Genetic counselling

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Clinical genetics

- Dept. of medical genetics
- Genetic prevention
- Genetic diseases
- Patients
- Chromosome abnormalities
- AD,AR,XR inheritance, disorders
- Prenatal diagnosis
- Reproductive genetics
- Hereditary cancer
- Environmental hazards

Dept. of Medical genetics

- **Genetic counselling**

- **Laboratory part**
- **Cytogenetic lab. (pre- and postnatal)**
- **Oncocytogenetic lab.**
- **Molecular – cytogenetic lab.**
- **Lab. for DNA and RNA analysis (clinical genetics and oncogenetics)**

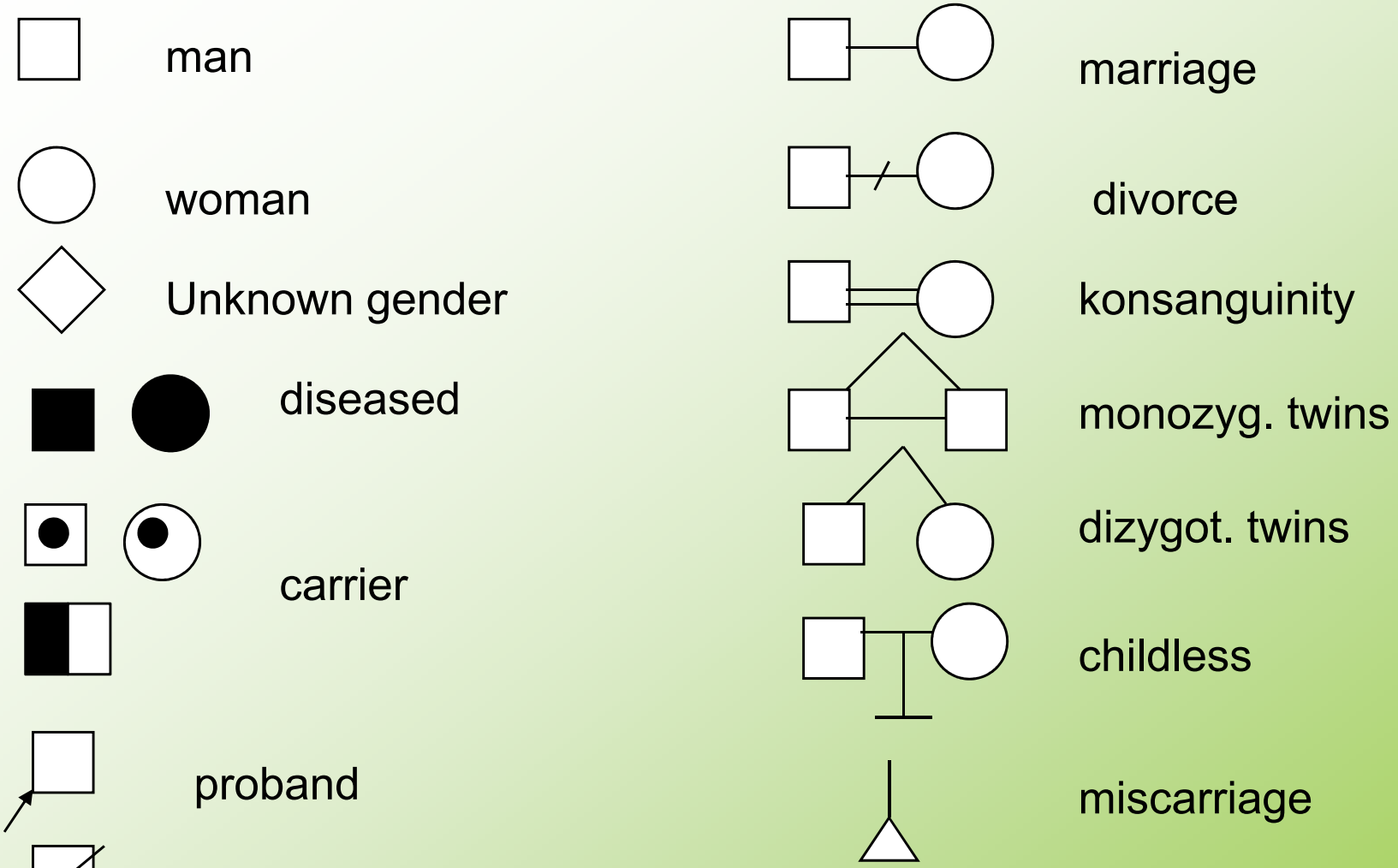
Medical genetics

- Preventive
- Interdisciplinary

- Information from genetics
- Voluntary choice for patients

Genetic counselling

- Family history
- Pedigree analysis
- Examining the patient
- Laboratory analysis
- Other examining - neurology, psychology, hematology, CT, MRI …


man
woman
Unknown gender
diseased
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proband
dead person
marriage
divorce
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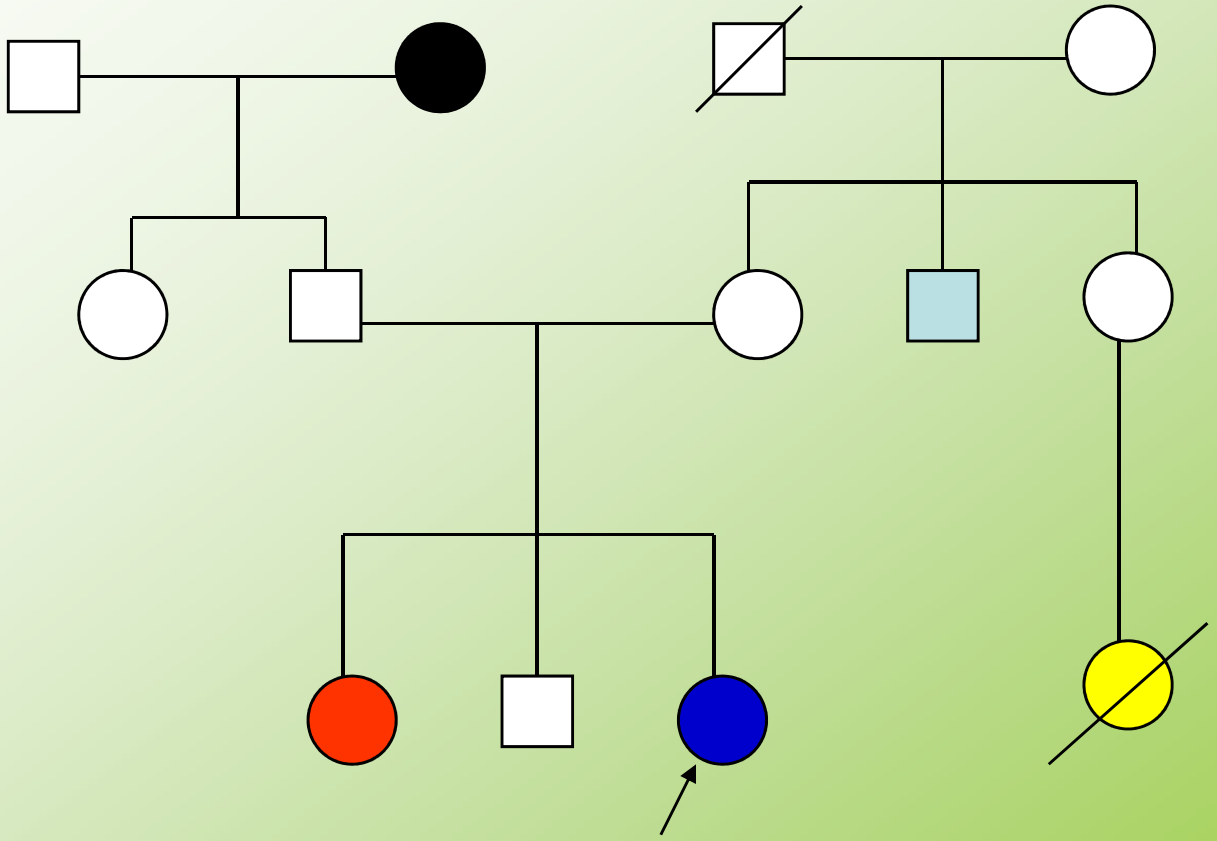
monozyg. twins
dizygot. twins
childless
miscarriage

Pedigree



Cleft lip

Neonatal death

syndaktilie

epilepsie

congenital heart disease

Genetic counselling

- **Exact diagnosis (if possible)**
- **Genetic prognosis**
- **inheritance, genetic risk for family members, treatment, prenatal analysis**

Genetic prevention – I.

- **Before pregnancy**
- **Folic acid (cca 1mg/day, 3+3 months)**
- **Vaccination (rubella)**
- **Genetic counselling**
- **Contraception, adoption**
- **Donor (oocytes, sperm)**
- **Pregnancy planning**
- **Environmental hazards (drugs, radiation, chemicals…)**

Prevention – II.

- **Prenatal diagnosis**
- **Prenatal screening**
- **Genetic counselling**
- **Termination of pregnancy (ČR - end of 24. week of gestation)**

Genetics diseases

- **Chromosome abnormalities – about 0,7%**
- **Monogen diseases – about 0,36% in 1000000 in newborns, most then 90% in childhood**
- **Multifactorial disorders – about 80%**

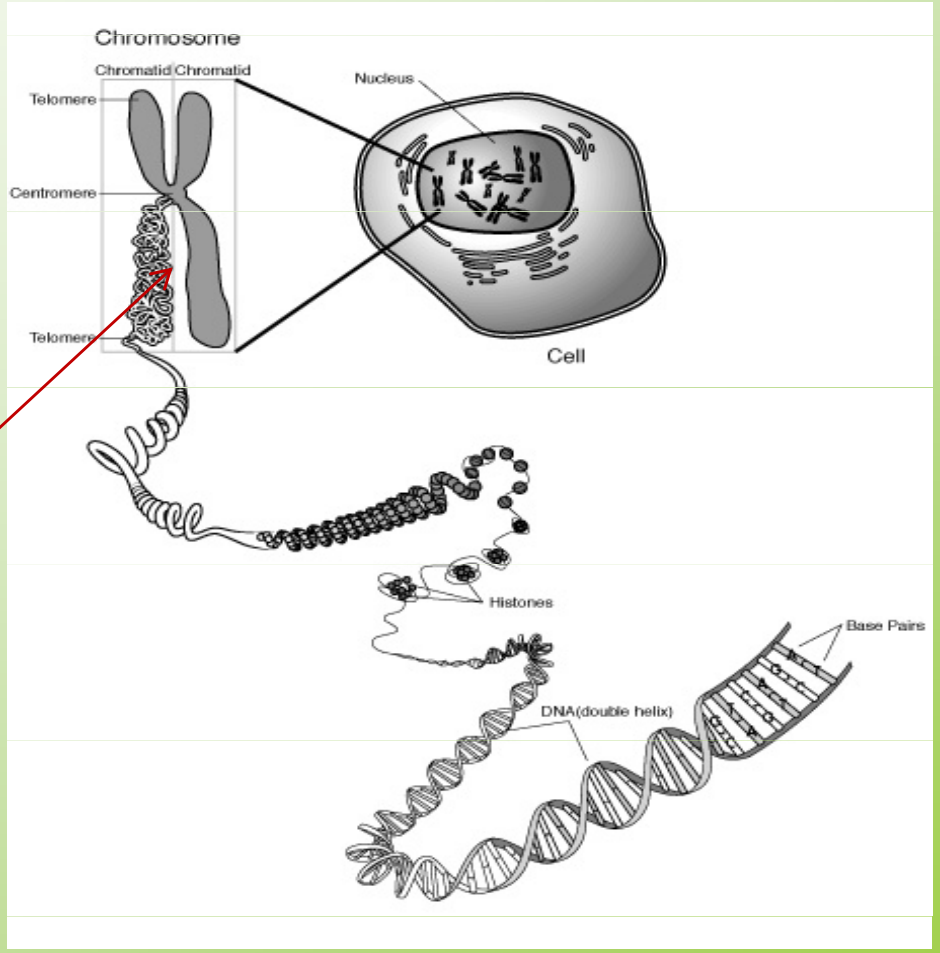
Patients on genetic departements

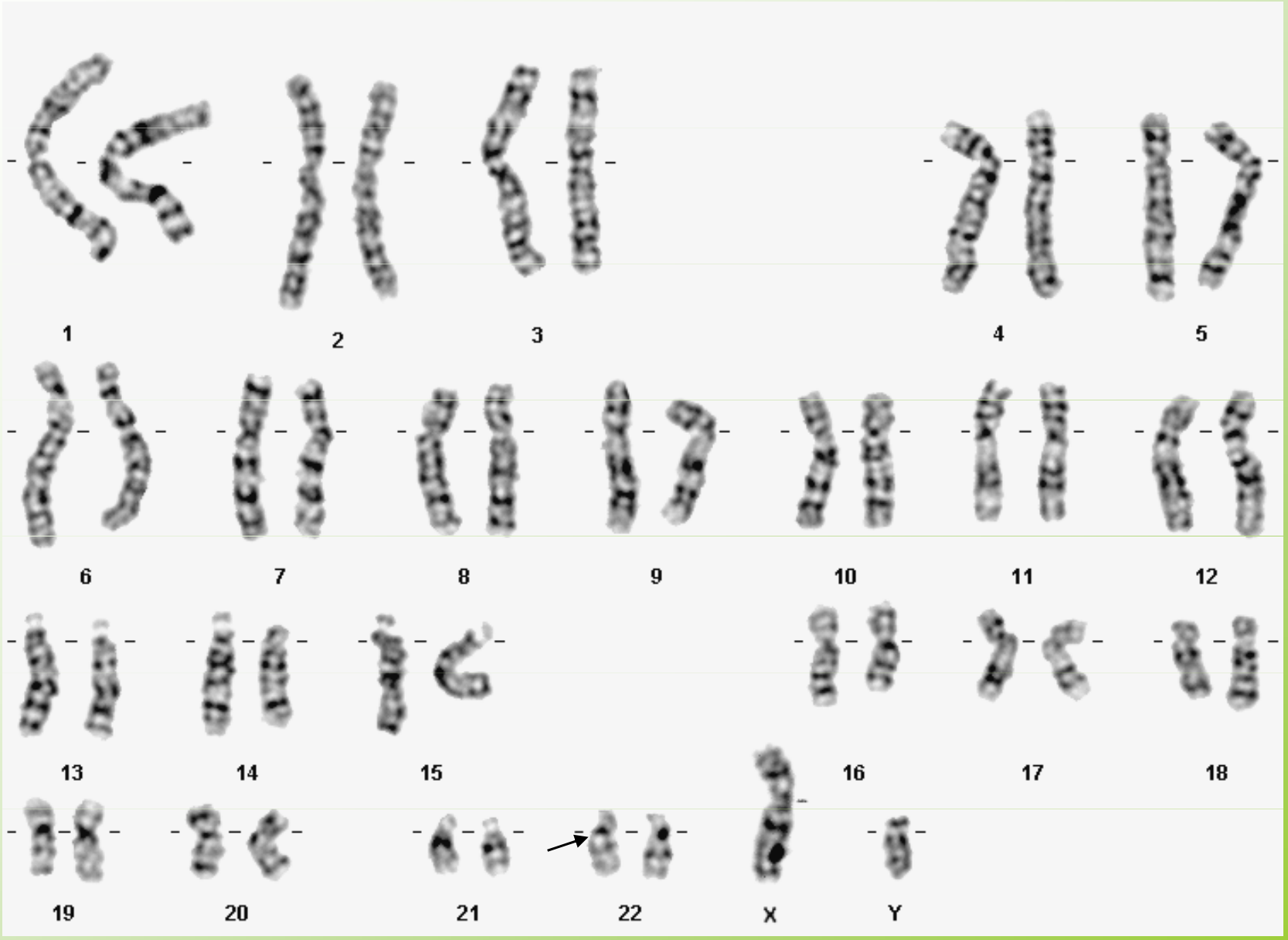
- Dead person
- Adults
- Pregnant women
- Fetuses
- Children

Patients on genetic departements

- Positive family history (chromosome abnormality, congenital malformations, mental retardation, diseases…)
- Pregnant women with encrease risk for the fetus
- Infertility – sterility, repeated fetal loss
- Donors (gametes)
- Patients with tumours

Chromosome abnormalities

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21
22
X
Y

Congenital chromosome abnormalities

- Autosomes
- Gonosomes

- Numerous
- Structural

- Balanced
- Unbalanced

Populations frequency

Trisomy 21	1,5 per 1000 live births
Trisomy 18	0,12
Trisomy 13	0,07
Klinefelter syndrome	1,5
Turner syndrome	0,4
XYY syndrome	1,5
XXX syndrome	0,65

Chromosome abnormalities in spont. abortions

All spont. abortions	50 %
Up to 12 weeks	60 %
12-20 weeks	20 %
stillbirths	5 %
trisomies	52 %
45,X	18 %
Translocations	2 – 4%

Maternal age and chromosome abnormalities in AMC (per 1000)

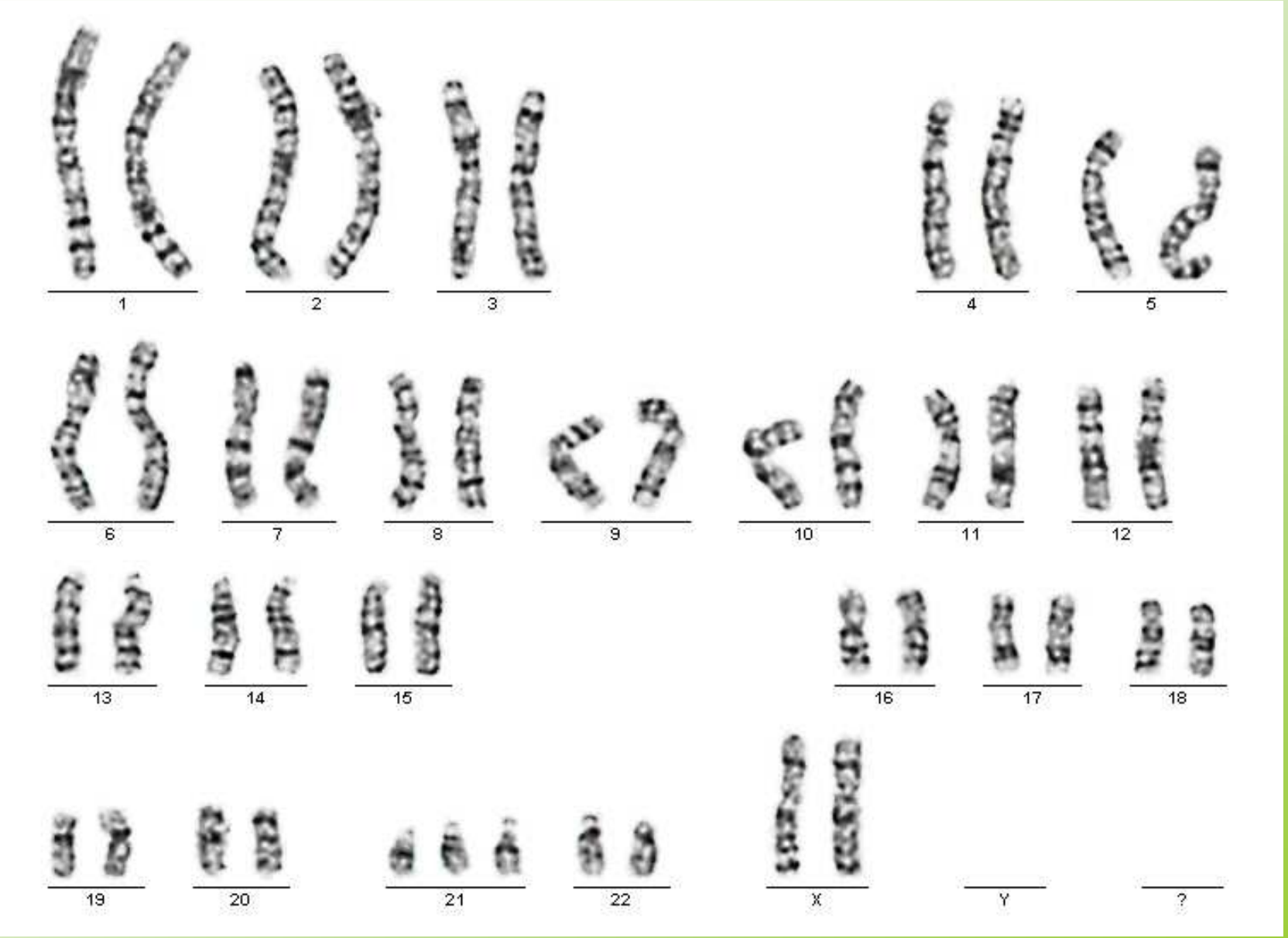
years	+21	+18	+13	XXY	All
35	3,9	0,5	0,2	0,5	8,7
37	6,4	1,0	0,4	0,8	12,2
40	13,3	2,8	1,1	1,8	23,0
43	27,4	7,6		4,1	45,0
45	44,2			7,0	62,0
47	70,4			11,9	96,0

Risk of Down syndrom (live births)

Maternal age (years)	Risk
15	1/1578
25	1/1351
35	1/384
40	1/112
45	1/28
50	1/6

Down syndrome

- 47,XX,+21 or 47,XY,+21
- About 1/800-1000 newborns, 1/75 SA
- Hypotonia, joint laxicity, soft skin, flat face, prominent intercanthal folds, slanted palpebral fissurs, specling of the irides (Brushfield´s spots), small, down set ears, small nose, protruding tongue, simian crease in the hands (about 45%), short statue, mental retardation, congenital heart disease (50%), A-V communis

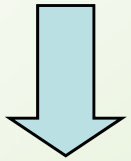
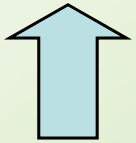
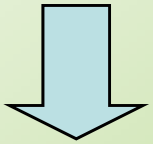


47,XX,+21

+21- prenatal diagnosis

- Ultrasound - 10.-12. week of. gest.
- Nuchal translucency more than 2,5-3 mm
- Absence of nose bone
- I. trimester screening – PAPP-A
- 16. week – AFP, HCG, ue3 – II. trimester screening
- 20. week – congenital heart disease – not all

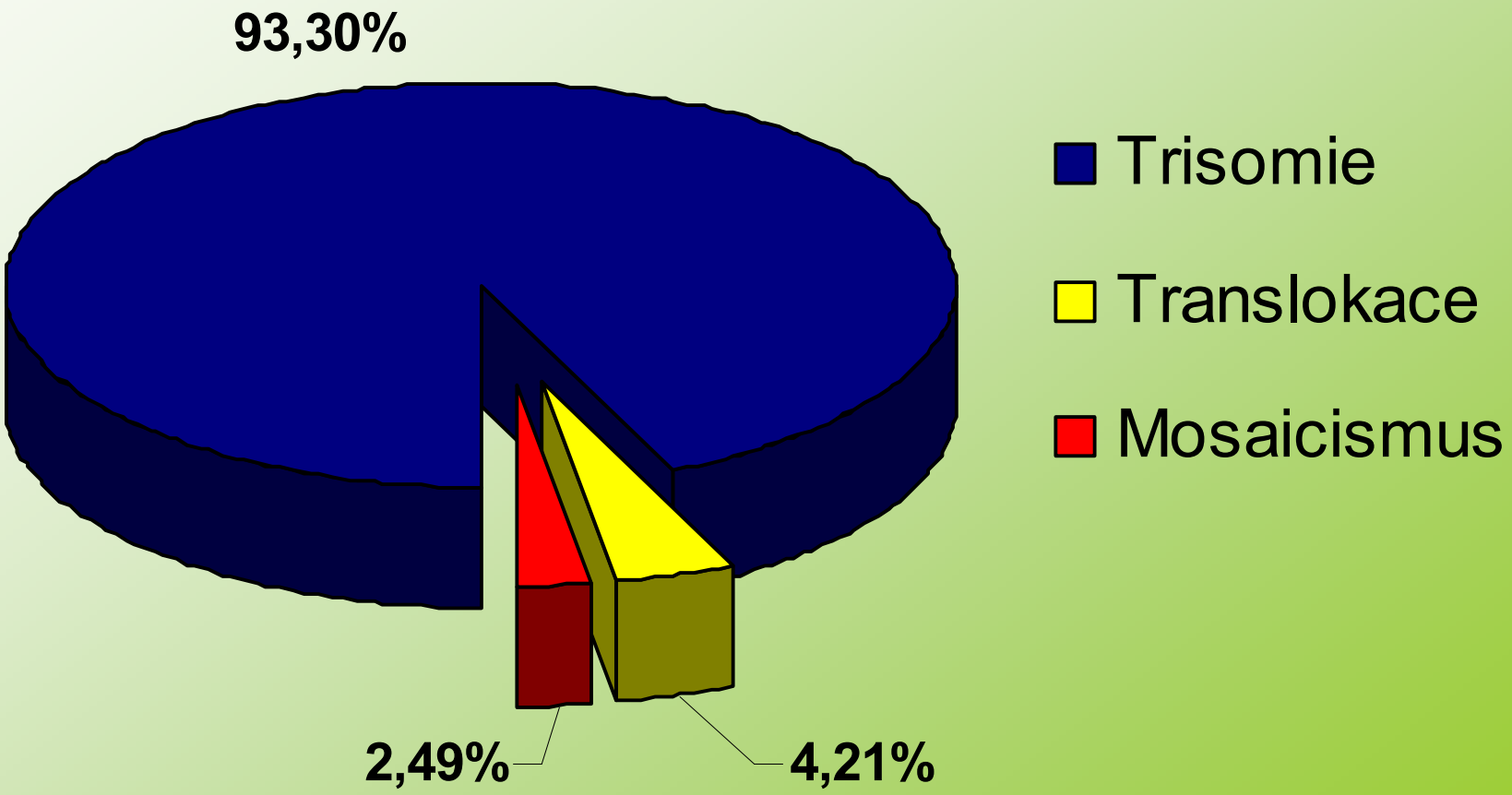
II. Trimester screening

- **AFP** 
- **HCG** 
- **uE3** 

- **Risk 1 in 250 – borderline**
- **Maternal age, week of gestation by** US

Cytogenetic findings in DS in Czech republic

1994 - 2001



Edwards syndrome

- 47,XX(XY),+18
- 1/5000-10 000 in newborns, 1/45 SA
- gynekotropie 4:1
- SA - 95%, death before 1 year mostly

- hypotrophy, atypical hands and foots, profil, prominent nose, small chin, congenital defects

Edwards syndrome

- 1:5000
- růstová retardace IU
- microcephalie
- dolichocephalie
- rozštěp patra
- nízko posazené uši
- micromandibula
- držení prstů
- další závažné VVV

Prenatal dg. +18

- AFP, HCG, uE3 ⇩
- Risk 1/250 - borderline
- Ultrasonography

Patau syndrome

- 47,XX(XY), +13
- 1/5000-10 000 in newborns, 1/90 SA
- 95% SA
- death before 1 year mostly

- cleft lip and palate bilateral, congenital defects (CNS, eyes, postaxial hexadaktily…)

Patauův syndrom + 13

- microcephalie
- trigonocephalie
- kožní defekty ve vlasaté části calvy
- vrozené vady mozku (holoprosencephalie , arinencephalie)
- micro-anophthalmia
- oboustranný rozštěp
- hexadactilie
- VCC a jiné

Turner syndrome

- 45,X (in about 55%), mosaicism, structural abnormalitites of X chromosome
- 1/2500 newborn girls, min. 95% SA
- prenat.- hydrops foetus, hygroma coli

- postanatal lymphedema on foots, pterygium coli, congenital heart defect coarctation of aorta, small stature, other congenital defects, hypogenitalismus, hypergonadotropins, sterility

Turner syndrom 45,X

- 1:2000
- hygroma colli
- hydrops
- Low weight in newborns
- Lymfoedema
- Pterygia
- cubiti valgi
- Aortal stenosis
- Small statue
- Sterility

Klinefelter syndrome

- 47,XXY
- relatively frequent 1/600-1000 liveborn males
- tall stature
- hypogonadism, gynekomastia
- sterility, infertility

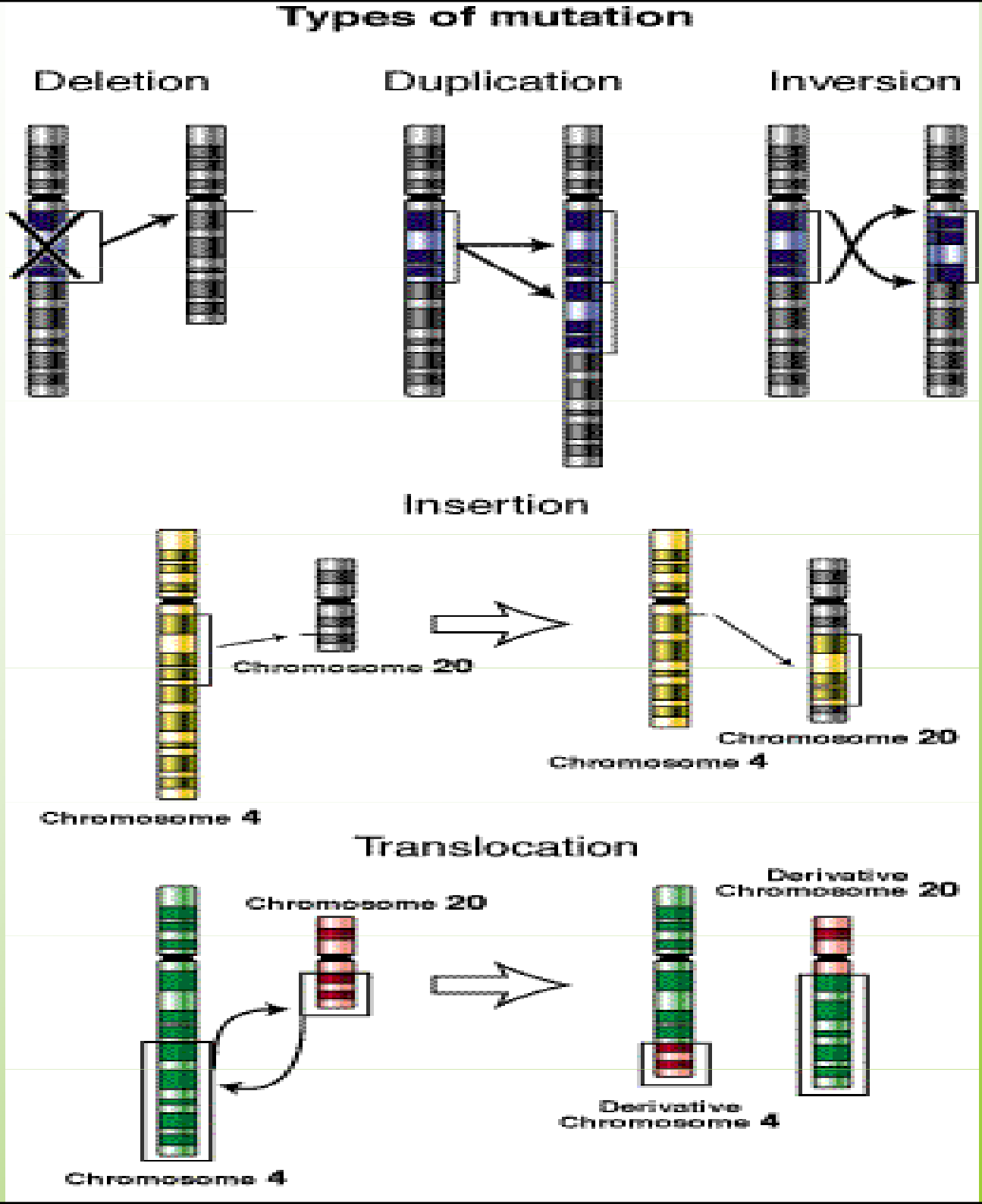
Others

- 47,XXX
- 47,XYY
- 48,XXXX
- 48,XXYY….

Structural aberations

- **46,XX(XY),4p-**
  (Wolf-Hirshorn syndrome)

- **46,XX(XY)5p-**
  (Cri du chat)


Types of mutation
Deletion
Duplication
Inversion
Insertion
Chromosome 20
Chromosome 4
Chromosome 20
Chromosome 4
Translocation
Chromosome 20
Derivative Chromosome 20
Derivative Chromosome 4
Chromosome 4

Cri du chat 5p-

- 1:50 000
- Typicaly cri in newborns
- laryngomalacie
- antimongoloid
- epicanthi
- hypotonie
- hypotrofie

Wdf-Hirshan syndrome

46,XX(XY),4p-

Microdeletions

- **Di George syndrome (del 22q11)**
- **Prader-Willi / Angelman syndrome (del15q11-13)**
- **Williams Beuren syndrome (del7q11.23)**

Syndrom Di George

- Veb - Kardio- Facial syndrome
- CATCH 22
- Congenital heart desease - conotruncal, craniofacial dysmorfism, thymus aplasie, imunodefitientcy, hypoparathyreoidismus

Williams - Beuren syndrom

- del 7q11.23
- Facial dysmorfie - Elfin face, congenital heart disease, aortal or pulmonal stenosis, hypokalcemie, small statue, MR, hernie,...

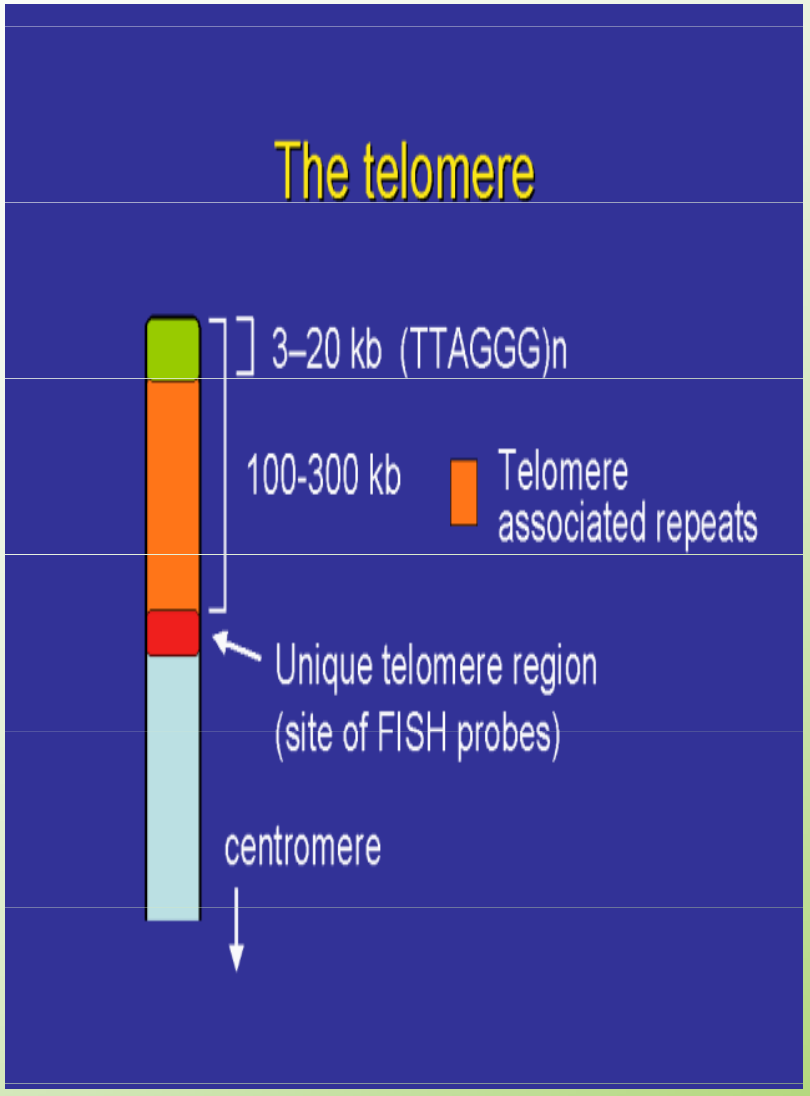
Prader-Willi syndrom

- Hypotonie, hypotrofie in small children
- PMR, small statue, obesity, hyperfagie, akromikrie, hypogonadismus
- mikrodeletion 15q11-12 paternal

Angelman syndrom

- těžká PMR, epilepsie, záchvaty smíchu, těžce opožděn vývoj řeči
- mikrodelece 15q11-12 mat

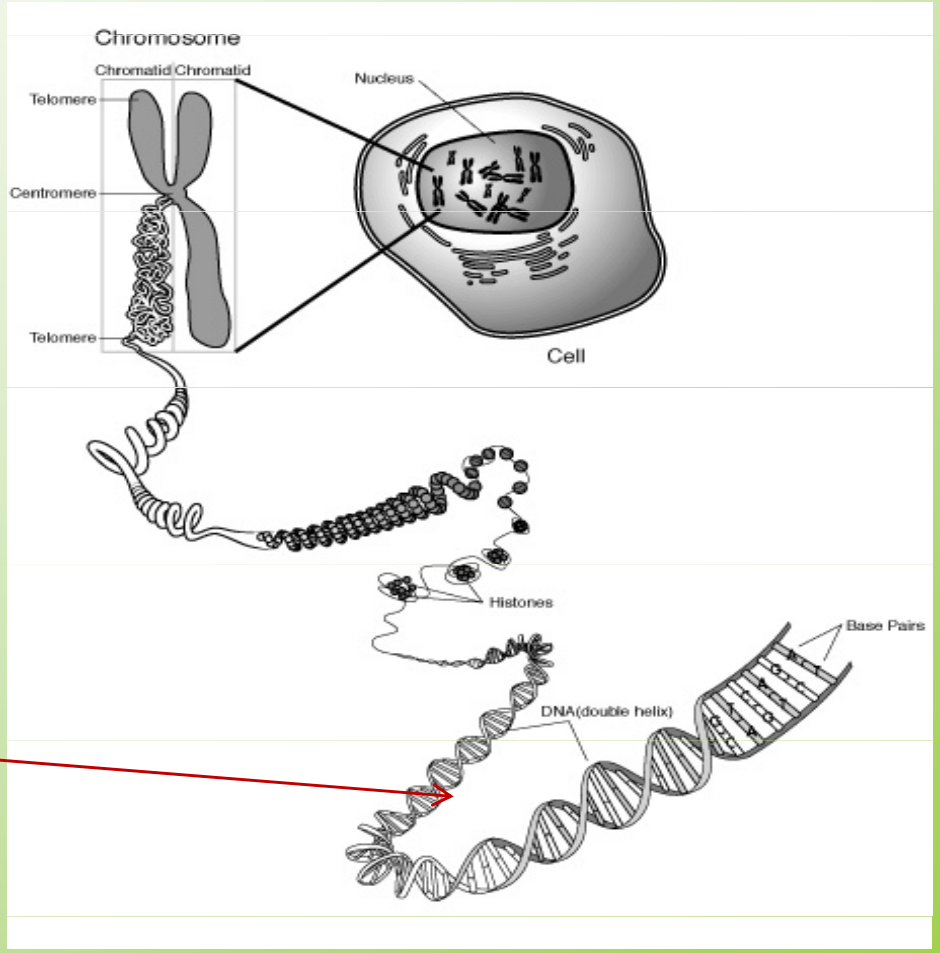
Telomere



Rearrangement in about 6-8% children with mental retardation with or without congenital defect

Mendelian inheritance

Monogenetic diseases

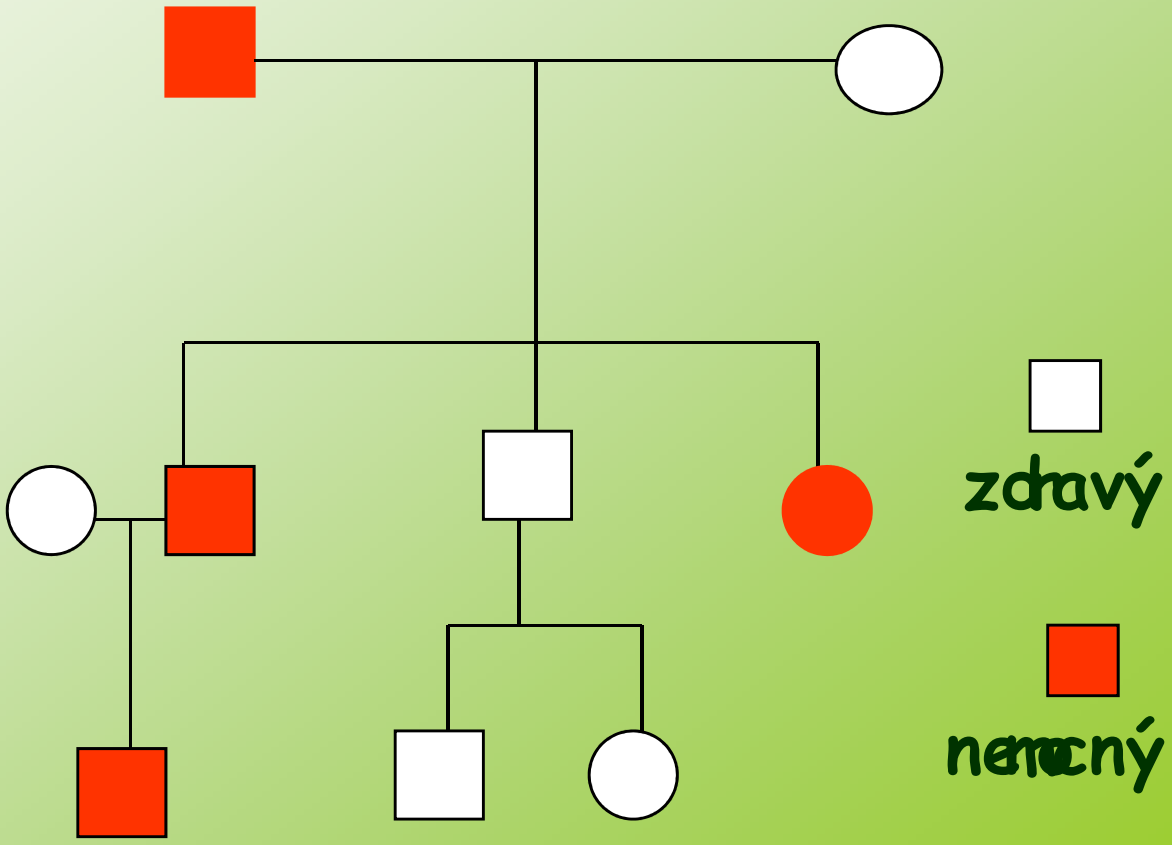


AD

- The sexes are involved equaly
- Heterozygotes are mostly affected clinically
- risk 50% for sibs and children
- new mutations
- penetrance, expresivity

Pedigree AD inheritance

- the risk 50%



AD - diseases

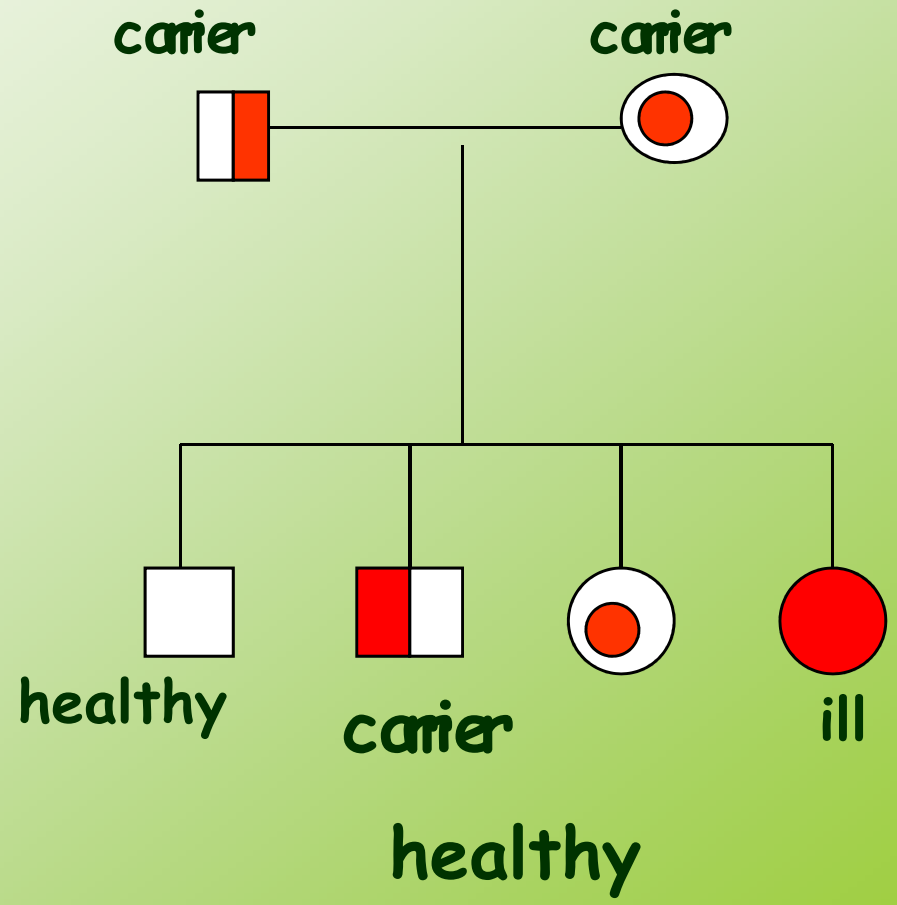
- Neurofibromatosis 1 and 2
- Achondoplasia
- Huntington disease
- Marfan syndrome
- Myotonic dystrophy

AR

- Heterozygotes are generally unaffected clinicaly
- The sexes are involved equaly
- An individual manifesting a recesive disorder usually has heterozygous parents
- Once a homozygote is identified, the recurence risk for other child of some parents is 25%

Rodokmen - AR dědičnost

- The risk for next child 25%



AR - diseases

- Cystic fibrosis (carriers in Czech Republic 1/26)
- Phenylketounria (1/40)
- Congenital adrenal hyperplasia (1/40)
- Spinal muscular atrophy

Cystic fibrosis

- Localized on chromosome 7q
- Frequency of Cystic Fibrosis in the Czech Republic:

  about 1/2000 – 1/3000
- Frequency of heterozygots in the Czech Republic

  about 1/25-1/29
- In 2003 about 1006 mutations in CFTR gene were identified

Cystic fibrosis

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  about 1/2000 – 1/3000
- Frequency of heterozygots in the Czech Republic

  about 1/25-1/29
- In 2003 about 1006 mutations in CFTR gene were identified
- The most frequent mutation in Czech Rep. F508del – about 70%

Respiratory tract

liver

pankreas

intestine

reproductiv failure

sweat gland

The reason for CFTR gene analysis

- Suspition on Cystic fibrosis in a patient
- Cystic fibrosis in the family
- Partners of hyterozygots for Cystic fibrosis
- Repeated fetal loss
- Sterility
- Relationship of the partners
- Others

XR

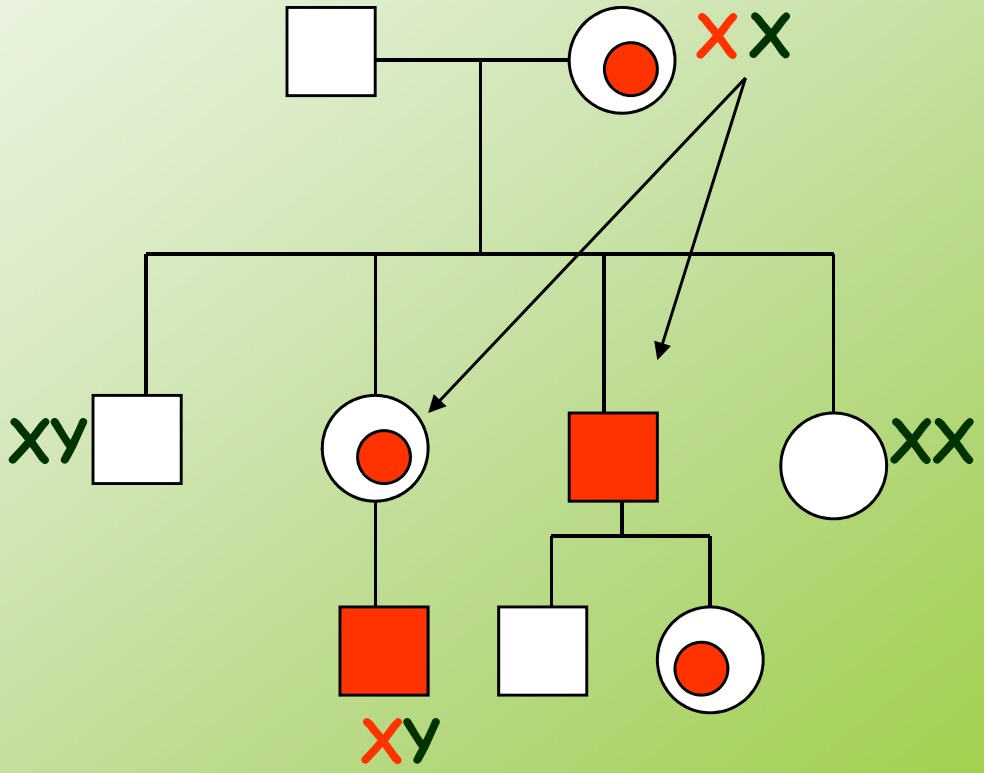
- Females are not affected as severaly as males or are not affected
- An affected male cannot transmit the train to his sons, becose the trait is on X-chromosome, and the father must necessarily transmit his Y-chromosome to a son
- All of the daughters of an affected male must be carriers, because the only X-chromosome that the father can give to a daughter contains the mutation

XR

- Risk for daughters of a carrier - mother
- 50% for carrier

- Risk for sons of carrier - mother
- 50% for diseas

X- recesive inheritance



XR - diseases

- Hemophilia A and B
- Duchenne and Becker muscular dystrophy
- Fragile X chromosome - X-linked disease

Common congenital defects

Congenital heart diseases

- 0,5 - 1% in liveborn infantsn - population incidence
- etiology not known mostly
- about 3% + chromosomal syndromes (+21,+13,+18, 45,X, 18q-, 4p-, del 22q11 Di George sy)
- some mendelian syndromes associated with congenital heart disease (Holt-Oram, Williams, Noonan, Ivemark...

Congenital heart diseases prenatal diagnosis

- For most serious congenital heart diseases
- Ultrasonography in 21. week of gestation - by specialists for prenatal kardiology

Congenital heart disease - genetic risks

condition	1 aff. sibling	1 aff. parent
Ventricular septal def.	3%	4%
Patent ductus art.	3%	4%
Atrial septal defect	2,5%	2,5%
Tetralogy of Fallot	2,5%	4%
Pulmonic stenosis	2%	3,5%
Koarctation of aorta	2%	2%

Congenital heart disease genetic risks

	Risk in %
More than two affected firstdegree relatives	50
Sib of isolated case	2 - 3
Second-degree relatives	1 – 2
Offsprin- affected father	2 - 3
Offsprin – affected mother	5
Two affected sibs	10

Cleft lip and palate

- Population incidence CL 1/500-1/1000
- Multifactorial mostly
- With chromosomal trisomies (+13,+18)
- Syndromes associated with CL/CP/CLP
- (van der Woude sy, EEC sy, Pierre Robin sequence…)
- Prenatal diagnosis by ultrasonography not sure

Cleft lip and palate- genetic risks

Relationship to index case	CLP	CP
Sibs (overall risk)	4%	1,8%
Sib (no other affected)	2.2%	
Sib(2 affected sibs)	10%	8%
Sib and parent affected	10%	
Children	4,3%	3%
Second-degree relatives	0,6%	

Neural tube defects

- Multifactorial inheritance (risk for I. degree relatives about 2 - 4%)
- Maternal serum AFP screening
- Prenatal diagnosis by ultrasonography
- Raised AFP levels in amniotic fluid
- Primary prevention in pregnancies by folic acid
- Risk populations - probably related to nutritional status

Prenatal diagnosis

Prenatal diagnosis

- **Non invasive - screening**
- **Invasive - CVS, AMC, kordocentesis**

Prenatal screening (CR)

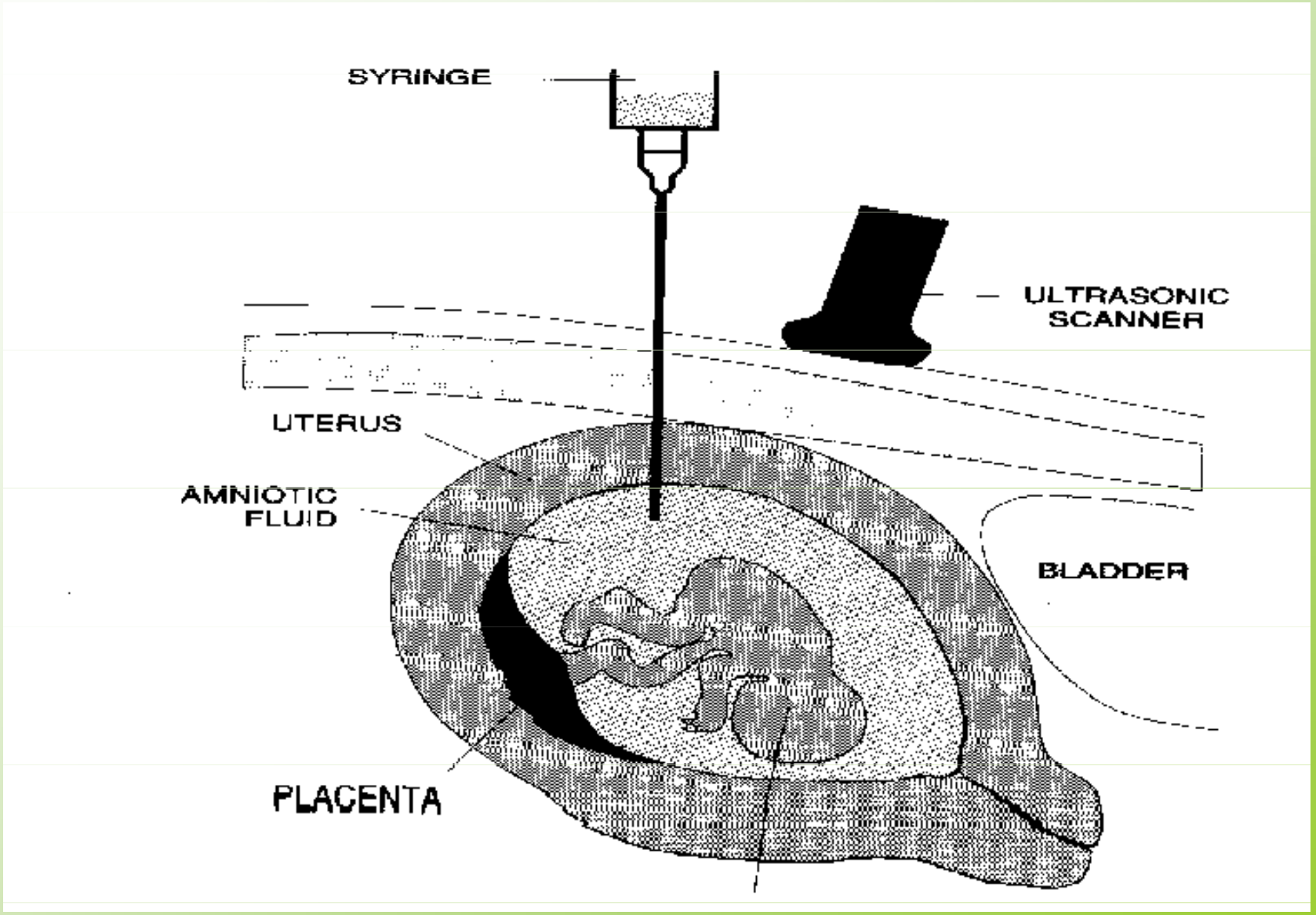
- Ultrasound (12. - 2 0. - 33. week)
- Ultrasound 20.week – cong. defect
- Ultrasound 20-22. week – cong. heart defect

- Blood - biochemical screening
- Free beta hCG and PAPP-A -10-14. week
- AFP, hCG, uE3 - 16.week

Indications for prenatal diagnosis / counselling

- Advanced maternal age (35)
- Risk factors for neural tube defects (US)
- Family history of known conditions for which diagnosis is possible (DNA)
- Known chromosomal abnormality (de novo finding in previous child, structural change in parents)
- Positive prenatal screening for chromosomal abnormalities

Amniocentesis



Genetic counselling in infertility

Infertility

- Is the infertility one aspect of a genetic disorder that might be transmitted?
- Will correction if infertility give an increased risk of malformations in the offspring?

Infertility

- Patological examination of the abortus where possible, this may identify major structural malformations.
- Cytogenetic study of parents, this is especialy important where a structural abnormality is present.
- In general the finding of a chromosome abnormality in the abortus but not in parent is not likely to be relevant or ti affect the genetic risks.

Infertility

- A search for possible lethal mendelian causes (consanguinity- risk for AR diseases, X-linked dominant disorders lethal in male, myotonic dystrophy which gives heavy fetal loss in the offspring of mildly affected women)
- Inherited trombophilias in women with recurrent abortions (factor V Leiden, factor II - G20210A, hyperhomocystinaemia ? (MTHFR - C677T)

Sterility in male

- AZF deletions (DAZ gene) Yq
- CFTR mutations and polymorphisms

Genetic risk in cancer

Genetic testing in the tumours

- Diagnosis
- Therapy
- Prognosis
- Minimal residual disease

Genetic risks in cancer

- Tumours following mendelian inheritance(most AD, about 5%)
- Genetic syndromes predisposing to malignancy

- Embryonal and childhood tumours
- Common malignant tumours of later life

Hereditary tumours

- AD
- Preventive, pre-symptomatic testing
- Assotiated problems
- Prevention
- Brest cancer – BRCA 1 and BRCA 2
- Familial Adenomatous Polyposis coli
- Von Hippel – Lindau syndrome
- Retinoblastoma
- Neurofibromatosis
- Li-Fraumeni syndrome
- Lynch syndrome

Familial tumours following AD inheritance

- Brest cancer – BRCA 1 and BRCA 2
- Familial Adenomatous Polyposis coli
- Von Hippel – Lindau syndrome
- Retinoblastoma (not all)
- Wilms´ tumour (syndromal form)
- Neurofibromatosis
- Li-Fraumeni syndrome
- Lynch syndrome

Genetic testing in cancer

- Tests are voluntary
- Mostly in adults only

- In children only when prevention in childhood is present and when the risk of tumours is in childhood