GENETIC and DEVELOPMENTAL DISORDERS II.

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November 2021.

250 years of EXCELLENCE in medical education, research & innovation and healthcare

Teratology

- Teratogenesis means malformation caused by environmental effects
- Forms:
  - → Isolated developmental disorders (one organcomplex is usually affected)
    - » Malformations
    - » Deformations
    - » Dysruptions
    - » Field defect (e.g. Pachygiria, Agyria or Lissenzepahlia, Mikropolygyria, Teleenzepahalon dev. problems: diminshed number of big comissura fibers: slim Corpus Callosum, Holoprosencephalia: uncomplete development of the brain, Zyklopia, celft lip or palate)
    - » Sequences – Potter Sequence
    - » Syndroms
  - → Multiple developmental disorders

Disturbed diferentiation/development

- Agenesia - organ is completely missing
- Aplasia - primitive organ development is histologically detectable but no mature organ development
- Dysgenesia – maldevelopment of the organ
- Hypoplasia - smaller size than nromal
- Stenosis - narrowing
- Atresia - completely closed opening/ending
- Dysraphia - disturbed closing of neural tube

Chromosomal Defects

- Numeric disorders
- Monosomy, Trisomy

  Cause: no-disjunction, late of the Anaphasis

  → Mosaicism

  Cause: damage in early embyogenesis
- Structural Disorders

  → Deletion, Addition

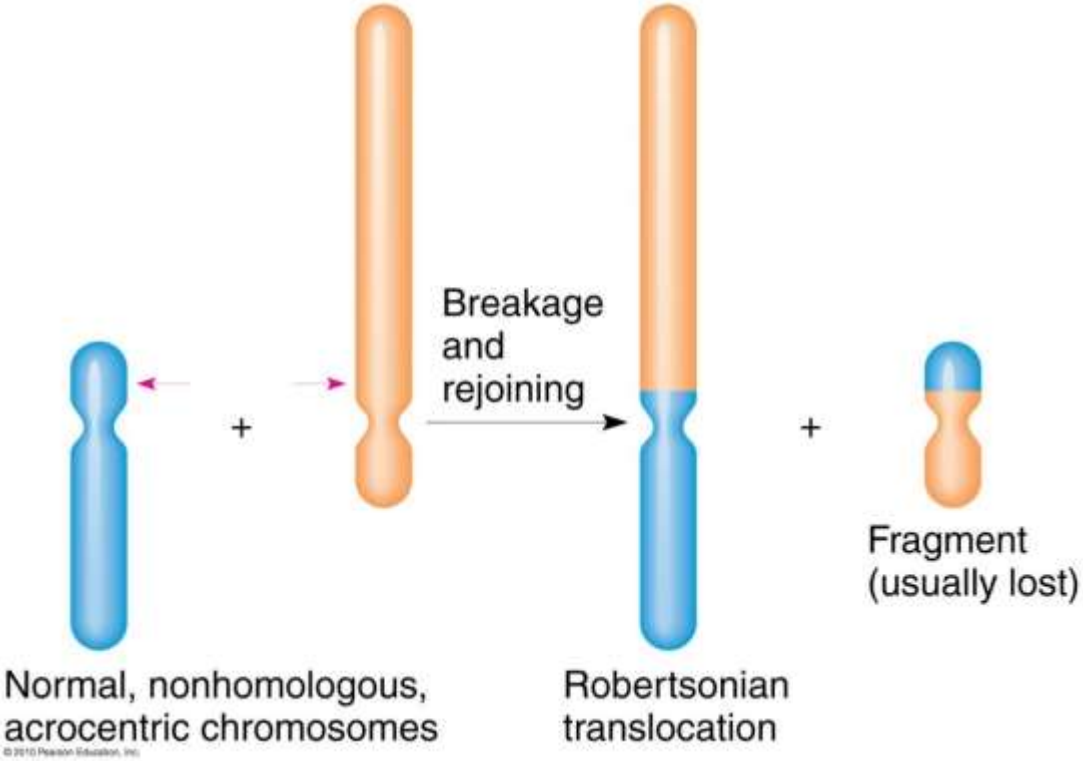
  → Inversion

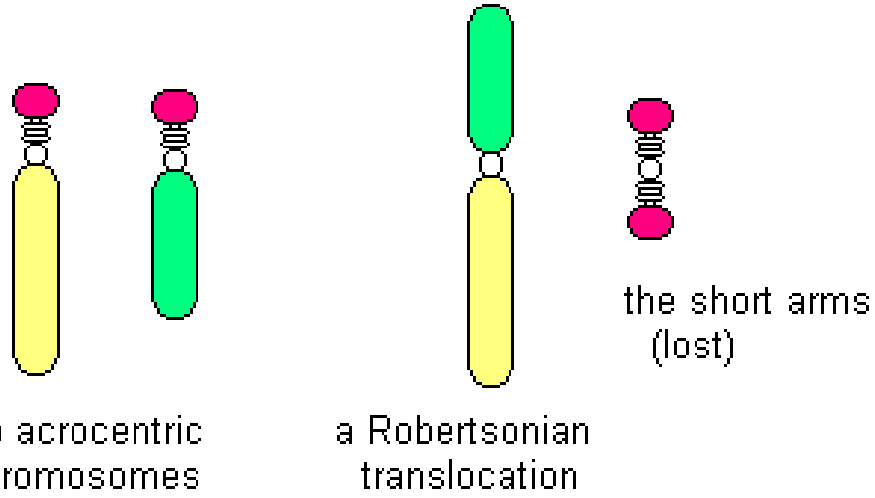
  → Isochromosom, ringchromosom

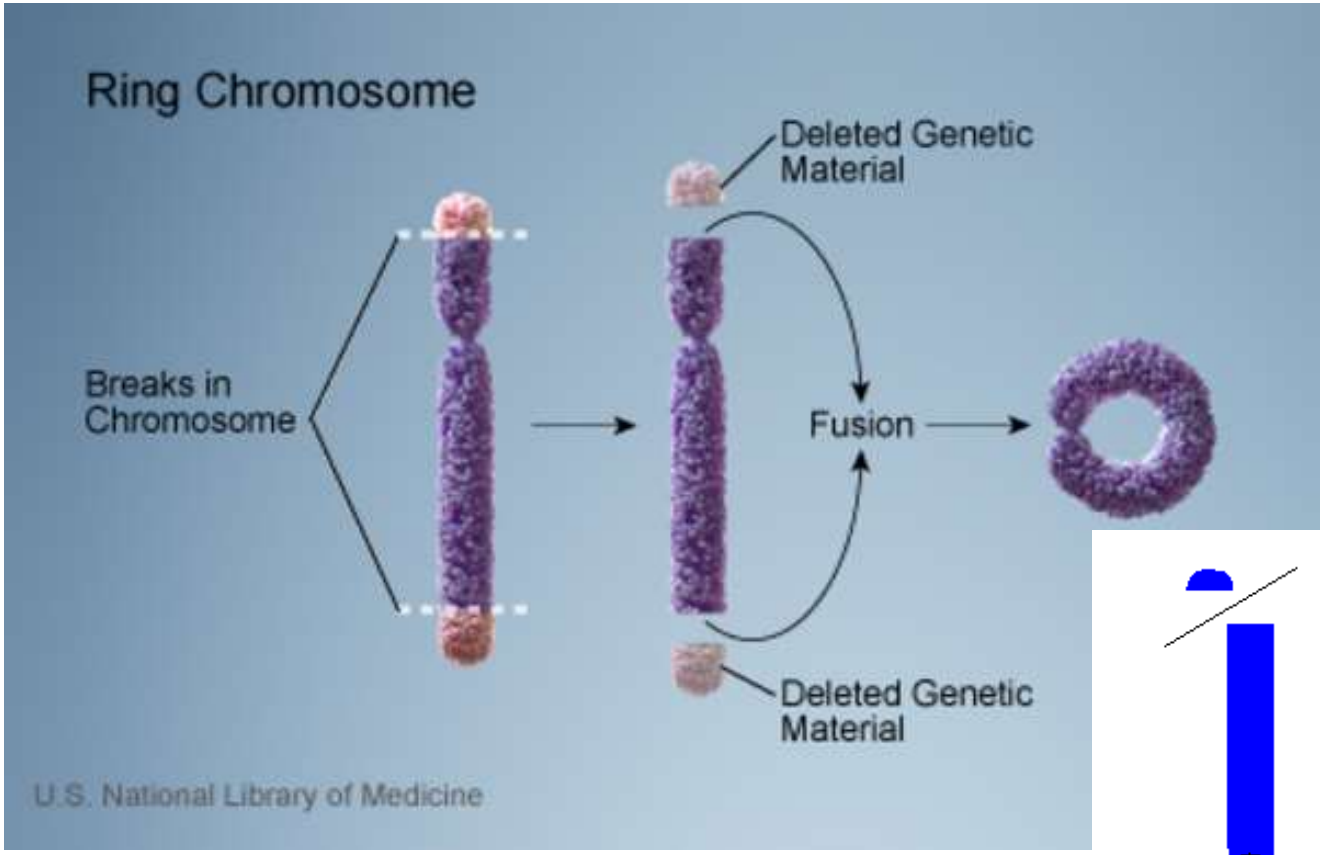
Chromosome defects

- Numerical alterations
- Monosomy, Trisomy
  - » Cause: Non-disjunction, delay of anaphasis
  - → Mozaicism
  - » Cause: Damage in early embryogenesis
- Structural alterations
  - → Deletion, Addition
  - → Inversion
  - → Iso-chromosome, ring chromosome

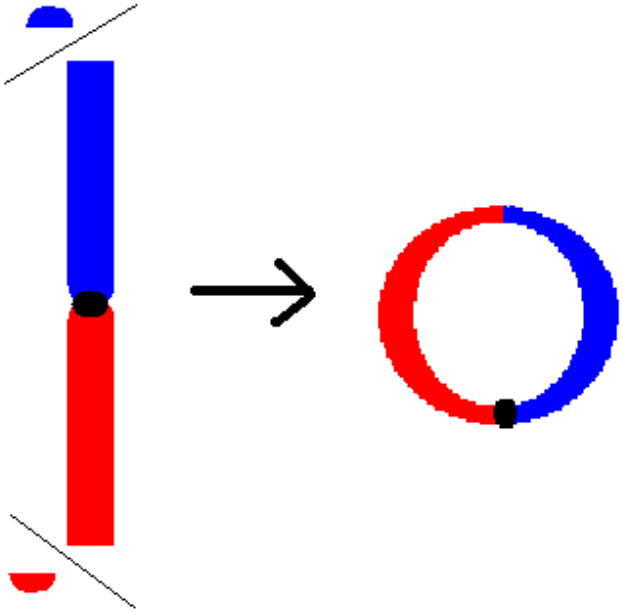
Robertson transzlokáció (akrális fúzió)

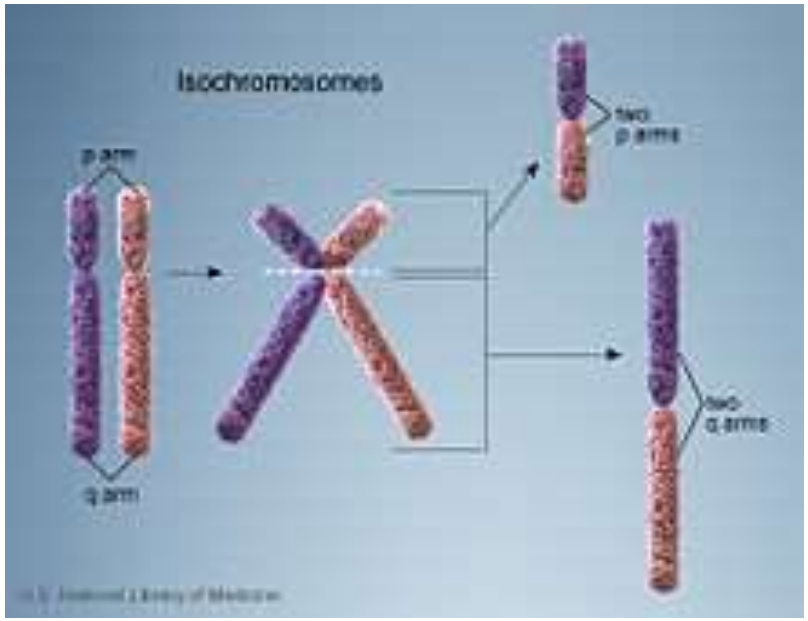




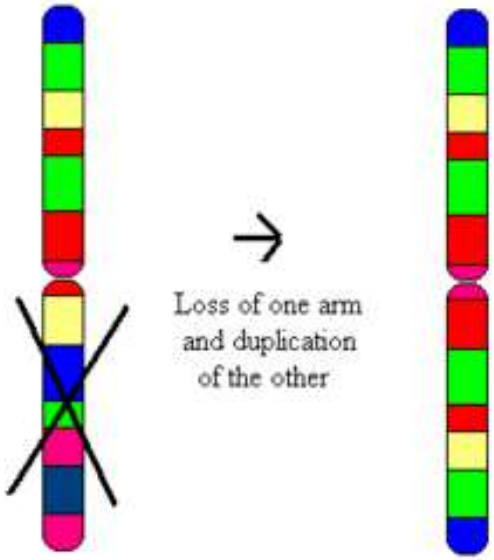


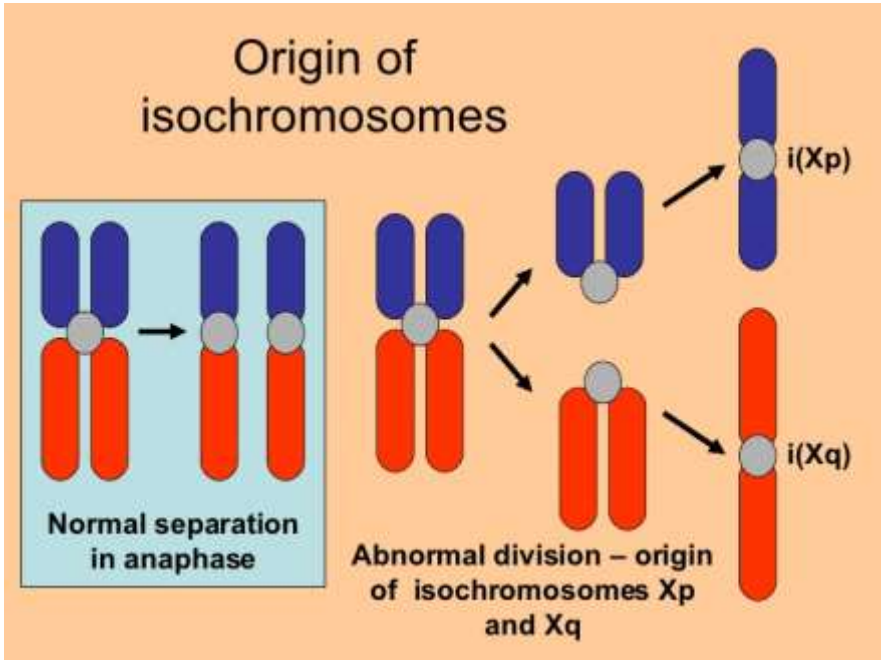
ring chromosome



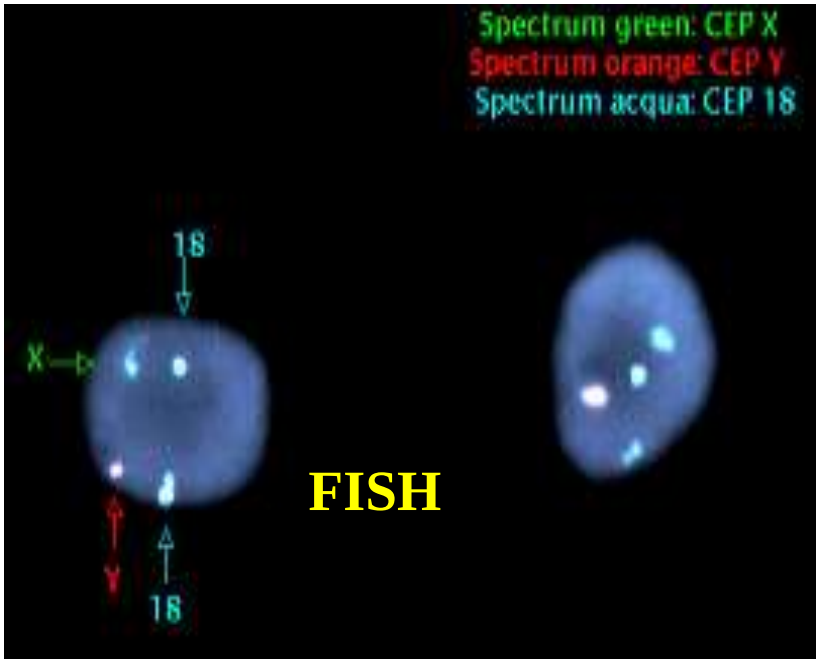


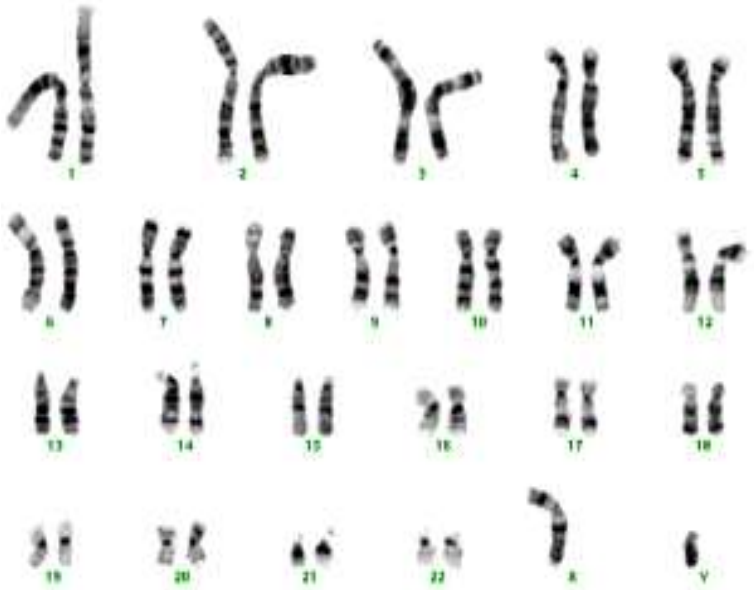
An **isochromosome** is an unbalanced structural abnormality in which the arms of the chromosome are mirror images of each other.[1] The chromosome consists of two copies of either the long (q) arm or the short (p) arm because isochromosome formation is equivalent to a simultaneous duplication and deletion of genetic material. Consequently, there is partial trisomy of the genes present in the isochromosome and partial monosomy of the genes in the lost arm.





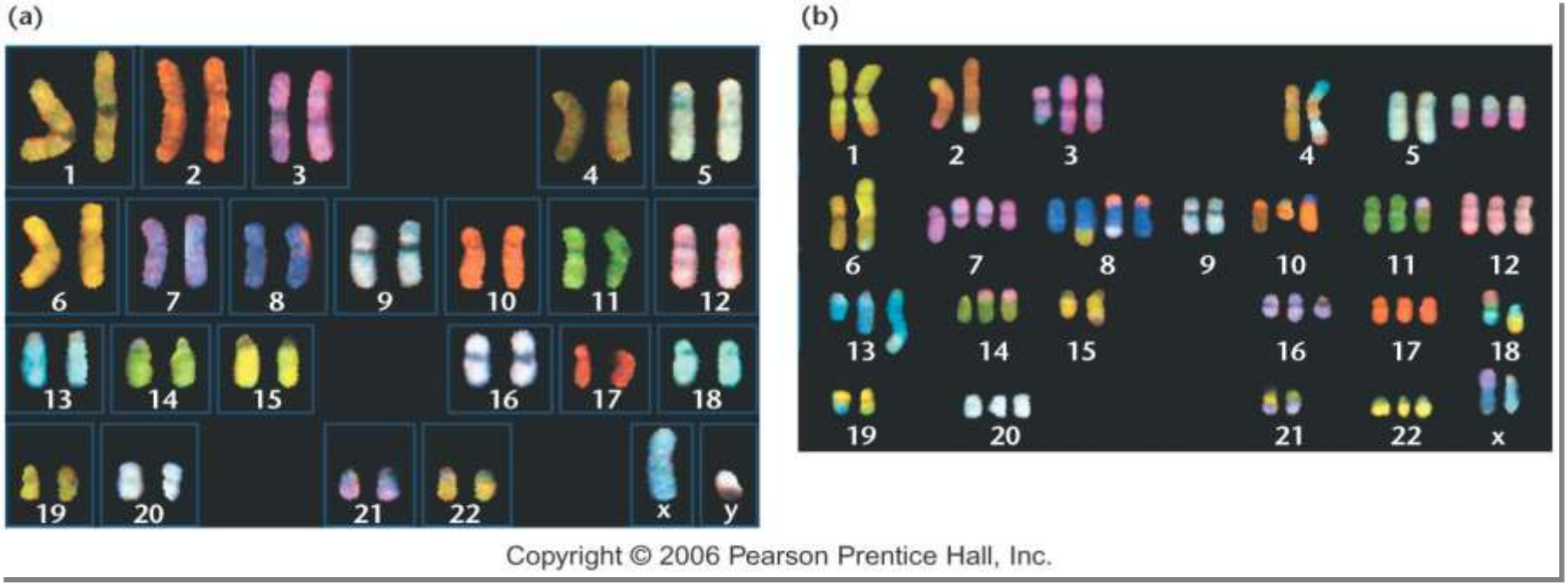
MOLECULAR MEDICINE
Cytogenetics





Cytogenetics- kariogram

Normal cell and tumor cell karyotypes

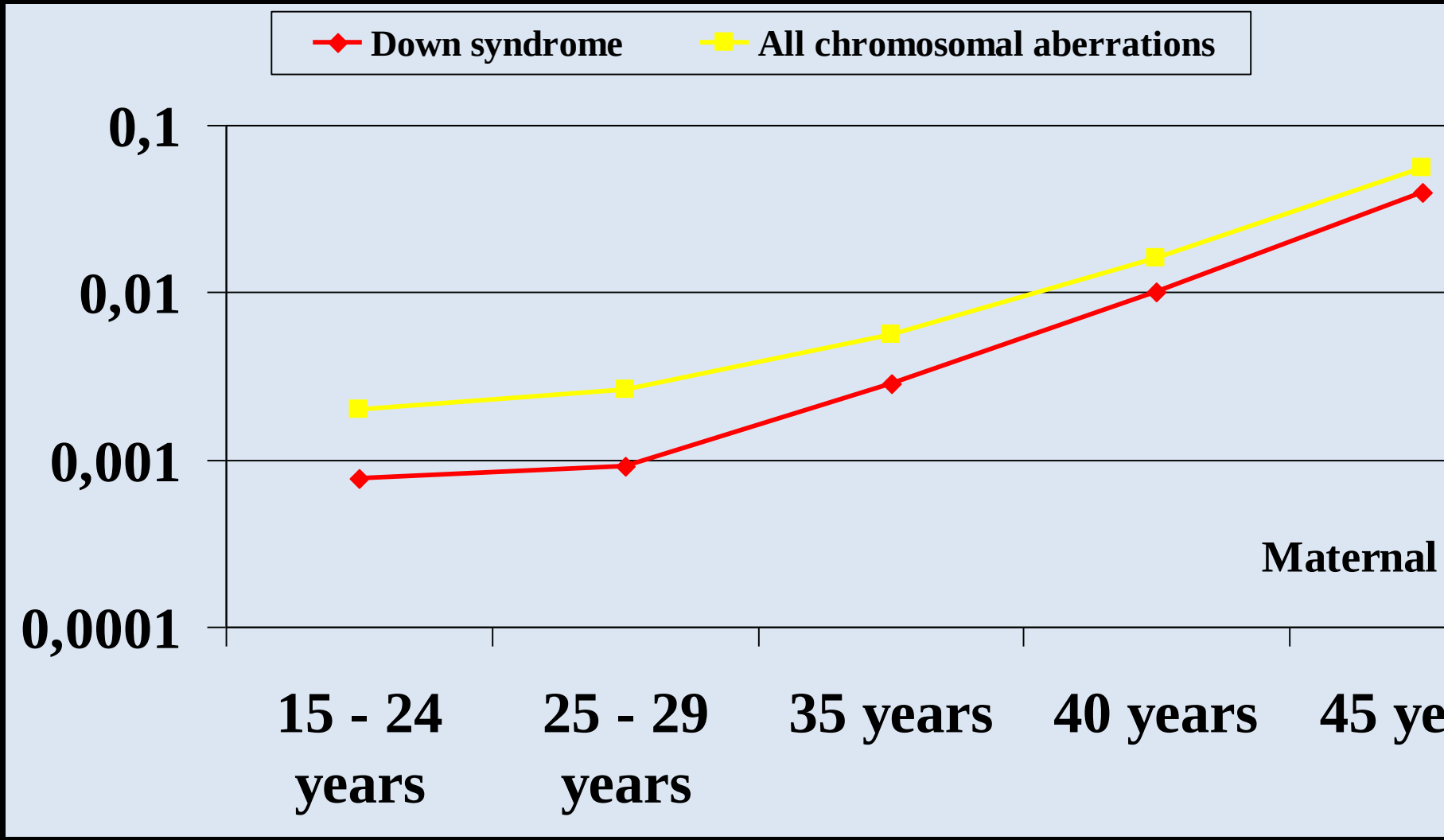


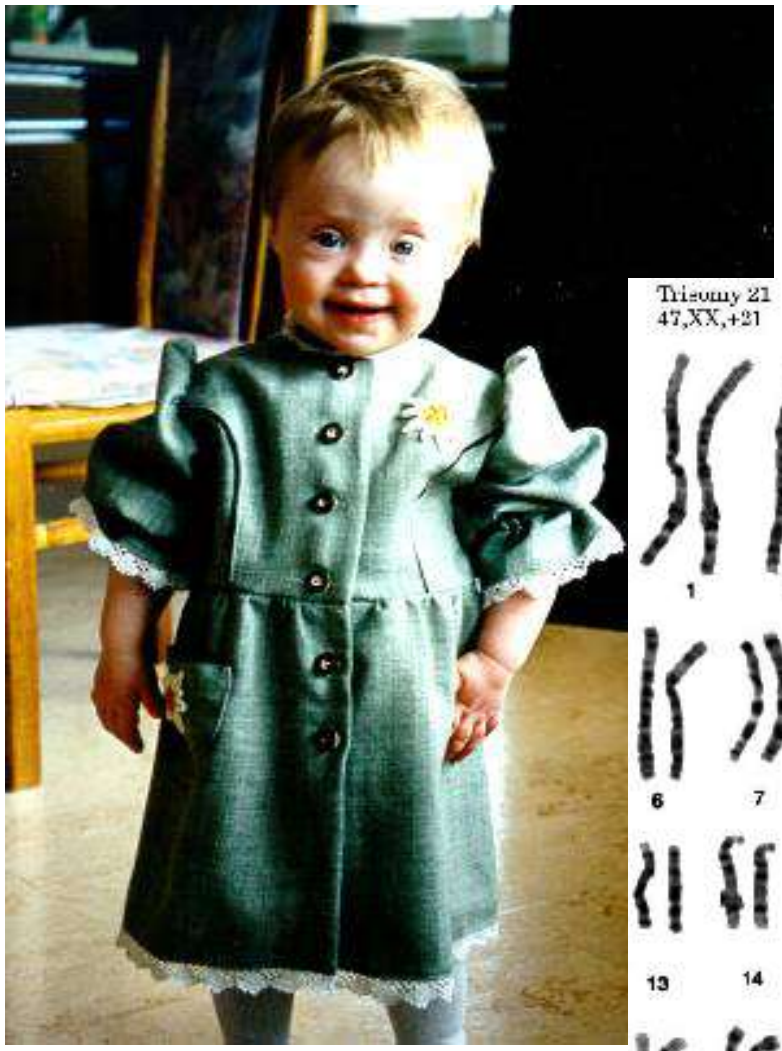
- Whole chromosome painting
- (a) normal cell (b) tumor cell with several chromosomal rearrangement

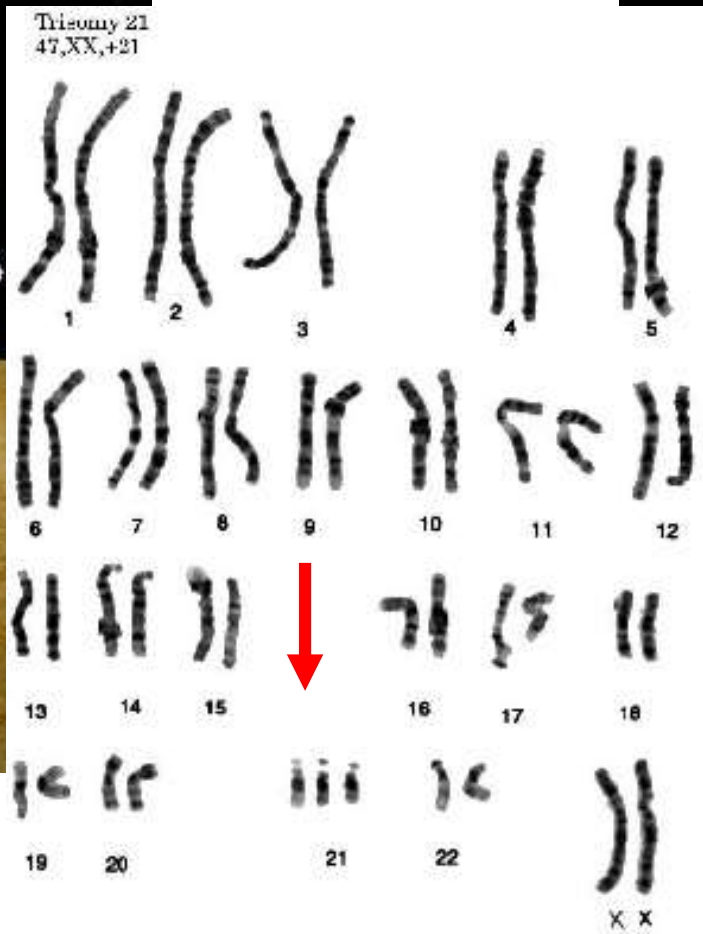
Autosomal Defects

- Trisomy:
  - → Down syndrom (21 Trisomy)
  - → Edwards syndrom (18 Trisomy)
  - → Patau syndrom (13 Trisomy)
- Deletions
  - → Cri du chat syndrom (5p Deletion)
  - → 4p Deletion

Frequency of the chromosomal Abnormaliti






Trisomy 21
47,XX,+21
1
2
3
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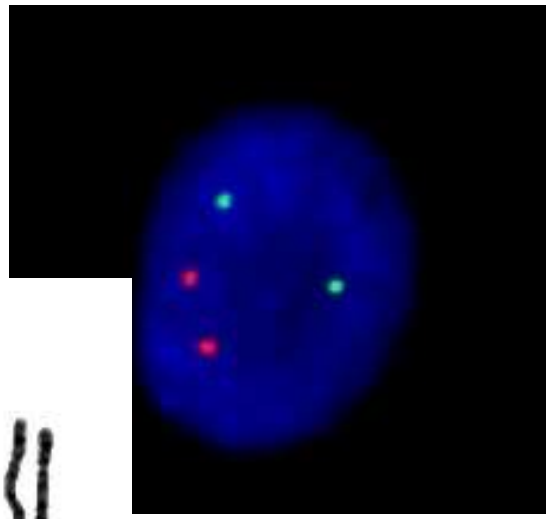
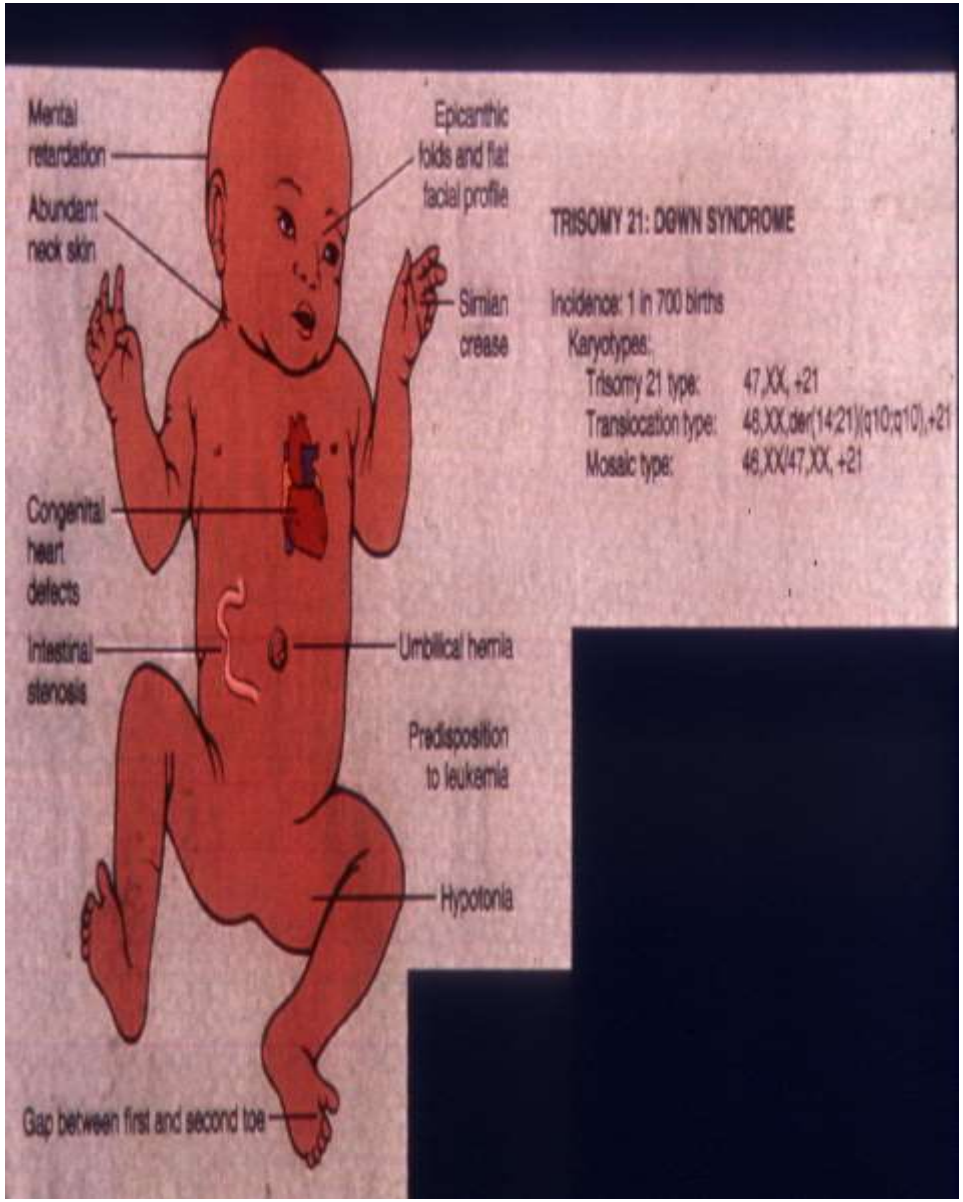
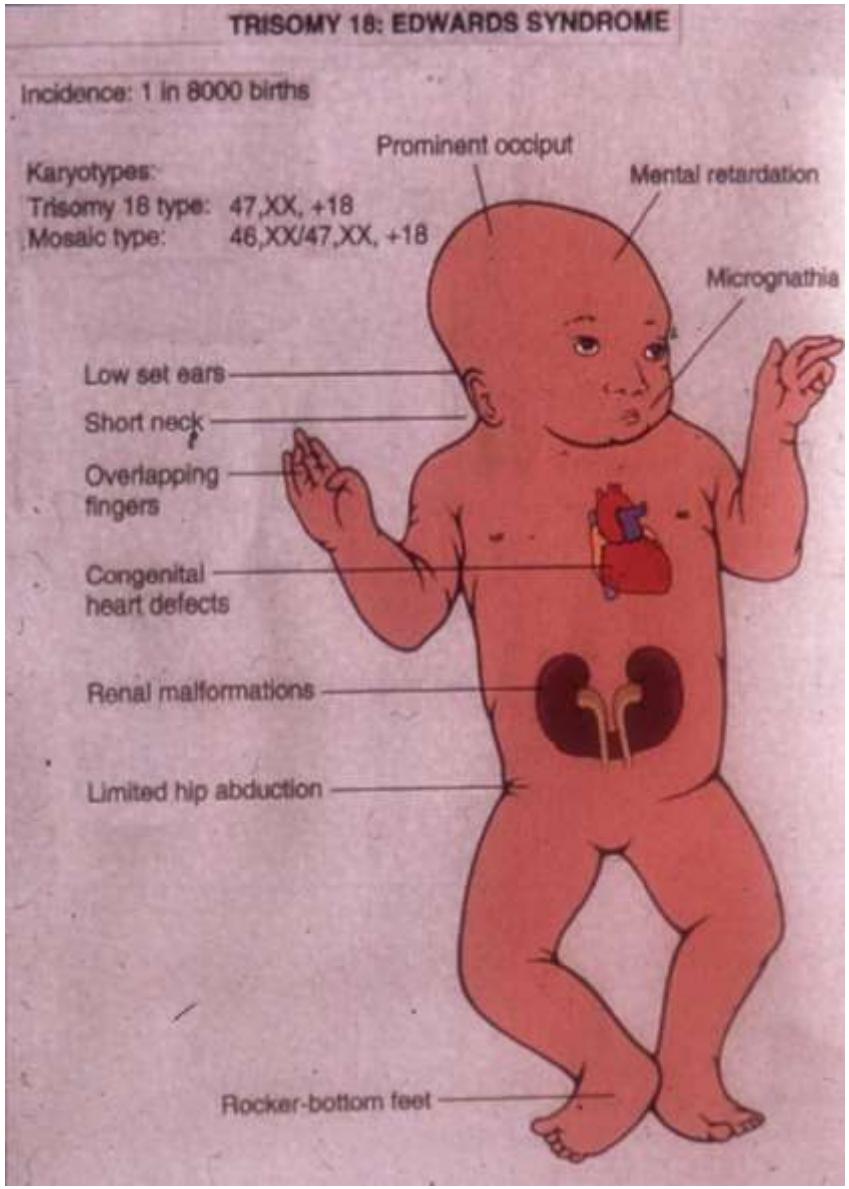
X X





Down syndrom:

broad, flat face
Epicanthus
Macroglossia
Simian crease
50 % heart dev. disorders (VSD, ASD)
Increased risk for leukemia

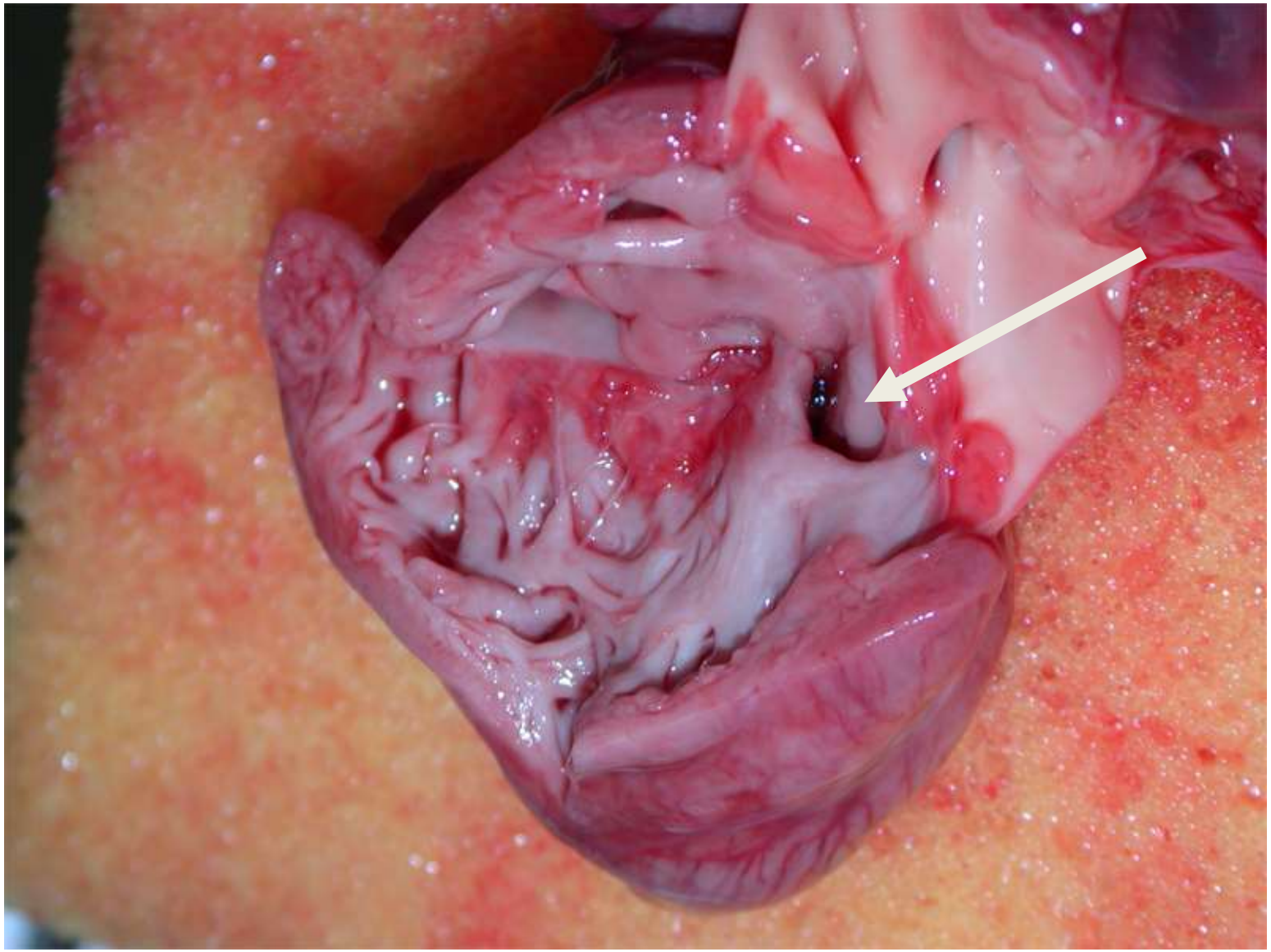


Edwards syndrom (surv.: 2-3 months):

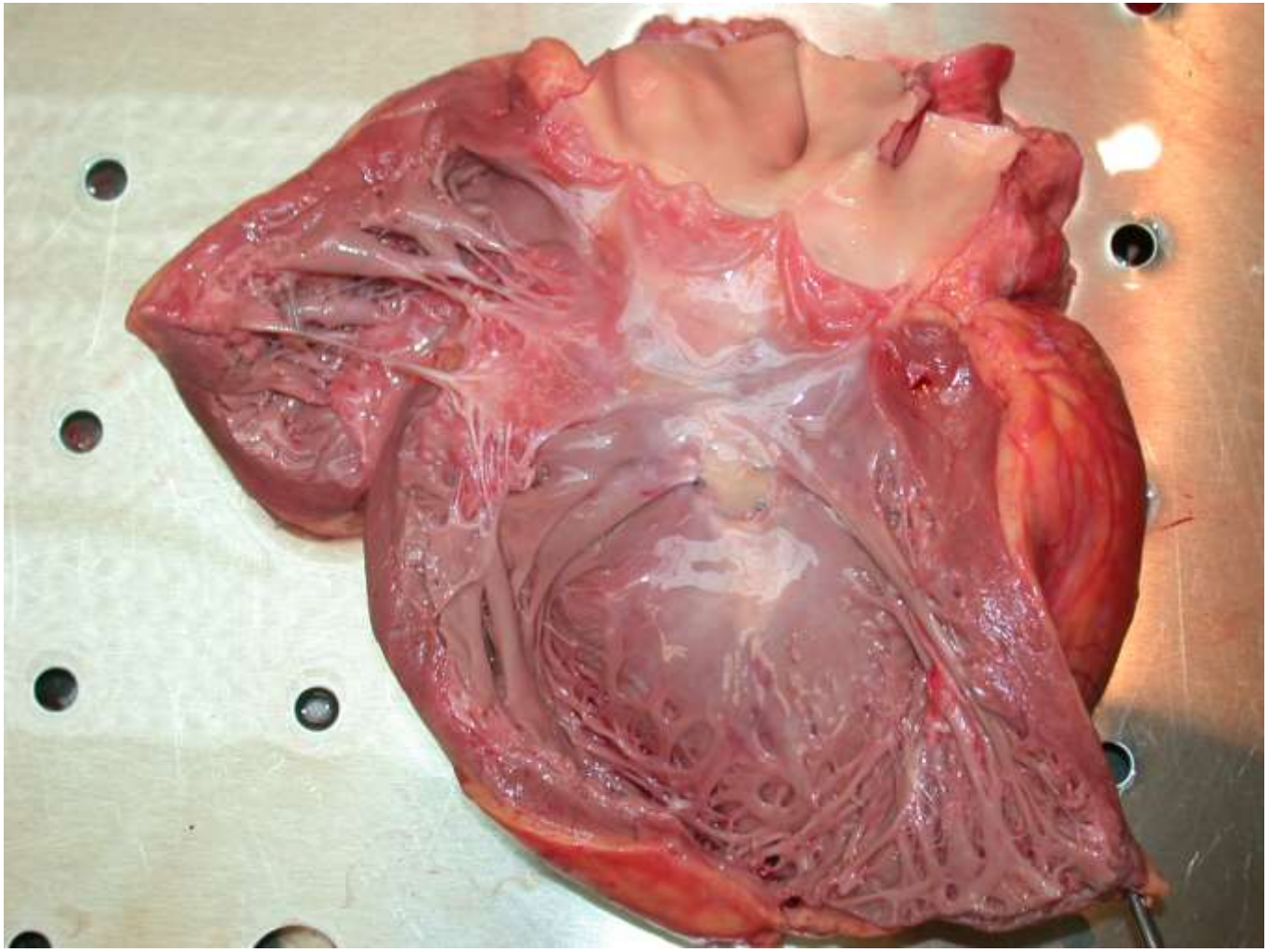
18 chr. trisomy
Mental retardation
Craniofacial dysplasia
short neck
heart defects (VSD)
horseshoe kidney
Mikropolygyri of temporal lobe

Patau syndrom (surv.: 2-3 months):

13 chr. trisomy
Cleft lip and palate
Rocker bottom feet
Polidactylia
Face deformity
mental retardation
cardiac defects
Holoprosenzepahlia, Agyria, Mikrozephalia



VSD
(ASD, aorta asc. atresia)



tricusp. insuff.
dilatatio ventr. ,
fixed pulm.
hypertension
progr. circ.
insuffitiency

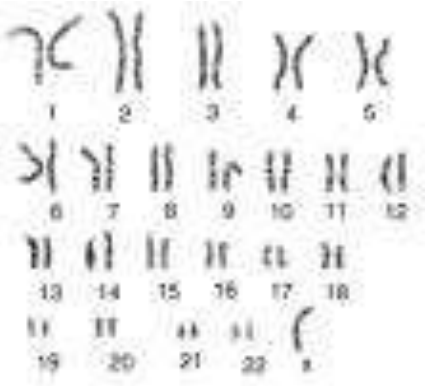
Exitus: 31 years

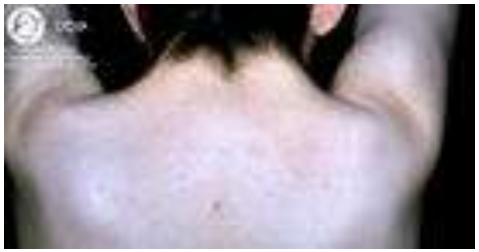
Medical history: corrected transpositions of the major arteries
12 years of age: closing of VSD, not attending med. controls after

Defects of the sex chromosoms

- Monosomies:
  - → Turner syndrom: 45 X
- Polysomies:
  - → Klinefelther syndrom: 47 XXY (48 XXXY, 49 XXXYY, etc.)
  - → Superman: 47 XYY (48 XYYY, 49 XYYYY, etc.)

Turner syndrom: 45 X



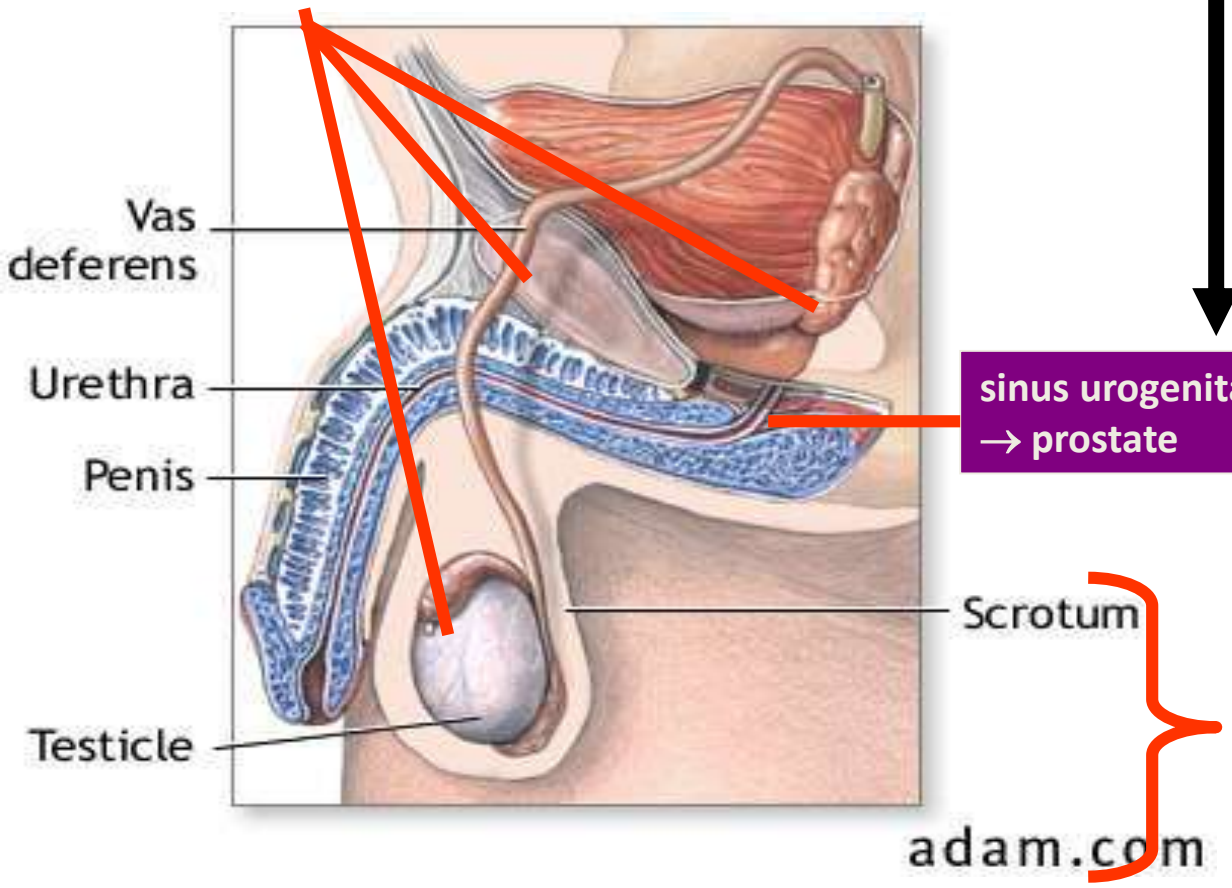


Short stature
Low posterior hairline
webbing of neck
streak ovaries
infertility
amenorrhea
coarctation of the aorta

Testosteron

Dihydrotestosteron

Wolffs duct → (2x) epididymis, vas deferens, vesicula seminalis 9-13 wk

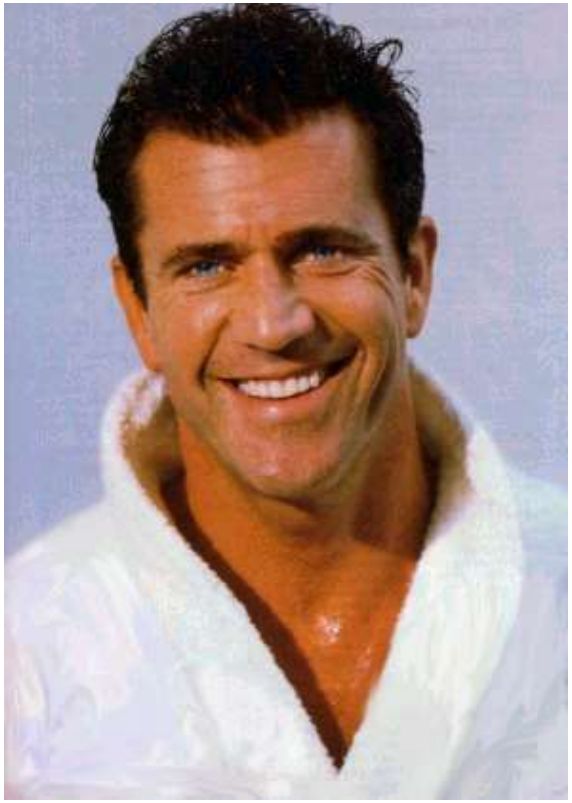


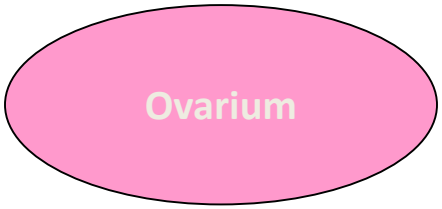
sinus urogenitalis → prostate

Differentiation of primitive genitals

→ male phenotype 8-13 wk

WHAT MAKES a WOMAN a WOMAN ?
WHAT MAKES a MAN a MAN ?





Ovaries (XX phenotpye) produce hormones which drive the sexual differentiation to female phenotype

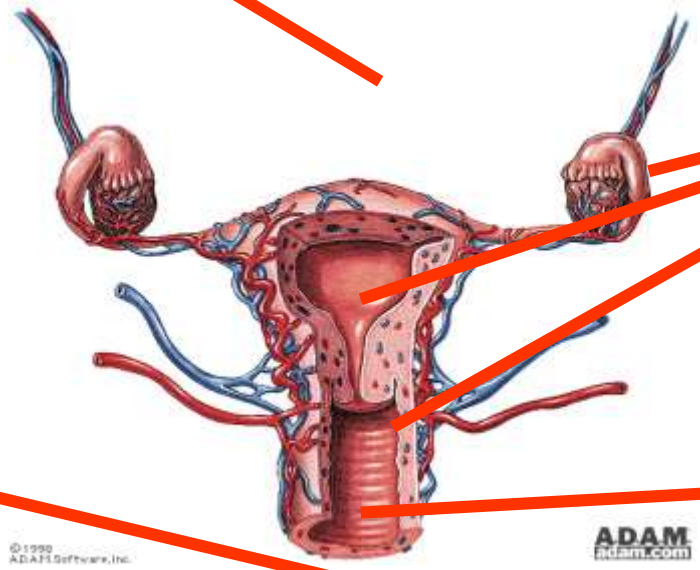
NB: (maternal and fetal) oestrogens play a big role in sexual differentiation

Ovarium

Release of little testosteron

Regression of Wolffs duct
9-13 wk

Differentiation of Mullers duct
7-12 wk



Differentiation of primitive genitals
→ female phenotype
7-12 wk

Sinus Urogenitalis
→ distal vagina

Genetic causes of disturbed sexual Differentiation

TERMS

Sex Reversal: karyotype does not match the genitals (XY female, XX male)
Pseudo-hermafroditism: (male of female) karyotype matches the gonads, bot not the genitals - disagreement between phenotypic and gonadal sex

Hermafroditism: presence of both ovarian and testicular tissue on different sides (contralateral) or combined ovotestis

Ambigous genitals: does not resemble either male or female

Hermaphroditos was a handsome son of Hermes and Aphrodite.

He was loved by the Nymphe Salmakis who prayed that she could be with him forever.

Some god, on hearing her prayer, merged their two forms into one, to form
a being that was both male and female

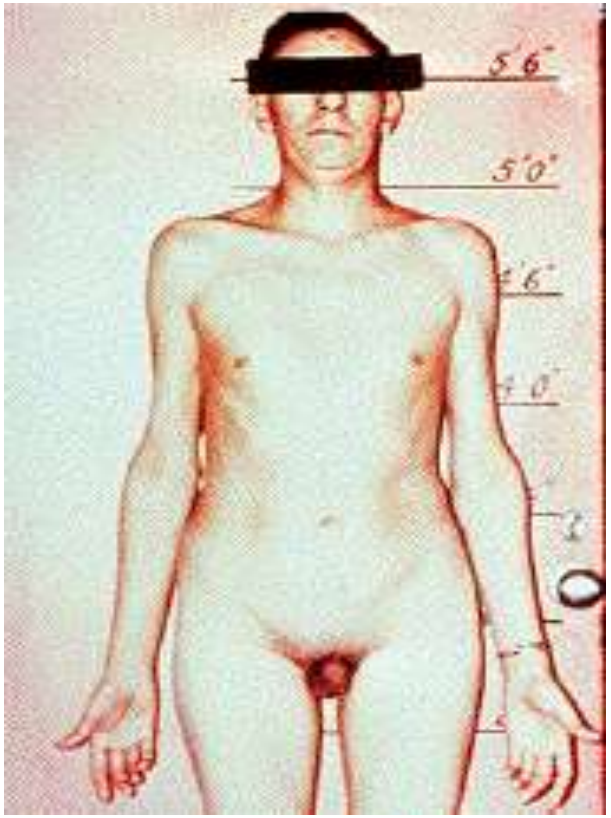
Klinefelter (XXY) syndrom

Bipotential gonads
XX

→

Testis: small,
little amount of SP

Eunuchoid body habitus with abnormnally long legs
infertility
small, atrophic testis
Klinefelter (XXY) syndrom



Pseudo-hermafroditism

karyotype mathces the gonads, external genitalia are ambiguous or female

XY, testes, female or ambiguous genitals

Hormonal:

5-alpha reductase deficiency

Androgen receptor insensivity

(testicular feminization)

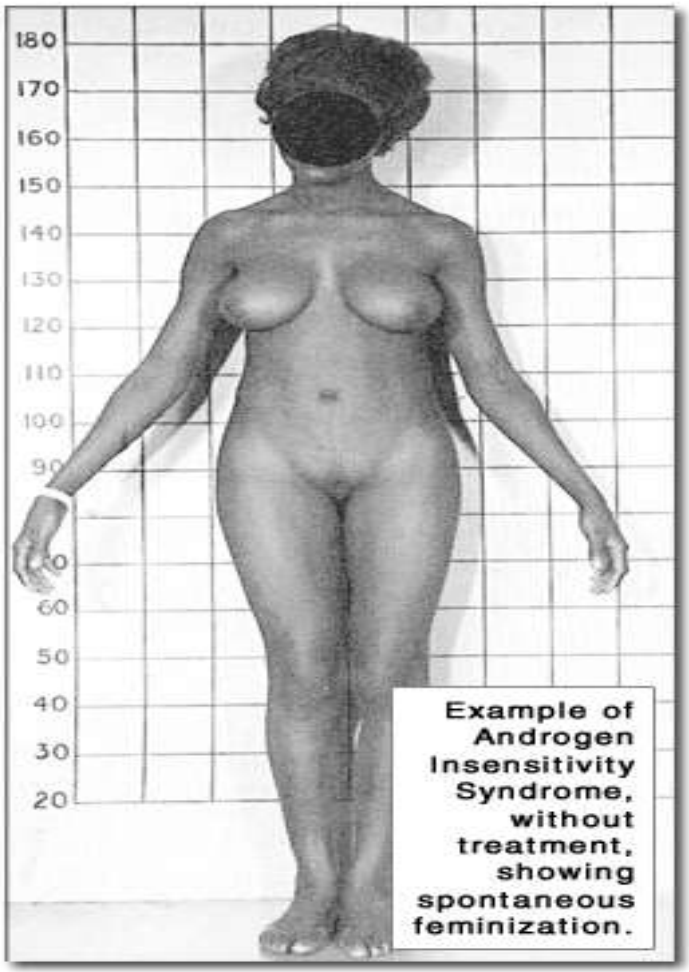
Persistent Mullerian Duct syndrom (I & II)

Leydig cell hypoplasia/agenesy

FTZF1 mutations

WAGR/Denys-Drash

Smith-Lemli-Opitz syndrom (I & II)



Androgen Receptor Insensivity – Hairless Woman

Complete androgen insensitivity syndrome

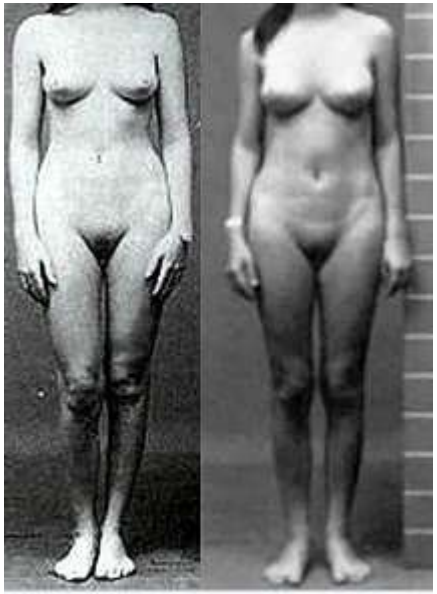
Complete androgen insensitivity syndrome (**CAIS**) is an AIS condition that results in the complete inability of the cell to respond to androgens.[1][2][3] As such, the insensitivity to androgens is only clinically significant when it occurs in individuals with a Y chromosome or, more specifically, an *SRY* gene.[1] The unresponsiveness of the cell to the presence of androgenic hormones prevents the masculinization of male genitalia in the developing fetus, as well as the development of male secondary sexual characteristics at puberty, but does allow, without significant impairment, female genital and sexual development[3][4] in those with the condition.

All human fetuses begin fetal development looking similar, with both the Müllerian duct system (female) and the Wolffian duct system (male) developing. It is at the seventh week of gestation that the bodies of unaffected individuals with the XY karyotype begin their masculinization: i.e, the Wolffian duct system is promoted and the Müllerian duct system is suppressed (the reverse happens with typically developing females). This process is triggered by androgens produced by the gonads, which in individuals with the XX karyotype had earlier become ovaries, but in XY individuals typically had become testicles due to the presence of the Y Chromosome. The cells of unaffected XY individuals then masculinize by, among other things, enlarging the genital tubercle into a penis, which in females becomes the clitoris, while what in females becomes the labia fuses to become the scrotum of males (where the testicles will later descend).

Individuals affected by CAIS develop a normal external female habitus, despite the presence of a Y chromosome,[1][5][6][7][8][9] but internally, they will lack a uterus, and the vaginal cavity will be shallow, while the gonads, having been turned into testicles rather than ovaries in the earlier separate process also triggered by their Y chromosome, will remain undescended in the place where the ovaries would have been. This results not only in infertility in individuals with CAIS, but also presents a risk of gonadal cancer later on in life.[10]

CAIS is one of the three categories of androgen insensitivity syndrome (AIS) since AIS is differentiated according to the degree of genital masculinization: complete androgen insensitivity syndrome (CAIS) when the external genitalia is that of a typical female, mild androgen insensitivity syndrome (MAIS) when the external genitalia is that of a typical male, and partial androgen insensitivity syndrome (PAIS) when the external genitalia is partially, but not fully masculinized.[1][2][5][6][7][11][12][13][14]

Androgen insensitivity syndrome is the largest single entity that leads to 46, XY undermasculinization.[15]



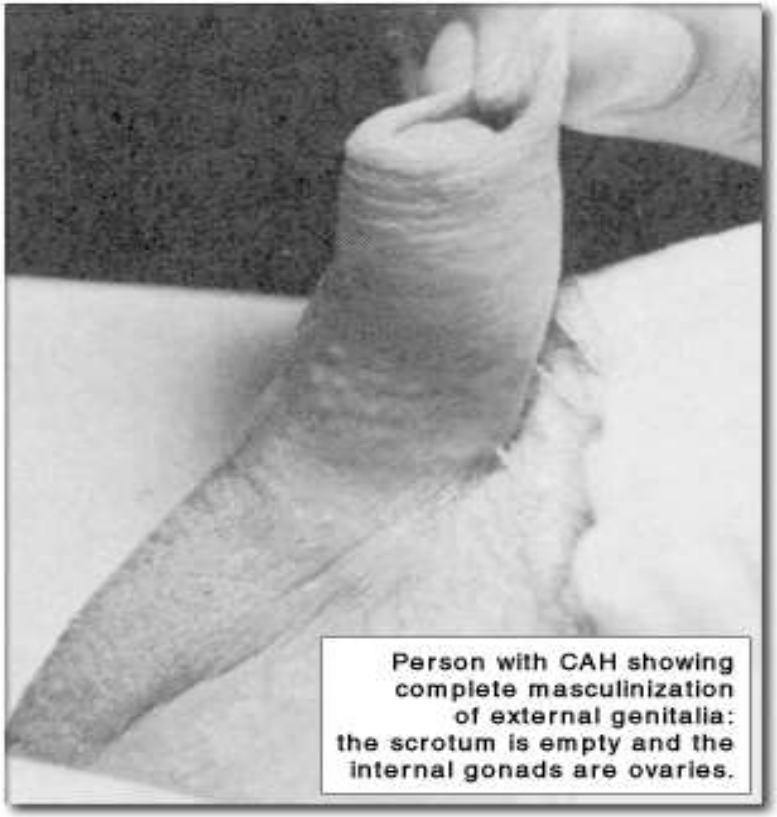
Persons with a complete androgen insensitivity have a typical female external phenotype, despite having a 46,XY karyotype.[16][17]

Model Hanne Gaby Odiele reveals she is intersex to help break stigma

Odiele's biological sex characteristics do not conform to typical notions of male or female. PHOTO: INSTAGRAM

Disturbed synthesis of sex hormons

21 hydroxylase deficiency (too much Androgens)



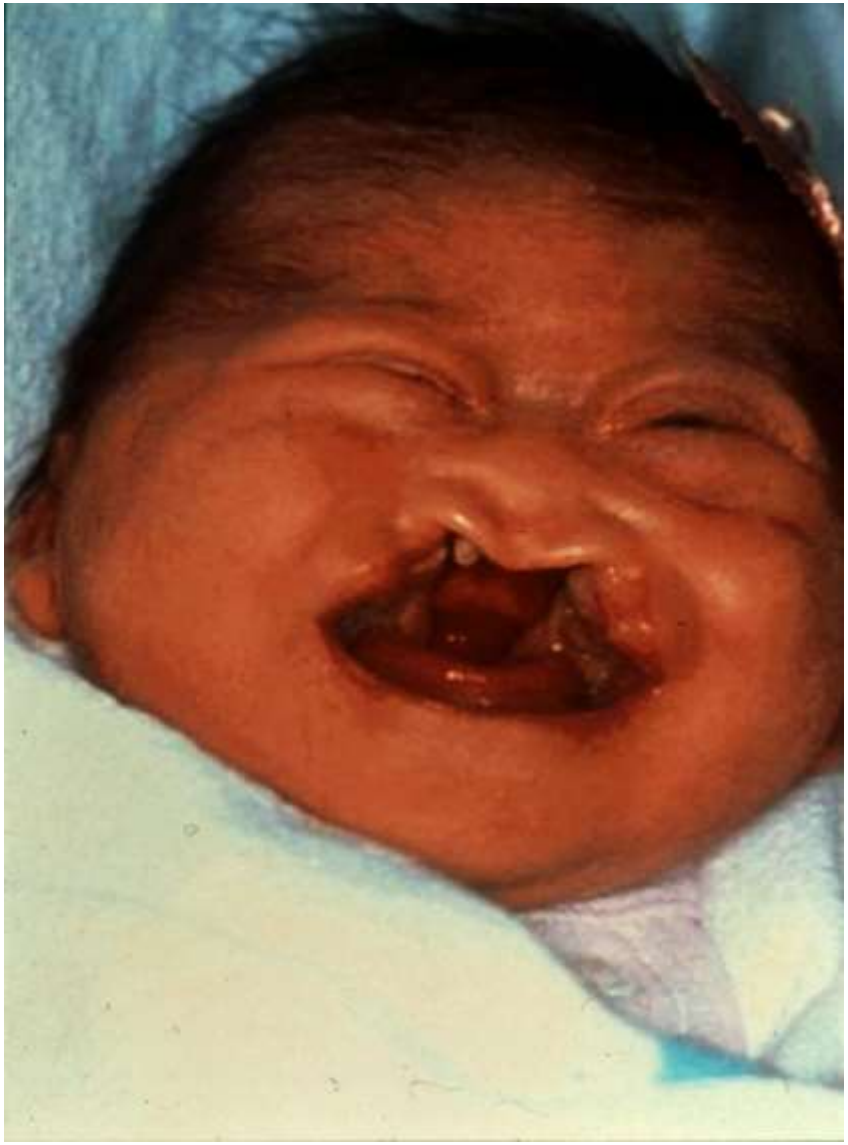
Person with CAH showing complete masculinization of external genitalia: the scrotum is empty and the internal gonads are ovaries.

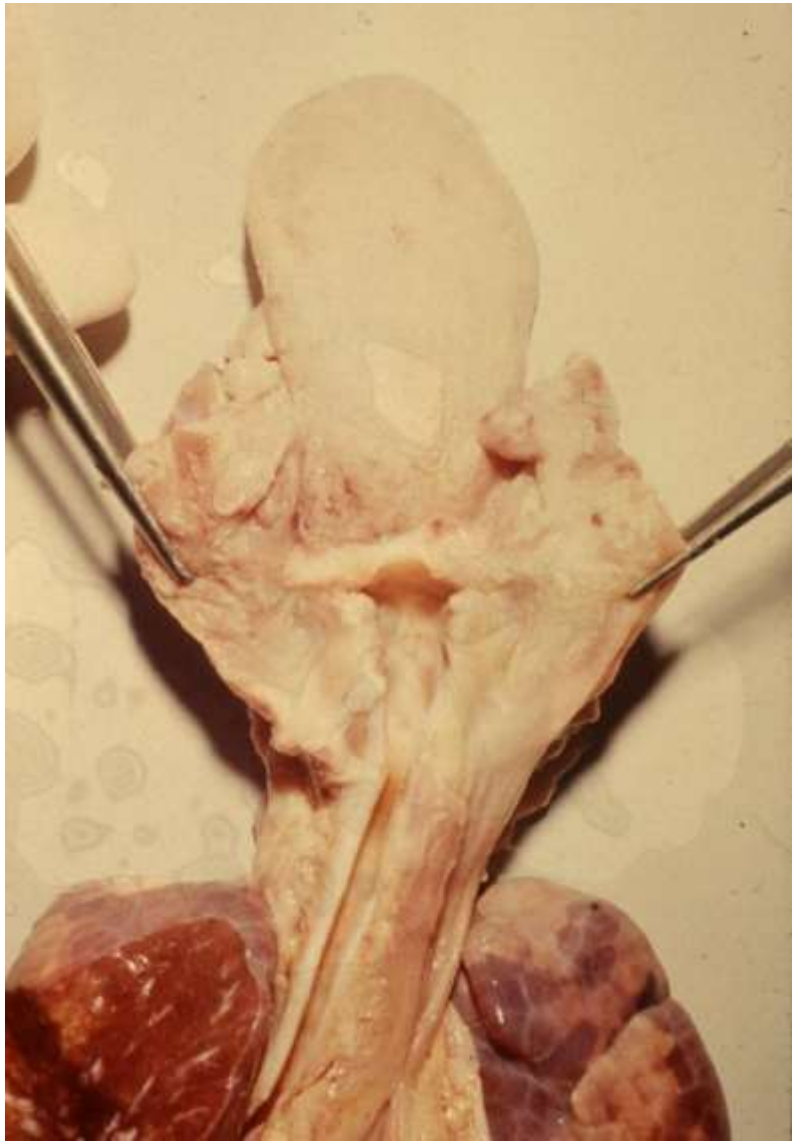
Multifactorial inheritance

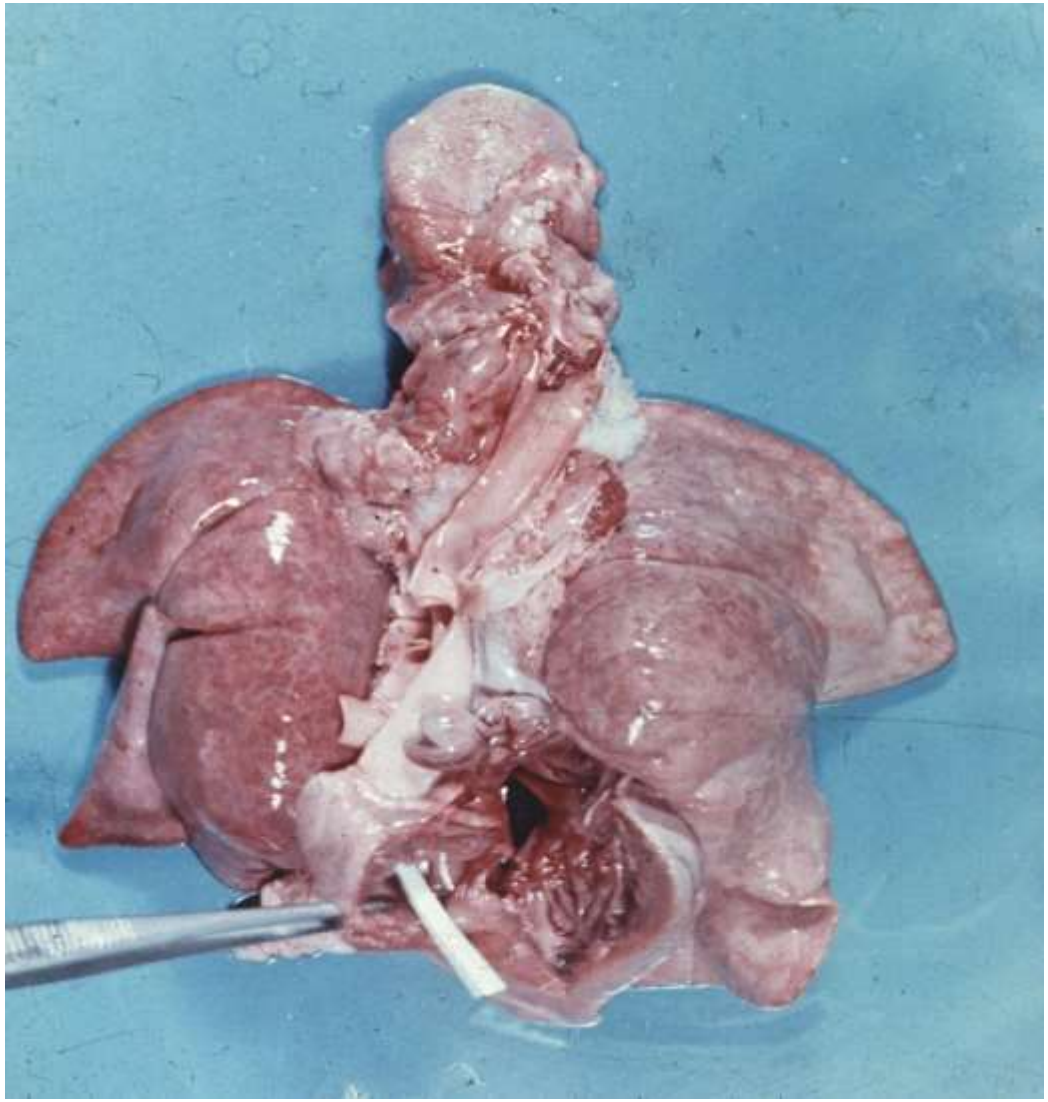
- joint effect of several (several hundred) genes (minor genes), together with exogenous factors
- different appearance in twins
- similar apperance compared to the autosomal diseases with low penetrance

Multifactorially inherited "diseases"

- Figure, color of skin and hair
- blood pressure, arteriosclerosis, diabetes mellitus type II.
- connatal dislocation of the hip, cleft lip (hare-lip), cleft palate, heart septum defects, pylorus stenosis, neurogenous closing defects, club-foot (pes equinovarus)





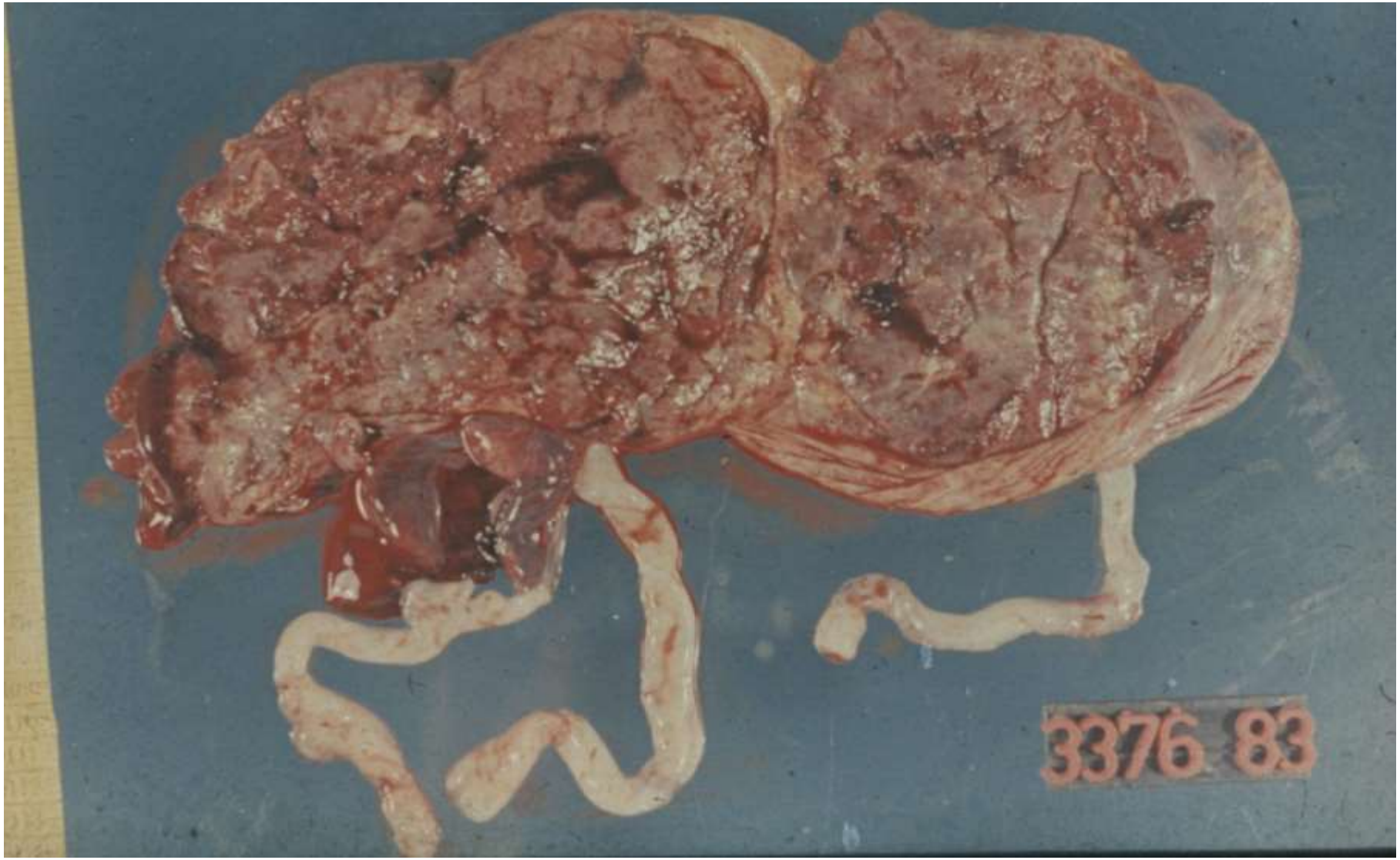


Diseases associated with mitochondrial DNA

- Disease is inherited from the mother.
- all of the children of the diseased mother are sick, depending on the mitochondrial heterogeneity
- a few diseases are known, mostly affecting the eyes, brain and muscles
  - → Kearns-Sayre syndrome
  - → Inheritable neuropathy of Leber

Environmental faktors

- according to the time of effect:
  - → Gametopathy: before fertilization
  - → Blastopathy: 0.-15. days
  - → Embryopathy: 16.-75. days
  - → Fetopathy: 75. day-birth
- Factors of influence:
  - → Infection
  - → chemicals, mutagens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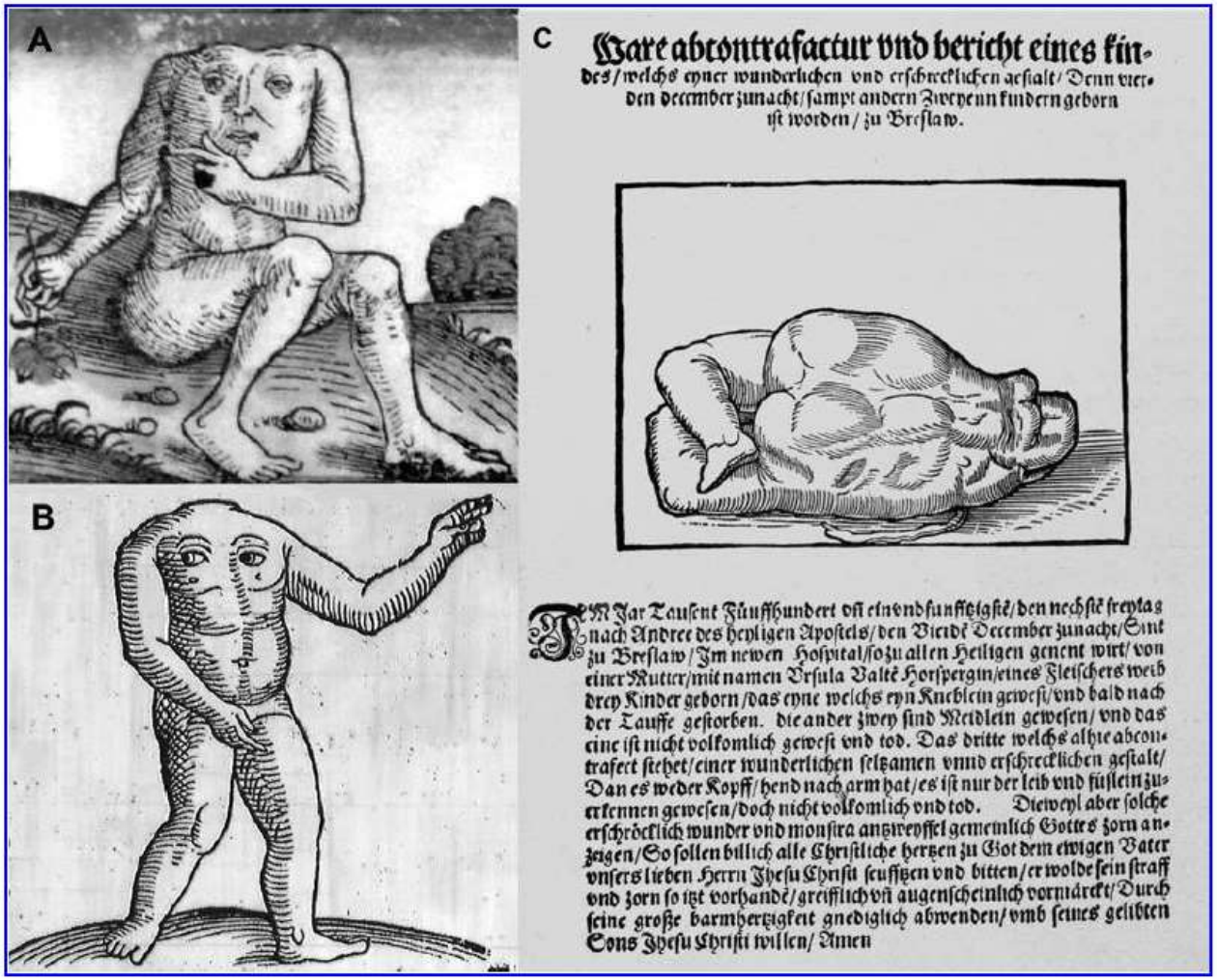


Figure 1 Pre-scientific accounts of acranius as a moral warning. (A) ''Headless blemmye'' from Schedel's Weltchronik 1493 [39]; (B) ''Brustbutzen'' from Lycosthenes' marvelous wonders 1557 [22]; (C) ''Frightening prodigy'' from a Breslau leaflet 1551, see text for details [17].

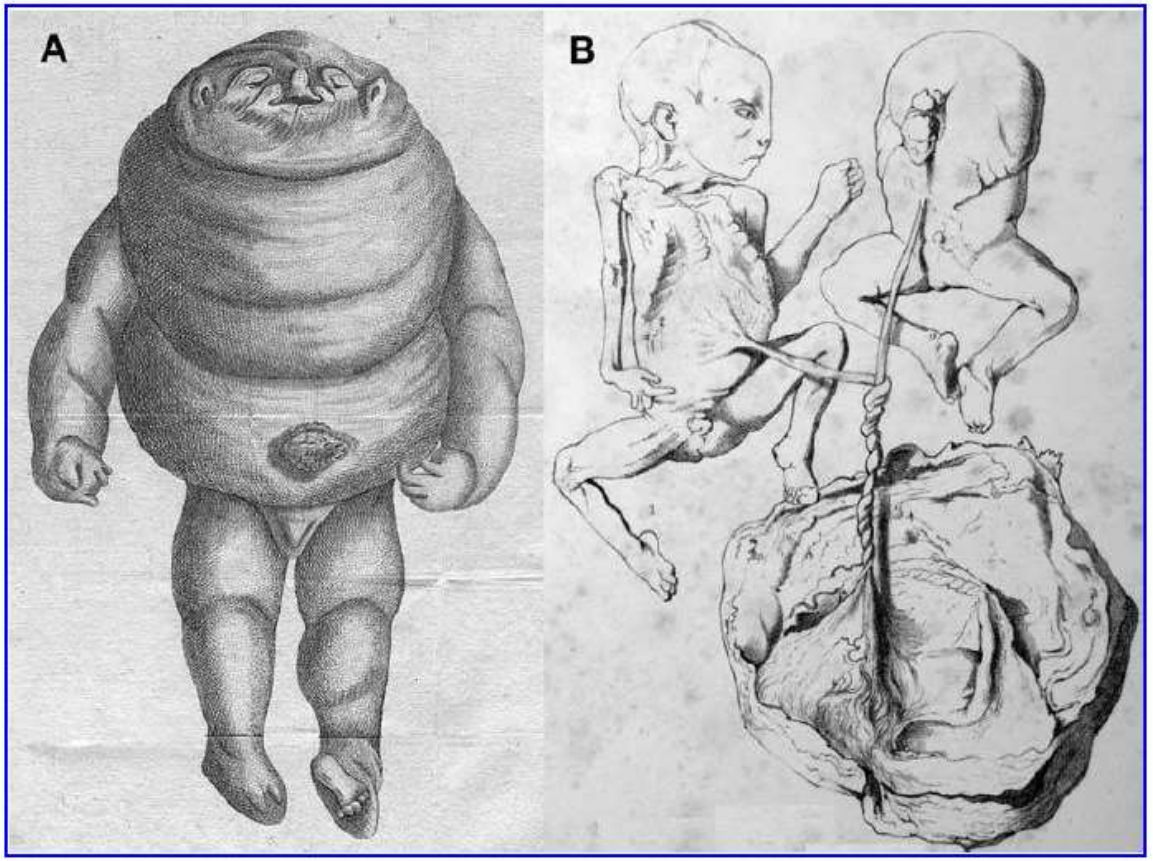


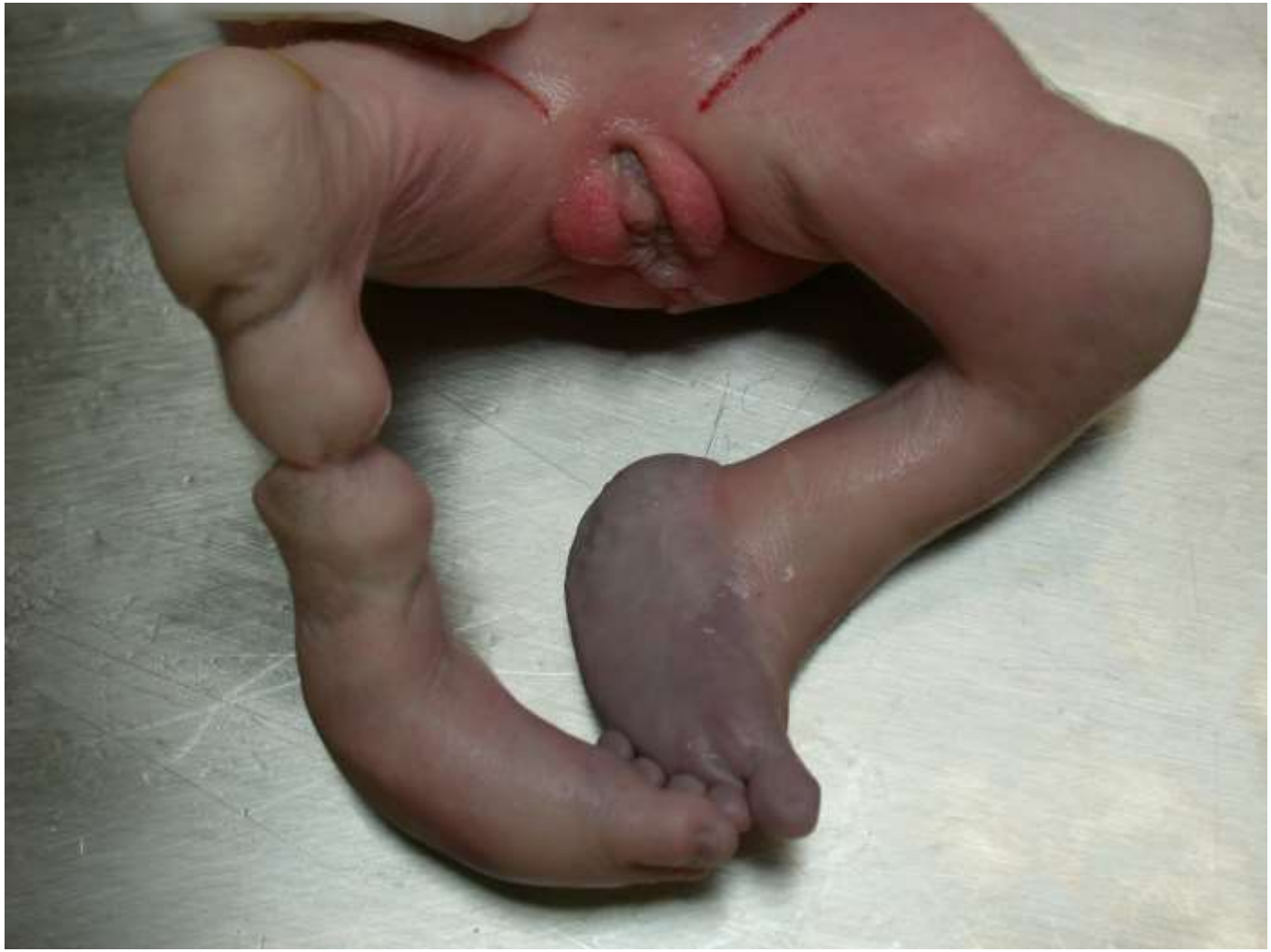
Figure 2 (A) Hydropic acardius anceps ''larger and heavier than the accompanying twins'', described by Kähler 1777 [18], (B) acardius acranius with twisted cord depicted by Ahlfeld 1882 to ''illustrate the connection of the acardiacus with his twin brother and the placenta'' [1].

Teratology- teratogenesis

- Teratogenesis is a deformed development - resulting teratoids (monstert) because of environmental effects
- Forms:
  - → Isolated deformations (one organcomplex is most frequently affected)
    - » malformations
    - » deformations
    - » dysruptions
    - » Sequences
  - → several developmental disorders

Malformations

- congenital dislocation of the hip
- club-foot (pes equinovarus)
- hare-lip (cheiloschisis)
- cleft-palate (palatoschisis)
- heart septum defects
- congenital pylorus stenosis
- neurogenous closing defects

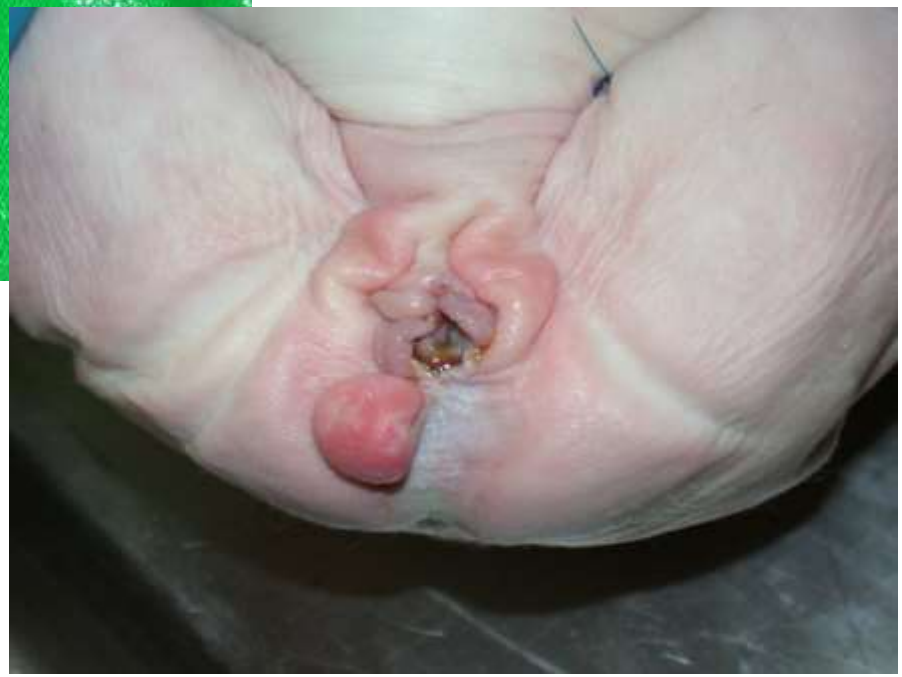


Club foot
Anus atresia
Dysruption – groove
by amniotic band

Deformations

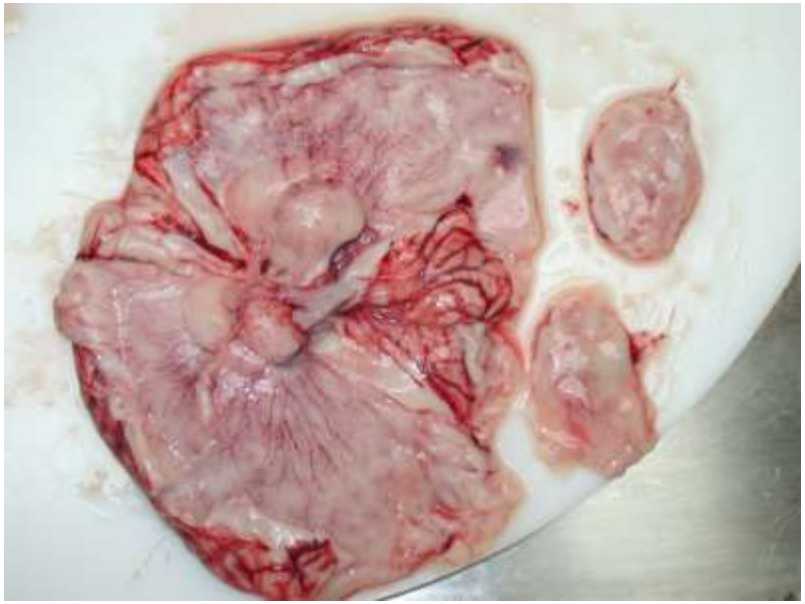
- locomotor **apparatus is most frequently involved**
- **Reason:**
  - →disproportion of space (oligohydramnion, twin pregnancy)
  - → disorders of motoric innervation, central defekts
  - → inherited dystrophy of the muscles

anus atresia



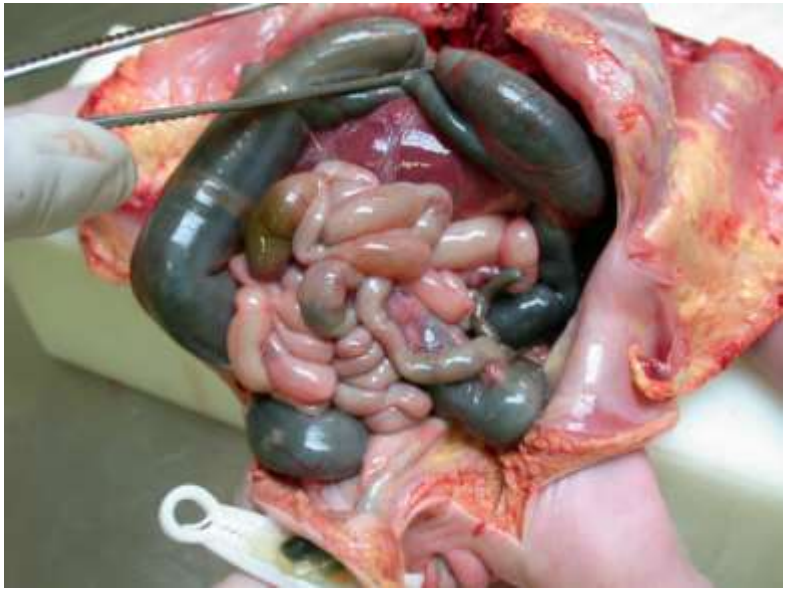
Dysruptions

- Development of deformity because of total or partial damage of one organ after full development of the organs
- Reason:
  - → compressed by amniotic band
  - → intrauterine closure of a vessel and following infarction
    - » atresias, porencephaly

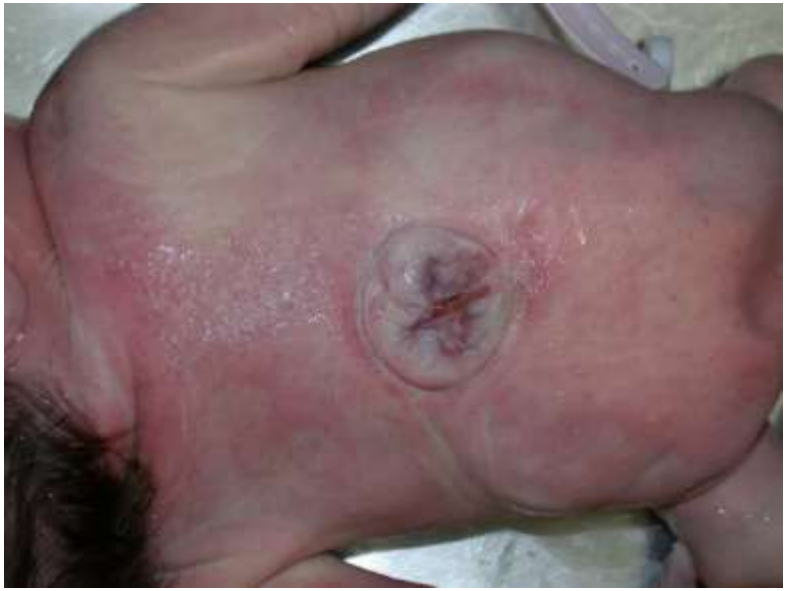


Hydrocephalus internus

Meningocele, spina bifida



atresias

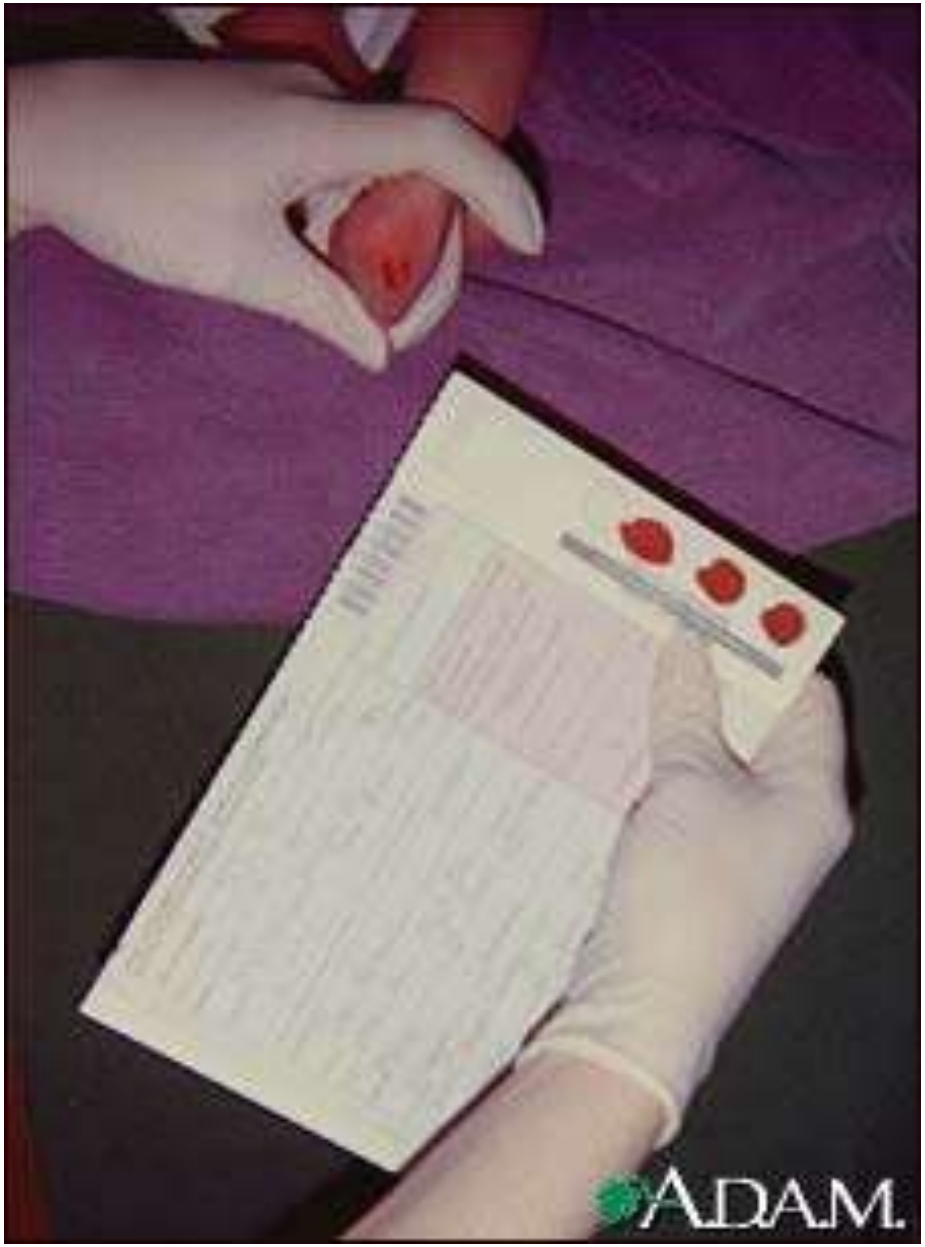


multiple developmental disorders

- two or several ogansystems are involved, the ethiology of the damage is the same
- Reason:
  - → Infection (TORCH complex, varicella)
  - → Chemicals
  - → Aberration of chromosoms
  - → e.g.: rubella (German measles) syndrom, fetal alcohol (consumption) syndrom, thalidomide (Contergan)

Diagnosis of the developmental disorders

- Prenatal Diagnostics - Prevention
  - → Ultrasonography, AFP, analysis of blood of the mother (non-invasive Methods)
  - → Definitive genetic diagnosis (invasive Methods)
    - » Amniocentesis
    - » Chorion biopsy
    - » Embryo Skin biopsy
- Necessary to perform:
  - » older mother
  - » parents are carrier of diseased genes or chromosomes
  - » previous pregnany with malformations



Diagnosis

Postnatal screening

Routine tests: cystic fibrosis, phenylketonuria, kretenism, galactosaemia

Diagnosis of developmental disorders

- Pre und postnatal prevention

- Routine clinical tests: Cystic fibrosis, phenylketonuria, cretenism, galactosaemia

  → further tests: in case of visible disorders, not explained underdevelopment or mental retardation specific genetic tests are necessary/recommended

Therapy

- Prenatal therapy
  - → abortions, induction of birth
  - → Intrauterine surgery
- Postnatal therapy
  - → treatment of symptoms
  - → gene therapy („gene-surgery”)
    - DNA viral or retroviral vectors