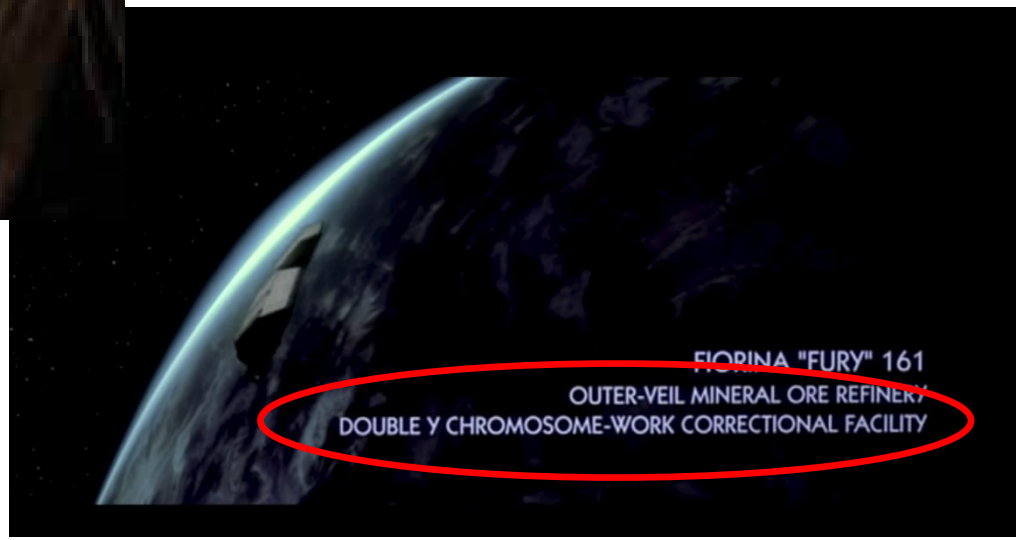
# Supermale syndrome (47,XYY)

- increased growth velocity
- no unusual physical features
- normal testosteron level, fertility and sexual development
- possible learning disabilities
- delayed development of speech and language skills
- behavioral and emotional difficulties



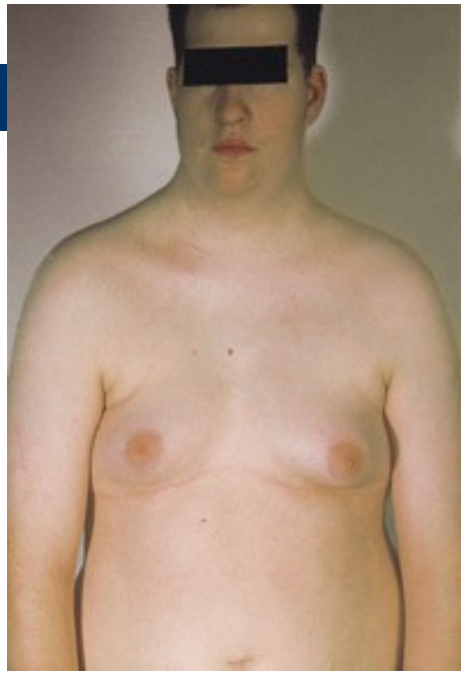
# 80´s – „double Y“ (Alien 3 – 1992)

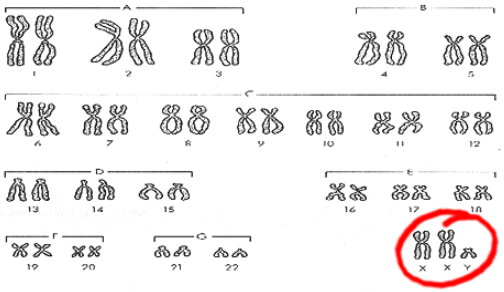


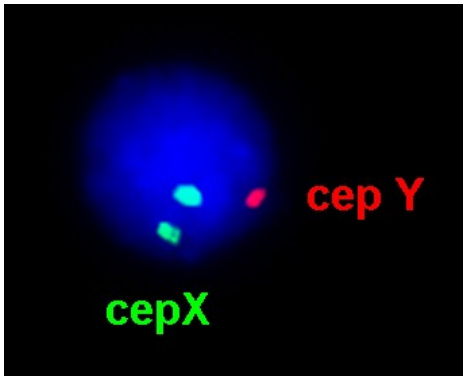
# Klinefelter syndrome (47,XXY)

**Variations 48,XXYY; 48,XXXY;**

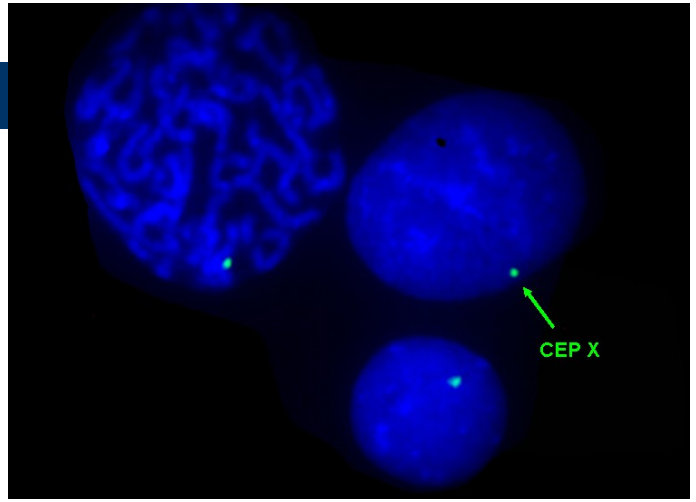
- tall figure
- less facial and body hair
- female distribution of body fat
- hypogonadism (decreased testicular hormon function)
- infertility
- gynecomastia (increased breast tissue)
- lower intelect degree



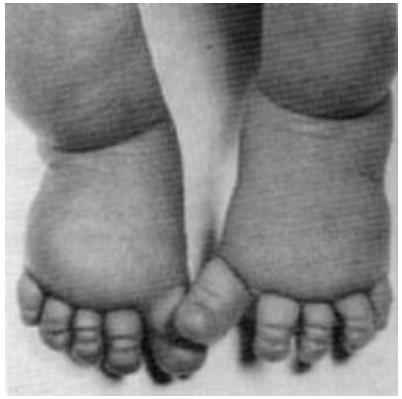


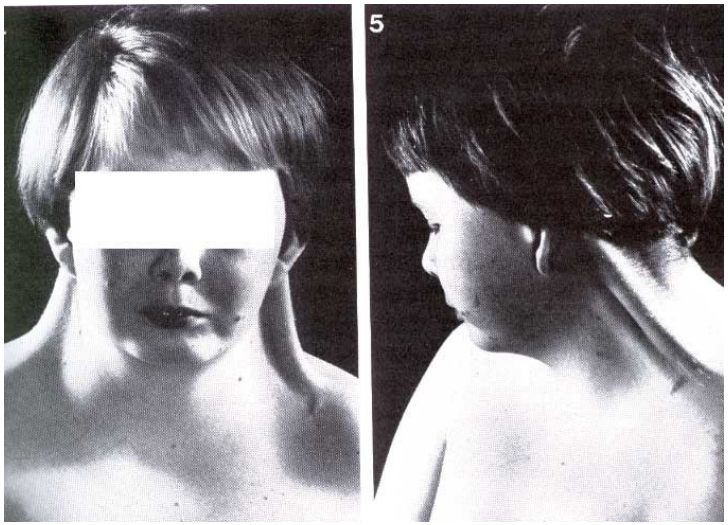


# Turner syndrome (45,X)



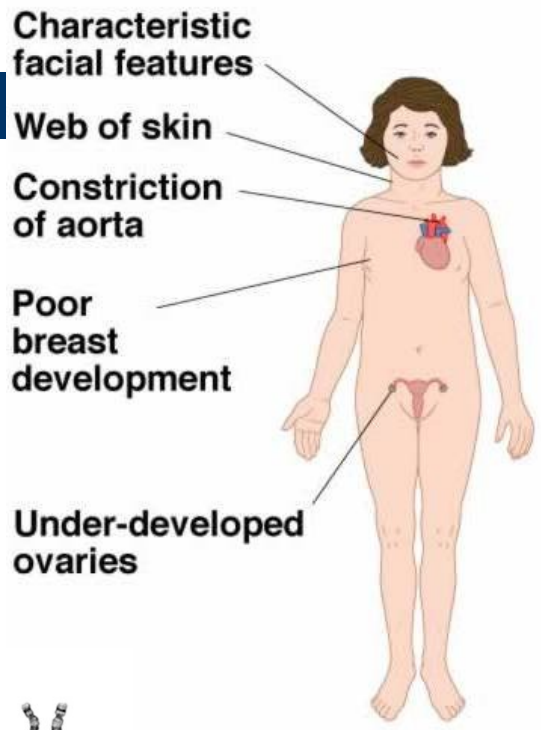

- lower birth length and weight
- low hairline
- pterigya
- broad chest, widely spaced nipples
- small growth
- infertility, absence of menstrual period
- coarctation of the aorta
- webbed neck
- lymphederma



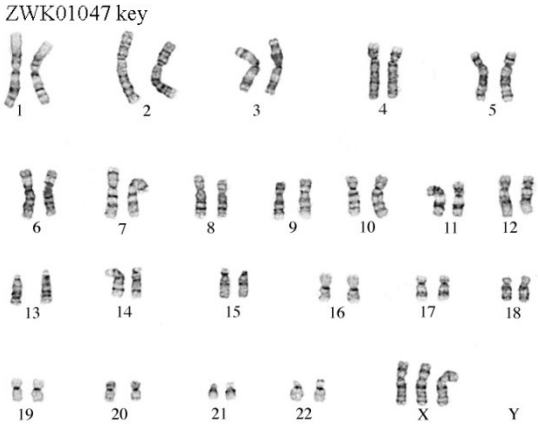


# XXX syndrome (47,XXX)

- **majority of triple X females are never diagnosed**
- normal fertility
- inactivated Barr body
- most often only mild effects
  - tall stature
  - small head
  - speech, language and learning disabilities
  - weak muscle tone




http://pics2.this-pic.com/image/triple%20x%20syndrome




https://www.google.cz/search?q=xxx+syndrome&source=lnms&tbm=isch&sa=X&ei=xMiIUvlHgrG0BpOYgLgL&ved=0CAcQ_AUoAQ&biw=1440&bih=783#facrc=_&imgdii=_&imgrc=Hz1JqrGzTyKpBM%3A%3BfZOiqHDJFB267M%3Bhttp%253A%252F%252Fworms.zoology.wisc.edu%252Fzooweb%252FPhelps%252FZWK01047k.jpg%3Bhttp%253A%252F%252Fwww.zappa.com%252Fmessageboard%252Fviewtopic.php%253Ff%253D5%2526t%253D7057%3B768%3B576