Chromosomal aberrations and their influence on the development

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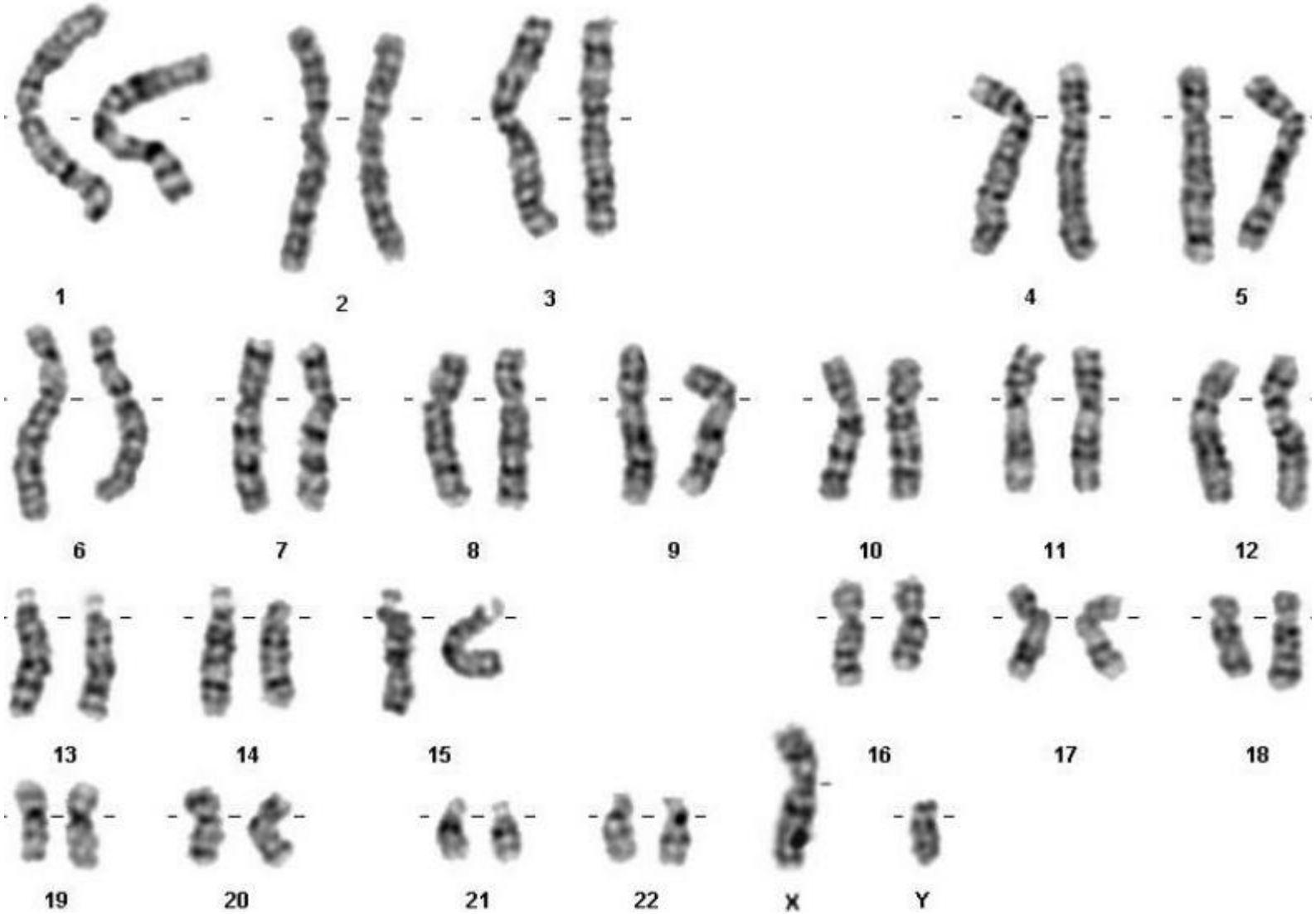


slide4-l.jpg (1024×768) (slideserve.com)

≈ 78 % of all conceptions are aborted; 15 – 20 % of diagnosed pregnancies and not carried to term;

50 % of early stage abortions displays abnormal karyotype

Chromosomal aberrations:

autosomal x gonosomal

non-mosaic x mosaic

Numeric

- trisomy
- monosomy
- polyploidy
- uniparental disomy (UPD)

Structural

Balanced:

- inversion
- translocation
- insertion

Unbalanced:

- duplications
- deletions
- dicentric chromosome
- acentric chromosome
- isochromosome
- ring chromosome
- marker chromosome
- complex rearrangements

Chromosomal aberrations:

1. Numeric

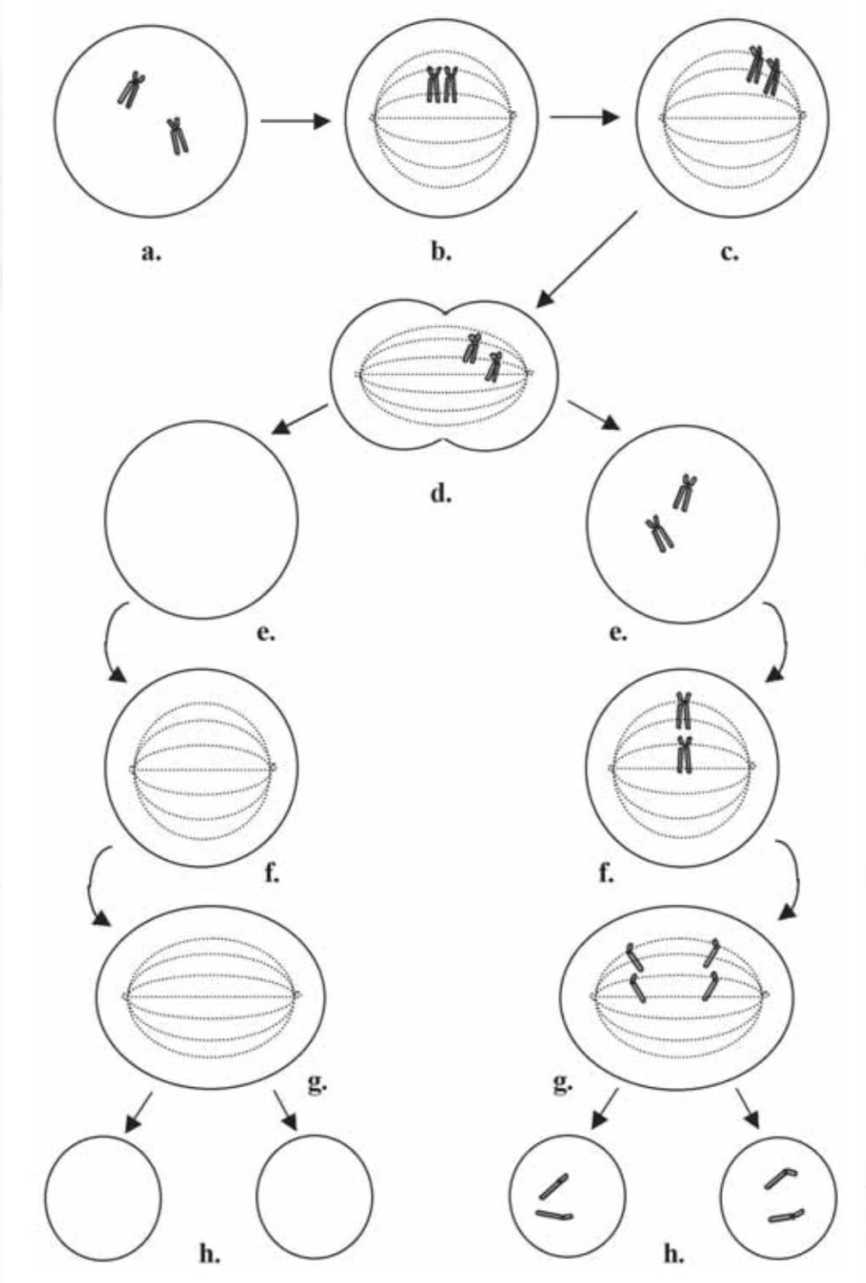
- *autosomal aneuploidies* – 0,2 % live births,
  up to 30 % in spontaneous abortions;
  constitute more than 90 % of all aberrations in oocytes
  and less than 50 % in sperms

Trisomy – all of the autosomes except for 1 a 11 (!!!) in liveborns
which are the most common ones???
frequency of the occurrence at the conception is the same for all autosomes

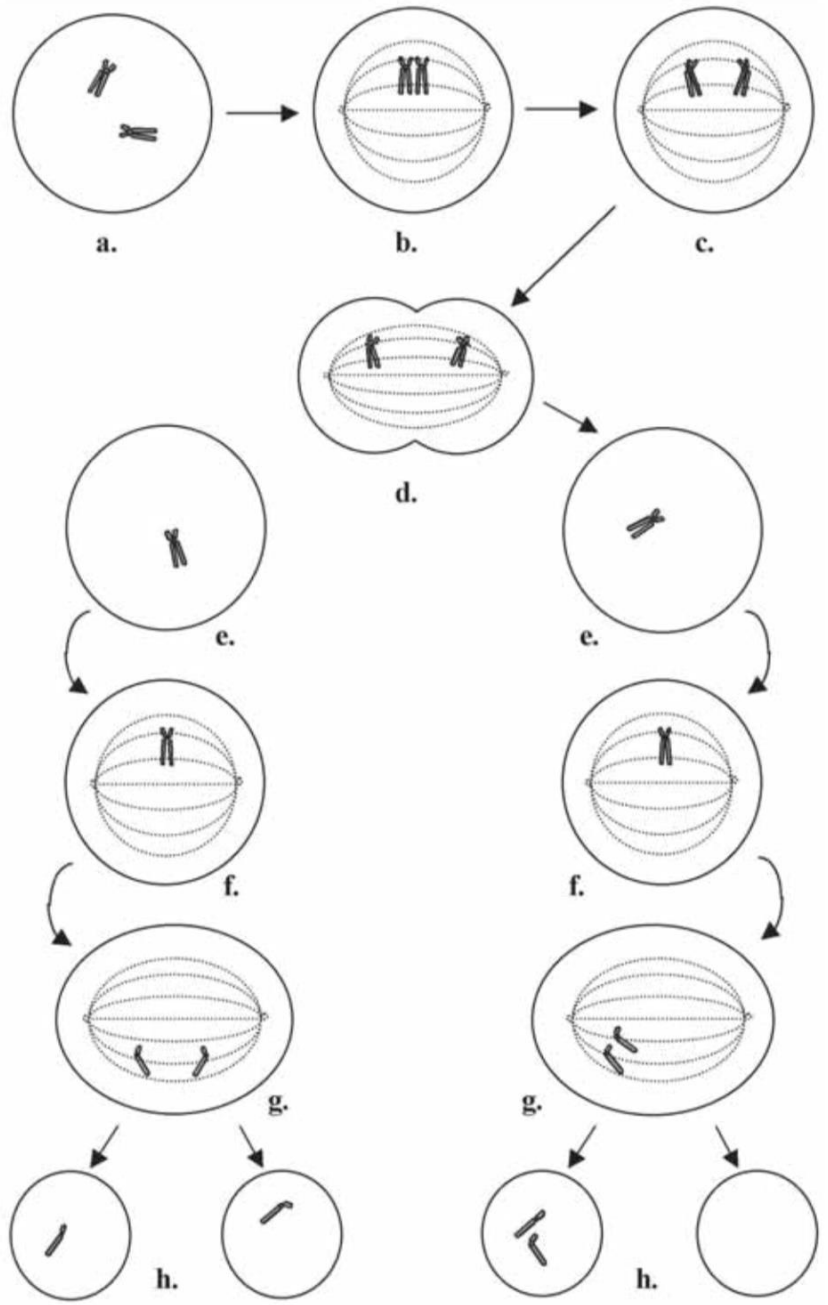
Unisomy, nullisomy – incompatible with life

Uniparental disomy

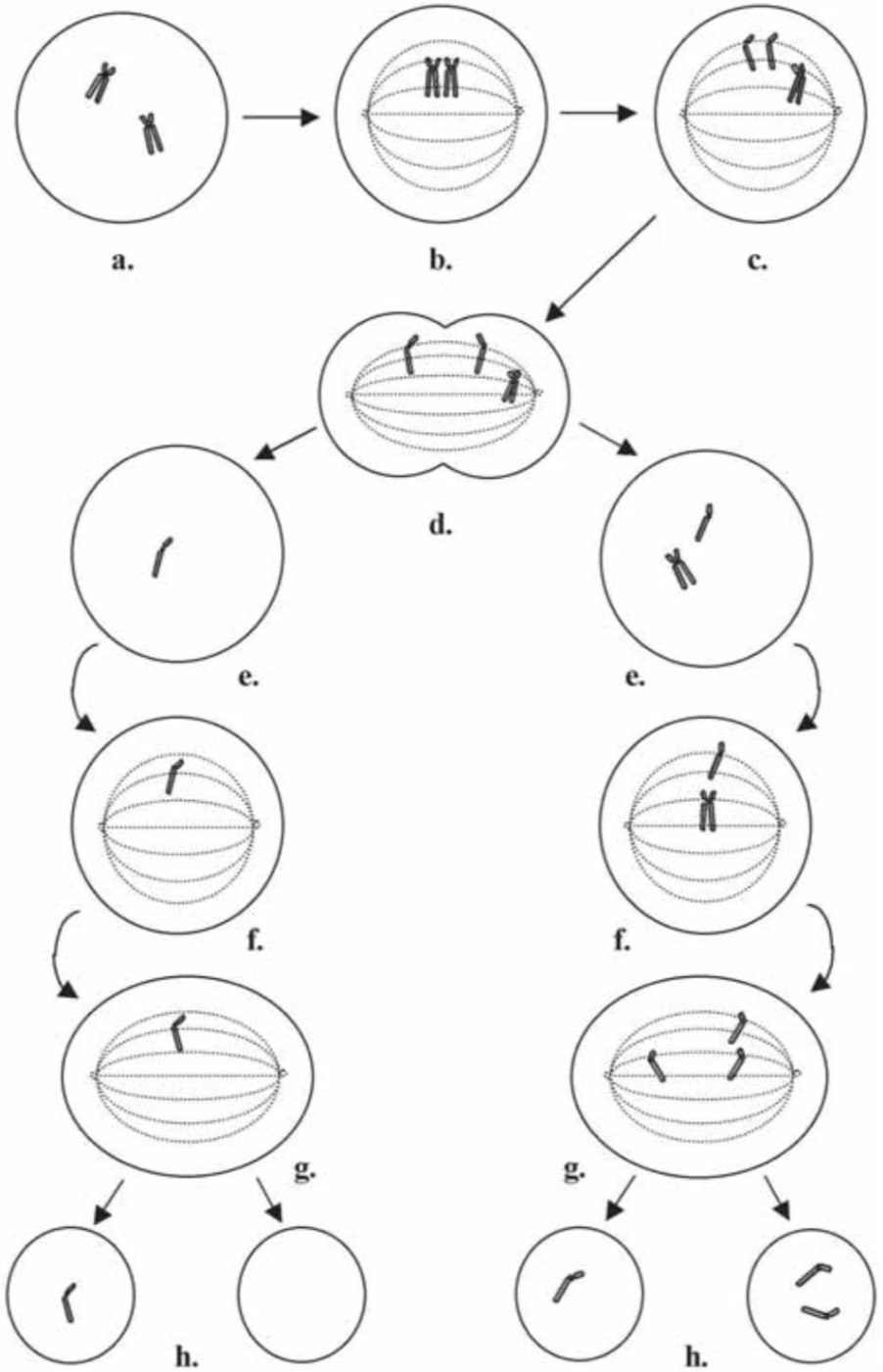
Nondisjunction I



Nondisjunction II



Premature separation of sister chromatids

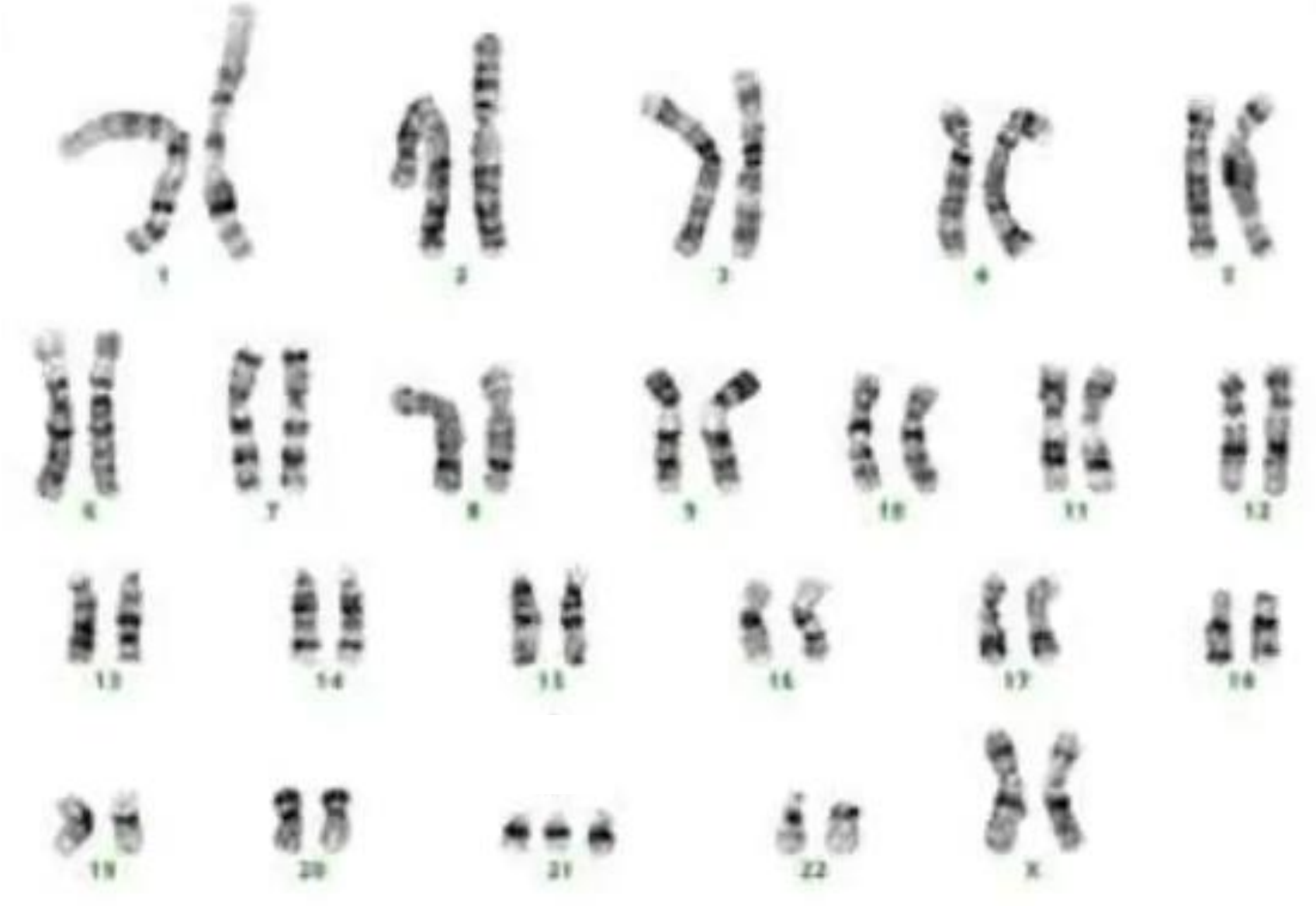


- *polyploidy* – triploidy (diandry/digyny): app. 1 % of all conceptions, 17-18 % of chromosomal aberrations in miscarriages; 50 described cases of live births (10 month the longest)

- tetraploidy: 6 -7 % chromosomal aberrations in miscarriages; 8 described cases of live births (22 months the longest)

- *partial autosomal aneuploidies* – presence of a supranumerary isochromosome [47,XX or XY,+i(5)(p10)] or marker (0,7 % live births; 40 % of all markers are comprised of 2 copies of a short arm of chromosome 15 with different amount of material from the long arm)

[47,XX or XY,+21]

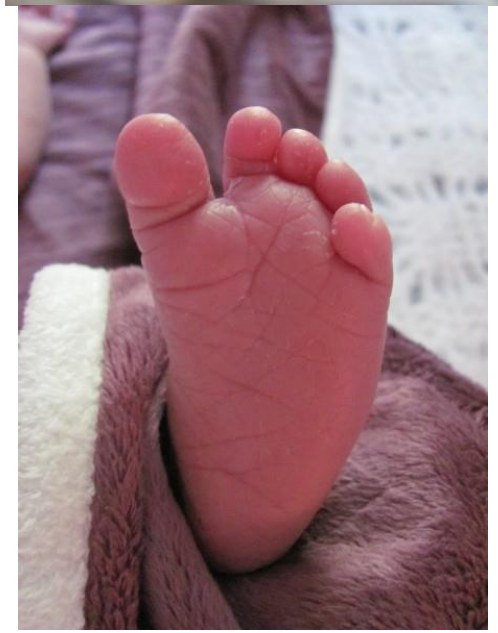


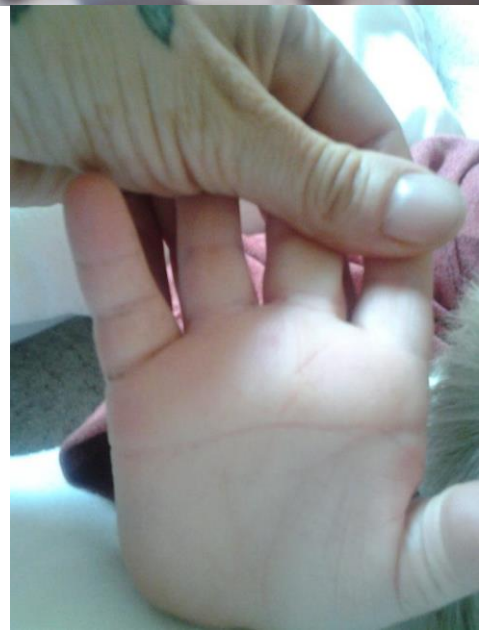
[47,XX or XY,+21]

- constitutes 95 % of Down syndrome cases (remaining 5 % - mosaics or Robertsonian translocation); 1,2:1 males:females
- hypotonicity
- up to 50 % of patients with congenital cardiovascular defect!

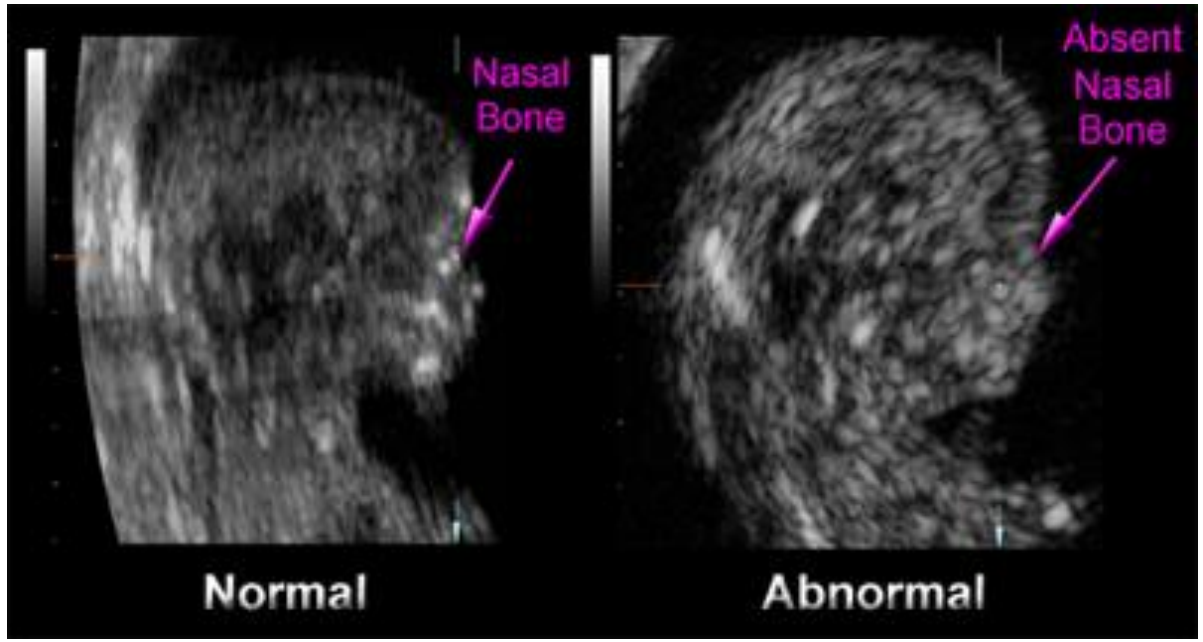
  atrioventricular canal defect, ASD, persisting ductus arteriosus
- duodenal atresia, pancreas annulare, megacolon, cataract
- 10 to 20 times higher leukemia incidence

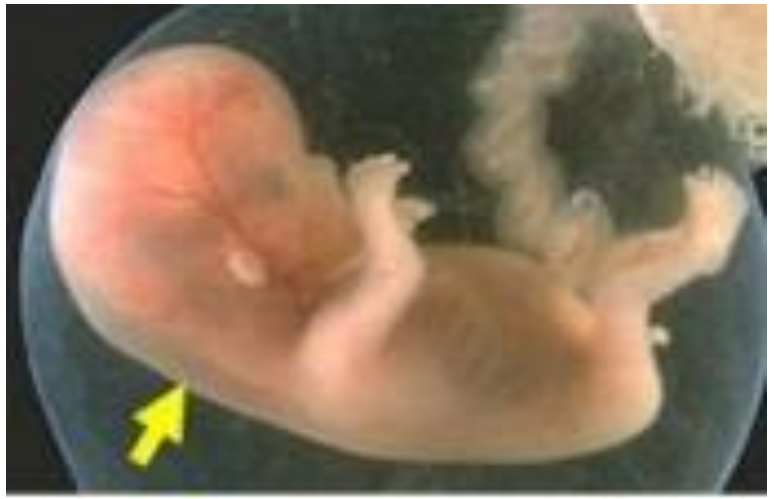
[47,XX or XY,+21]

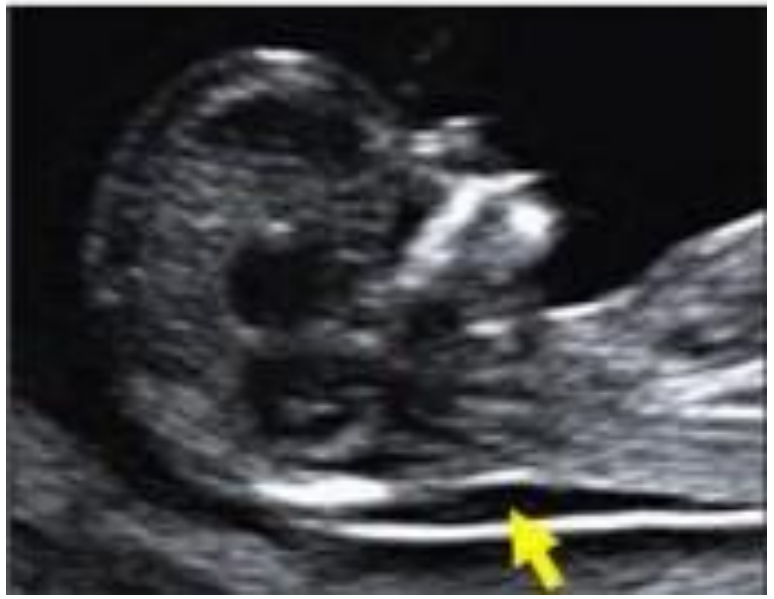


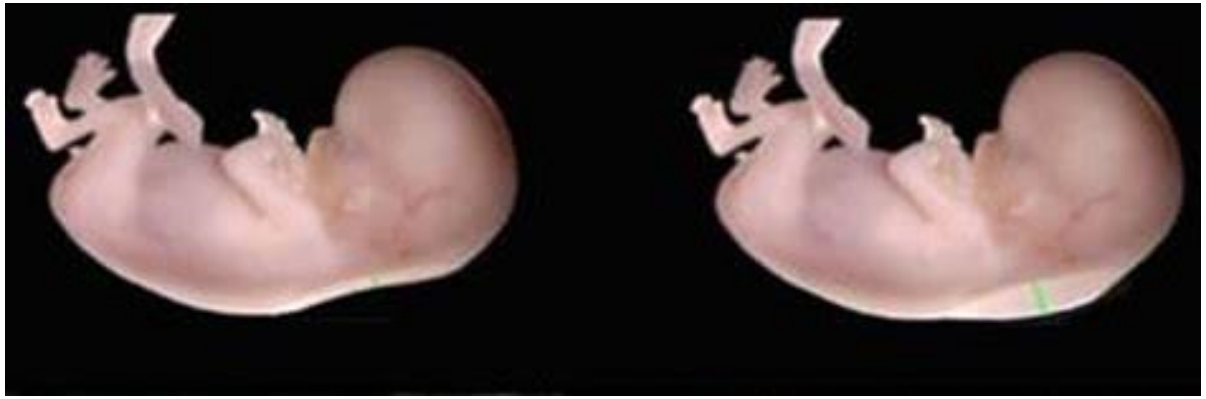


[47,XX or XY,+21]

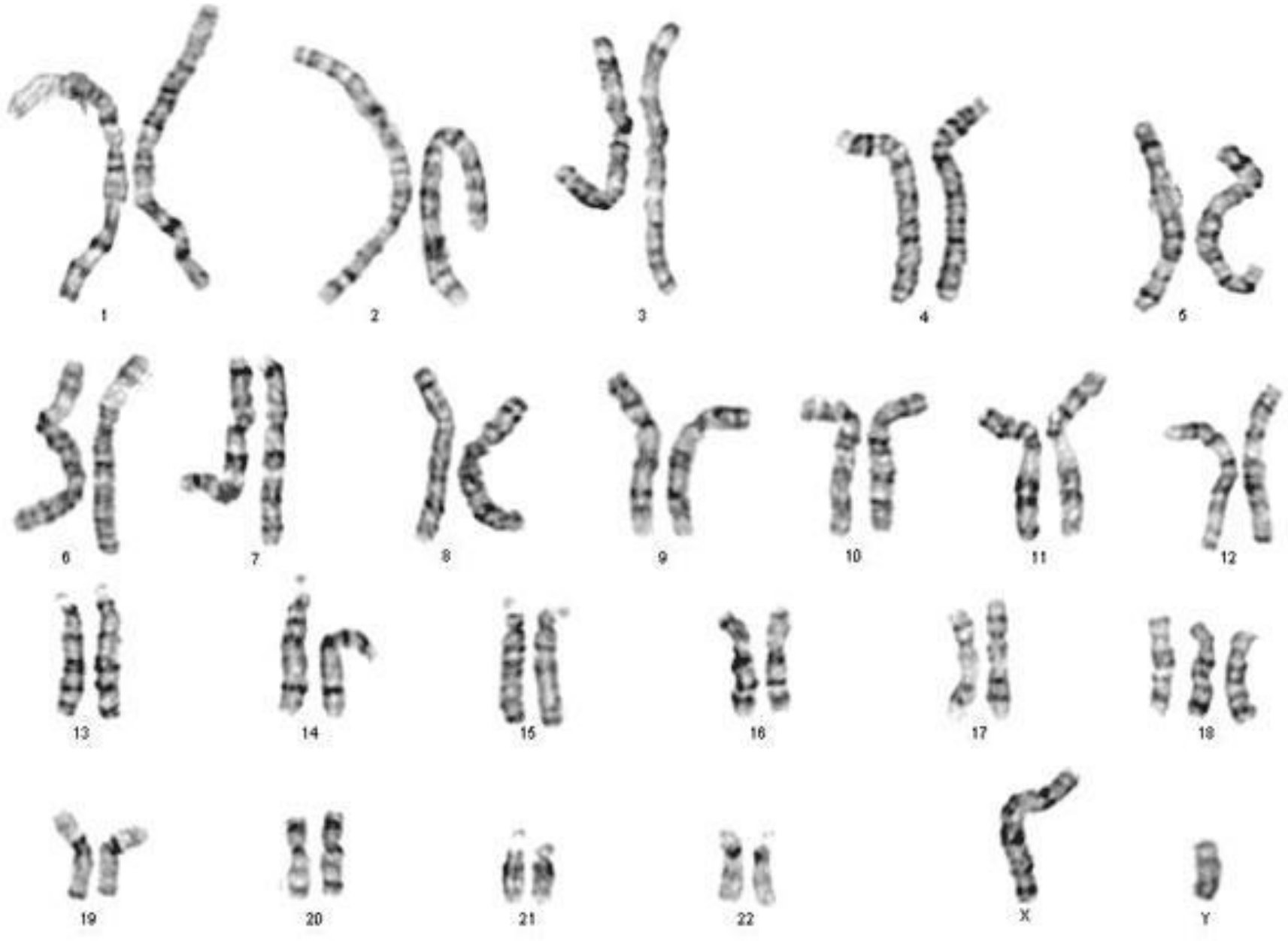






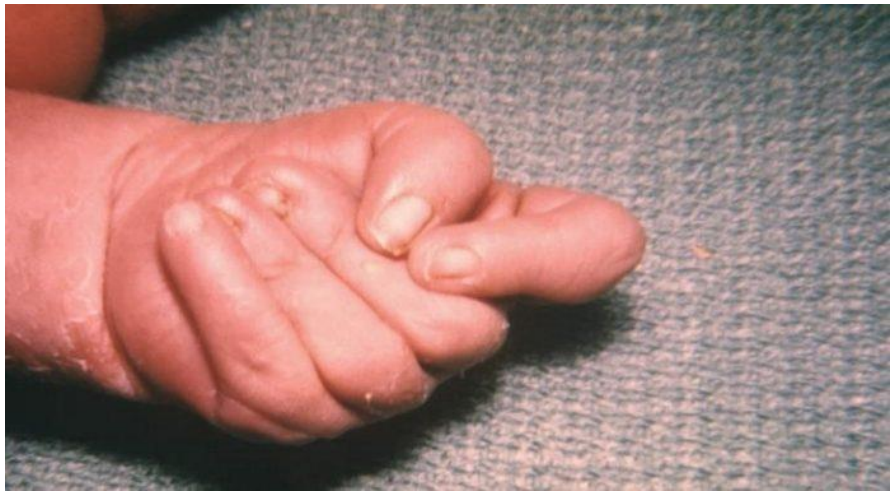


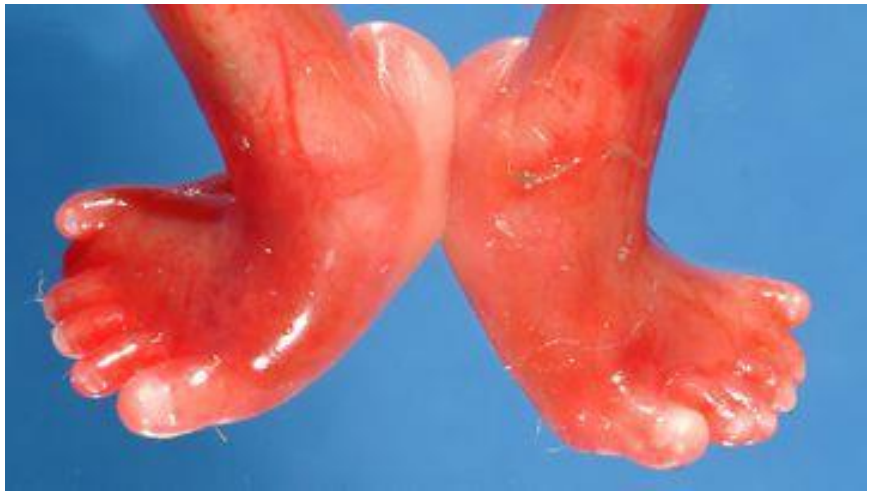
[47,XX or XY,+18]



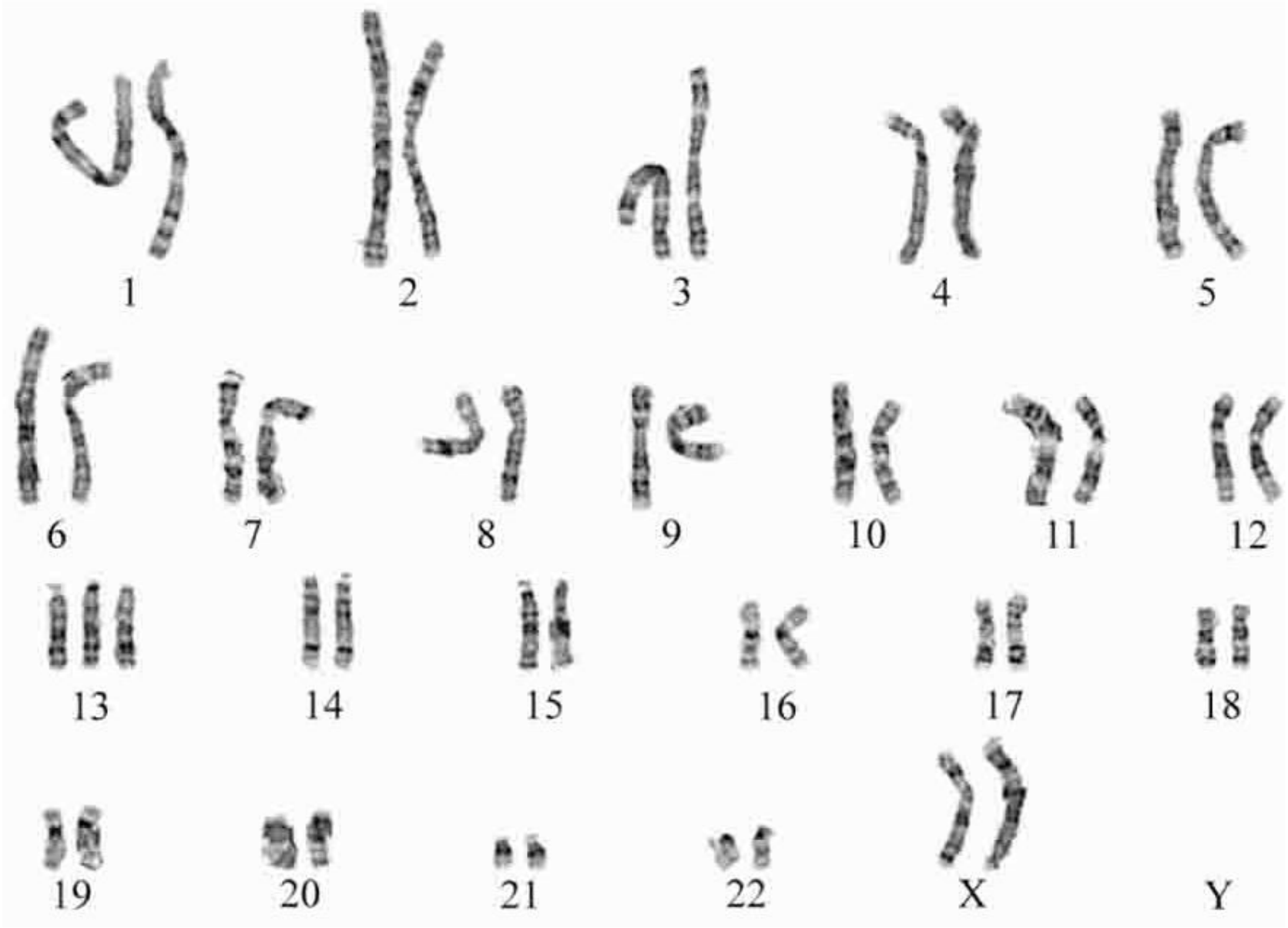
[47,XX or XY,+18]

- 1:3-4 males:females
- hypotonicity with following hypertonicity
- VSD, ASD, persisting ductus arteriosus
- hernia, one umbilical artery, cryptorchidism, short sternum, congenital vertical talus, micrognathia, narrow bifrontal diameter…
- median survival is app. 5 days, only 10 % of patients reaches 1 year



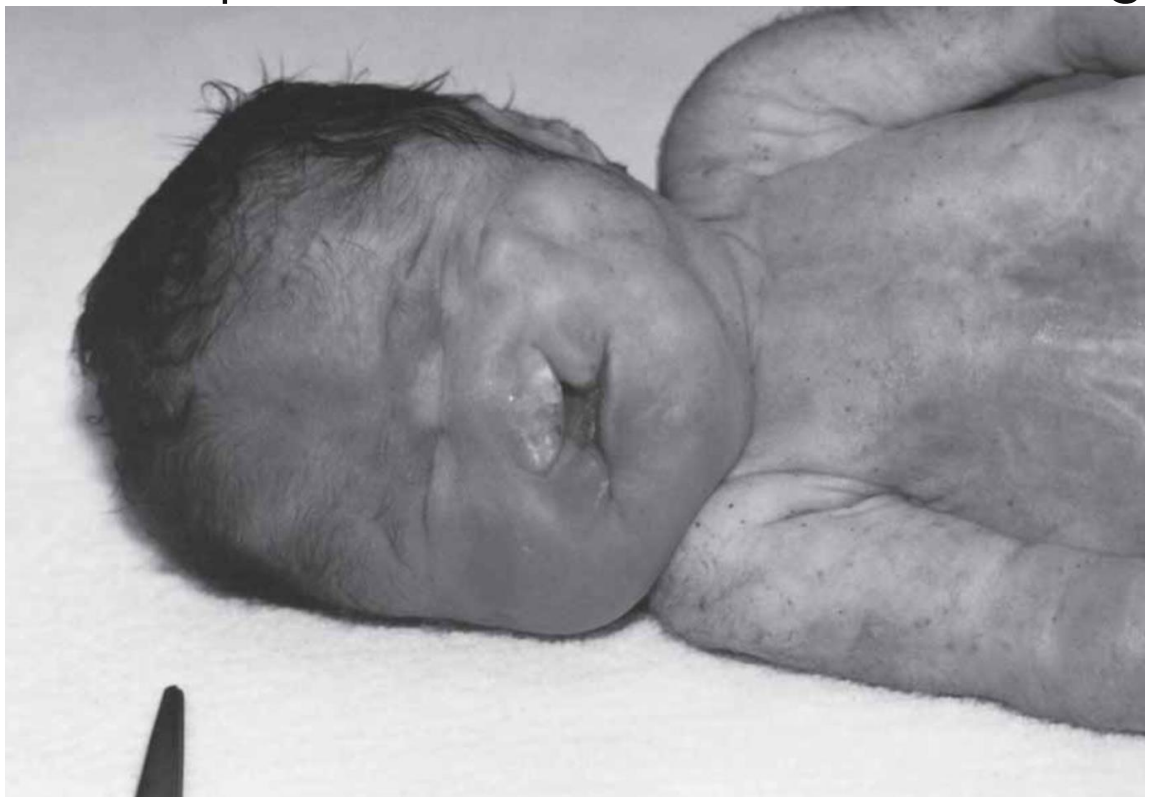


[47,XX nebo XY,+13]



[47,XX or XY,+13]

- holoprosencephaly
- hernia, one umbilical artery, cryptorchidism, uterus bicornus, polycystic kidney
- congenital heart defects in 80 % patients
- median survival is 2,5 days, only 5 % of patients reaches 6 months of age



Chromosomal aberrations:

2. Structural

- 75 % of structural aberrations are of paternal origin!!!

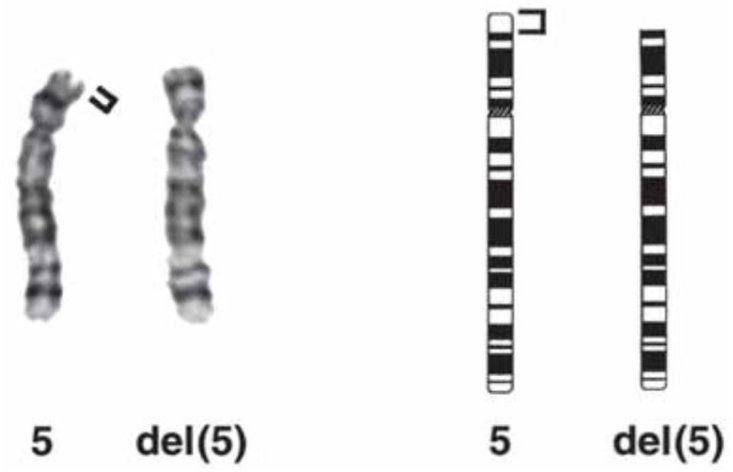
(exceptions: de novo non-homologous Robertsonian translocation and terminal deletion of the short arm of the chromosome 1)

- rare in mosaic form

- limitations of the classic cytogenetics (G-band+microscope) – maximum resolution is 2-5 Mb, there for implementation of a molecular cytogenetic methods (FISH, CGH)

Deletions

- [46,XX or XY,del(5)(p15.3)] [46,XX or XY,del(13)(q21.3q33)]
- terminal vs. interstitial
- resulting in monosomy; the phenotype depends on the size of the deletion and the quality of the material; (loss of the material of the short arms of acrocentric chromosomes or heterochromatin does not affect the phenotype)

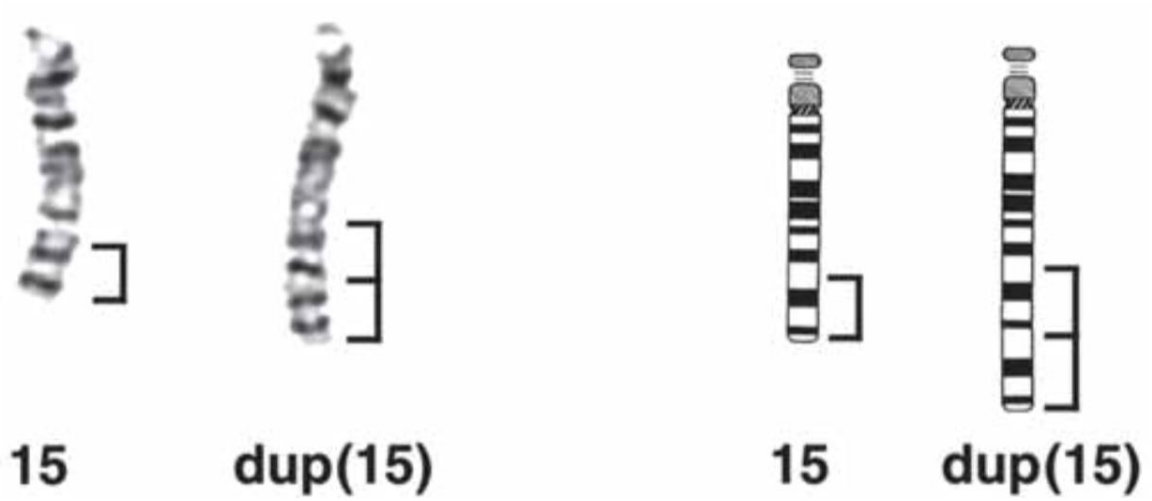


Deletions

- Cri du chat – 5p – cat like cry, growth and mental retardation, microcephaly
- Angelman syndrome – maternal deletion of 15q11-15q13 (or UPD!!!) – mental and growth retardation, inappropriate laughter, seizures
- Prader-Willi – paternal deletion of 15q11-15q13 (or UPD!!!) – mental and growth retardation, obesity – hyperphagia, hypogonadism
- DiGeorge/velocardiofacial syndrome – 22q11.2 – learning disabilities, cleft palate, velopharyngeal incompetence, conotruncal heart defects
- Ichtyosis (X-linked) – Xp22.3 – typically not apparent using traditional cytogenetics

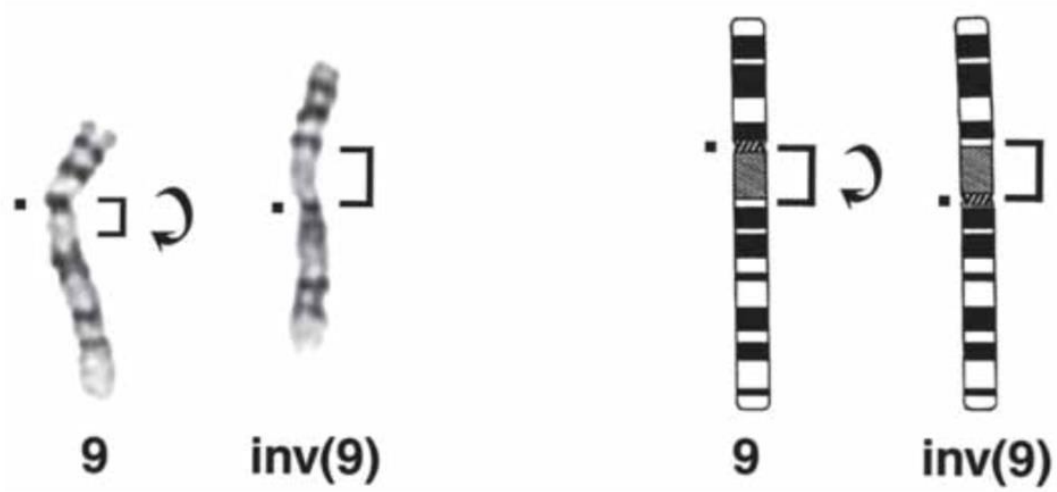
Duplications

- [46,XX or XY,dup(15)(q24q26.3)]
- direct vs. inverted
- „pure duplication“ vs. in combination with other rearrangement: isochomosome, dicentric chromosome, marker…
- results in partial trisomy



Inversions

- [46,XX or XY,inv(2)(p21q31)] vs. [46,XX or XY,inv(3)(q21q27)]
- pericentric vs. paracentric
- in 85-90 % of parents of patients with inversions inversion is found upon cytogenetic examination, there for inversions are inherited
- common underlying cause of infertility



All of the most common chromosomal syndromes and most of the less common have ear anomalies in their characteristics!!! (Langman's medical embryology, T. W. Sadler, 12th edition, p. 328)