

# Clinical Genetics

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# Clinical genetics

- Dept. of medical genetics
- Genetic prevention
- Genetic diseases
- Patients on the departement of clinical genetics
- Genetic counselling
- Chromosome abnormalities
- AD, AR, XR inheritance, disorders
- Multifactorial inheritance
- Teratogenes, Environmental hazards
- Prenatal diagnosis
- Reproductive genetics
- Hereditary cancer

# Dept. of Medical genetics

- Genetic ambulance

genetic counselling

- Laboratory part

- Cytogenetic laboratories

Prenatal cytogenetics

Postnatal cytogenetics

Oncocytogenetics

Molecular - cytogenetics

- Lab. for DNA and RNA analysis  
(clinical genetics and oncogenetics)

# Characteristic of Medical Genetics

- Preventive Medicine
- Interdisciplinary cooperation
- Information from genetics (disease, testing, possibilities)
- Voluntary choice for patients
- Informed agreement

# Primary prevention of genetic

- **Before pregnancy**
- Folic acid (cca 0,8 mg/day, 3+3 months)
- Vaccination (rubella)
- Genetic counselling
- Contraception, family can opt for adoption or donor of gamets (oocytes, sperm)
- Pregnancy planning
- Rediction of environmental hazards (drugs, radiation, chemicals...)

# Reproduction of the optimal age

- In women increases the risk of accidental congenital chromosomal aberrations in the offspring
- In men may increase the risk of de novo mutations in monogenic diseases (Neurofibromatosis, Achondroplasia..)

# Prevention of spontaneous and induced mutations

- **Healthy Lifestyle**
- **The restriction of harmful substances - drugs, environmental hazards**

# Vaccination, infection prevention

- Prevention of rubella embryopathie

Prevention of congenital toxoplasmosis

- Testing for infectious disease risk in mothers (CMV, varicella-zoster virus, ...)



# Vitamin prevention of neural tube defects, anterior abdominal wall defects, clefts

- Folic acid at a dose of 0.8 mg daily (twice the dose in non-pregnant) for 3-6 months prior to conception and till the end of 12. week of pregnancy

# Pre-conception consultation with the doctor

- Family history
- Long term therapy
- Chronic diseases

# Examination of acquired chromosomal aberrations

- Preventive examinations of persons exposed to environmental risks at work or persons with risk of long-term therapy (immunosuppressants, cytostatics, ....)
- The possibility of vitamin therapy to improve repair of DNA (3-6 months)

# Contraception, sterilization

- **Contraception** - temporarily prevents conception in the limited impact of risk (treatment)
- **Sterilization** - the long-term inhibition of pregnancy in a high risk of disease in the offspring (Hereditary disease)

# Adopce

- Alternative family care as an option at high genetic risk families

# Donor (oocytes, sperm)

- The possibility of sperm, oocytes and embryos donor
- reduction in high genetic risk
- reproductive problems

# Secondary prevention of genetic

- Prenatal diagnosis
- Prenatal screening
- Prenatal tests
- Genetic counselling
- Termination of pregnancy (the law in Czech Republic- end of 24. week of gestation)
- Postnatal screening
- Newborn screening

# Genetics diseases

- **Chromosome abnormalities**
  - about 0,6 - 0,7%
  
  - **Monogen diseases**
  - about 0,36%
- (study in 1 000 000 newborns)
- most then 90% of monogen diseases occur in childhood
  
  - **Multifactorial (polygenic or complex) disorders**
  - Occur in about 80% in the population



# Patients on genetic departments

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

# Patients on genetic departments

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

# Children

- **Congenital malformations**

# Children

- Suspicion of mongenic hereditary diseases or inherited metabolic disorders and their families

# Children

- Suspicion on congenital chromosom aberations (children with congenital malformations, abnormal face, atypical visage, pre- or postnatal growth retardation, premature birth)

# Children

- Precocious or delayed puberty
- Malformations of the external or internal genitalia
- Low or high figure

# Children

- Before adoption

# Children or adults

- **Mental retardation**
- **Psychomotor retardation**
- **Developmental delay**



# Children and adults

- Gender identity disorder

# Children and adults

- people with long-term exposure to environmental pollutants
- (alcohol, cigarettes, drugs, radiation)

# Children and adults

- patients with suspected hereditary cancer
- patients with cancer (sporadic occurrence)

# Adults

- Gamete donors  
(preventive tests)

# Adults

- Related partners  
(increased risk for hereditary disease with  
AR inheritance)

# adults

- Infertility
- Repeated spontaneous abortions

# Pregnant women

- With unfavorable family history

# Pregnant women

- with adverse pregnancy history (chronic diseases with established therapies, acute disease in early pregnancy - temperature, drugs, X-rays, CT, vaccinations, toxoplasmosis, rubella, ...)



# Pregnant women

- Prenatal biochemical screening  
(Pathology results)

# Pregnant women

- **Ultrasound prenatal screening - pathology results**
- **Congenital malformations**
- **Risk of chromosomal aberrations in the fetus**

# Pregnant women

- ??? Age of parents ???  
relative indications

# Genetic clinic

# Genetic counselling

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

# Mother

- Name, surname, date of birth, maiden name
- Place of birth
- Place of birth of mothers parents
- Relationship
- Jobs - employment risks
- Addictive substances  
alcohol, cigarettes,  
medication ..

# Mother

- Health problems from birth until today
- Long-term medication
- Long-term monitoring of a doctor
- Gynecological anamnesis
- The number of births, children, pregnancy, birth weight children, the health status of the children
- The number of abortions, unsuccessful pregnancies
- Unsuccessful attempt to pregnancy

# Mother

- In the case of health problems, if possible, to provide medical records from the attending physician
- Long-term used drugs, how long



# Father

- Name, surname, date of birth
- Place of birth
- Place of birth of the father's parents
- Relationship
- Jobs - employment risks
- Addictive substances  
alcohol, cigarettes,  
drugs ..

# Father

- Health problems from birth until today
- Long-term medication
- Long-term monitoring of a doctor
- Number of children from any previous partners, their health status
- The number of abortions, failed pregnancy (if any previous partner)
- Unsuccessful attempt to become pregnant in previous partner

# Father

- In the case of health problems, if possible, to provide medical records from the attending physician
- Long-term used drugs, how long

# Child - Patient

- Pregnancy
- Swelling, nausea, protein in urine, sugar in urine, high blood pressure
- Diseases in Pregnancy
- Drugs in Pregnancy
- Prenatal tests results  
Ultrasound, blood tests

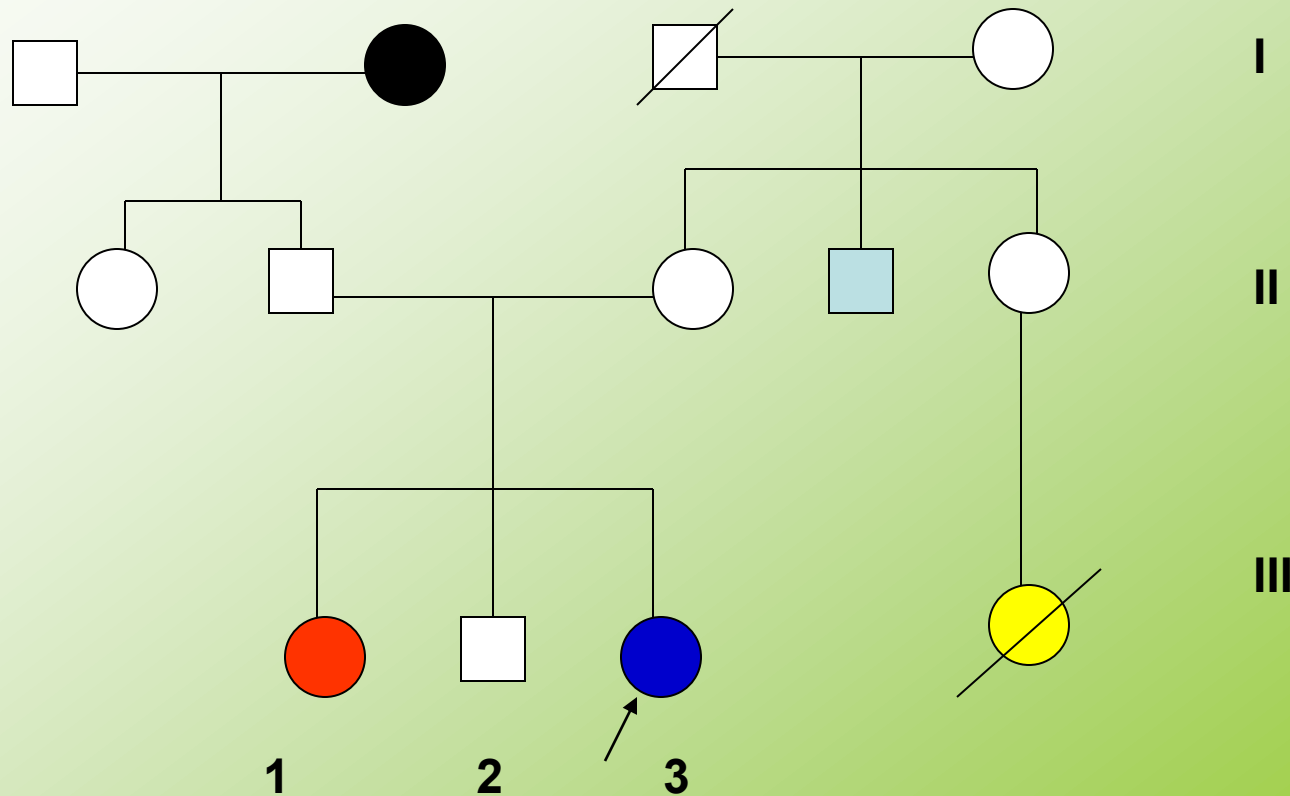
# Child

- Birth - in time, early, after the deadline?
- Complications, neonatal icterus, birth weight and length, nutrition
- The mental and motor development
- Diseases
- Monitoring of specialists
- Drugs
- Test results

# Child

- **Clinical genetic examination**
- **Weight, height**
- **Atypical visage**
- **Malformations**
- **Psychological state**
- **Behavior**

# Pedigree - our patient III/3



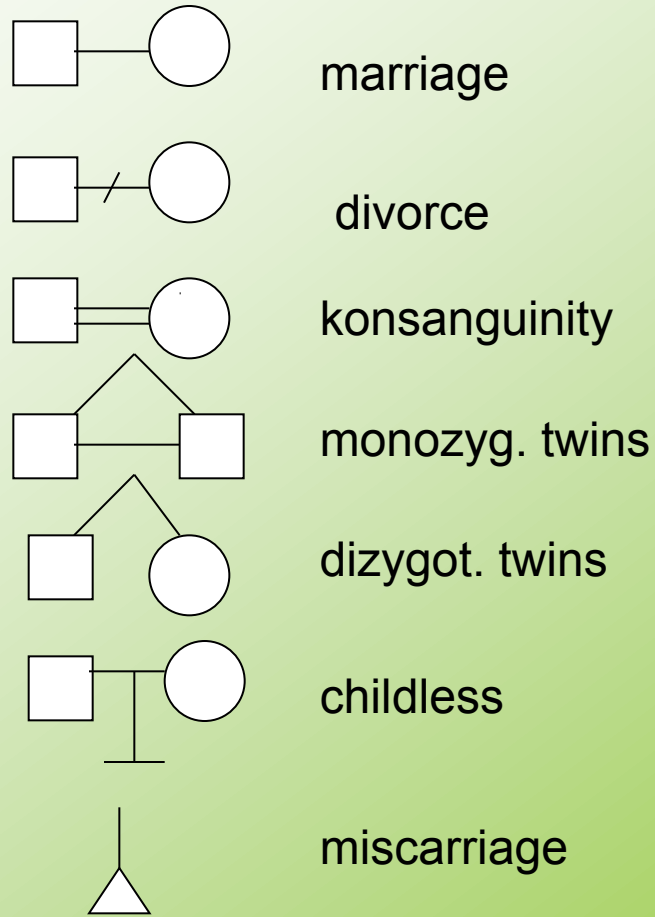
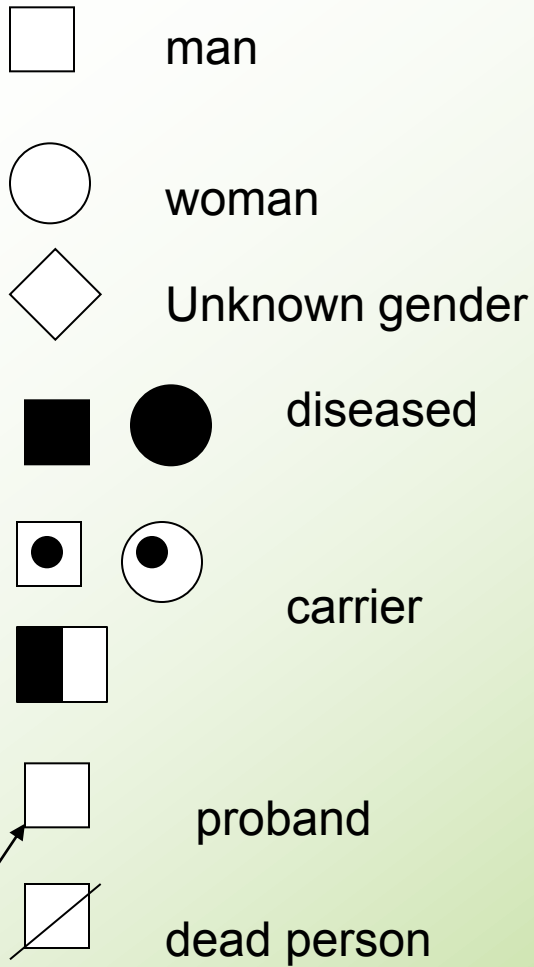
● Cleft lip

● Neonatal death

■ Syndaktilie

● Epilepsy

● Congenital heart disease





# Three-generation pedigree

- Patient
- Siblings
- Children siblings
- Parents
- Parents siblings
- Children of parents siblings
- Parents parents

# Genetic testing before family planning

- ? Know we well our health status ?
- ? Know we healt status our partners?
- ? Know we health status our relatives?

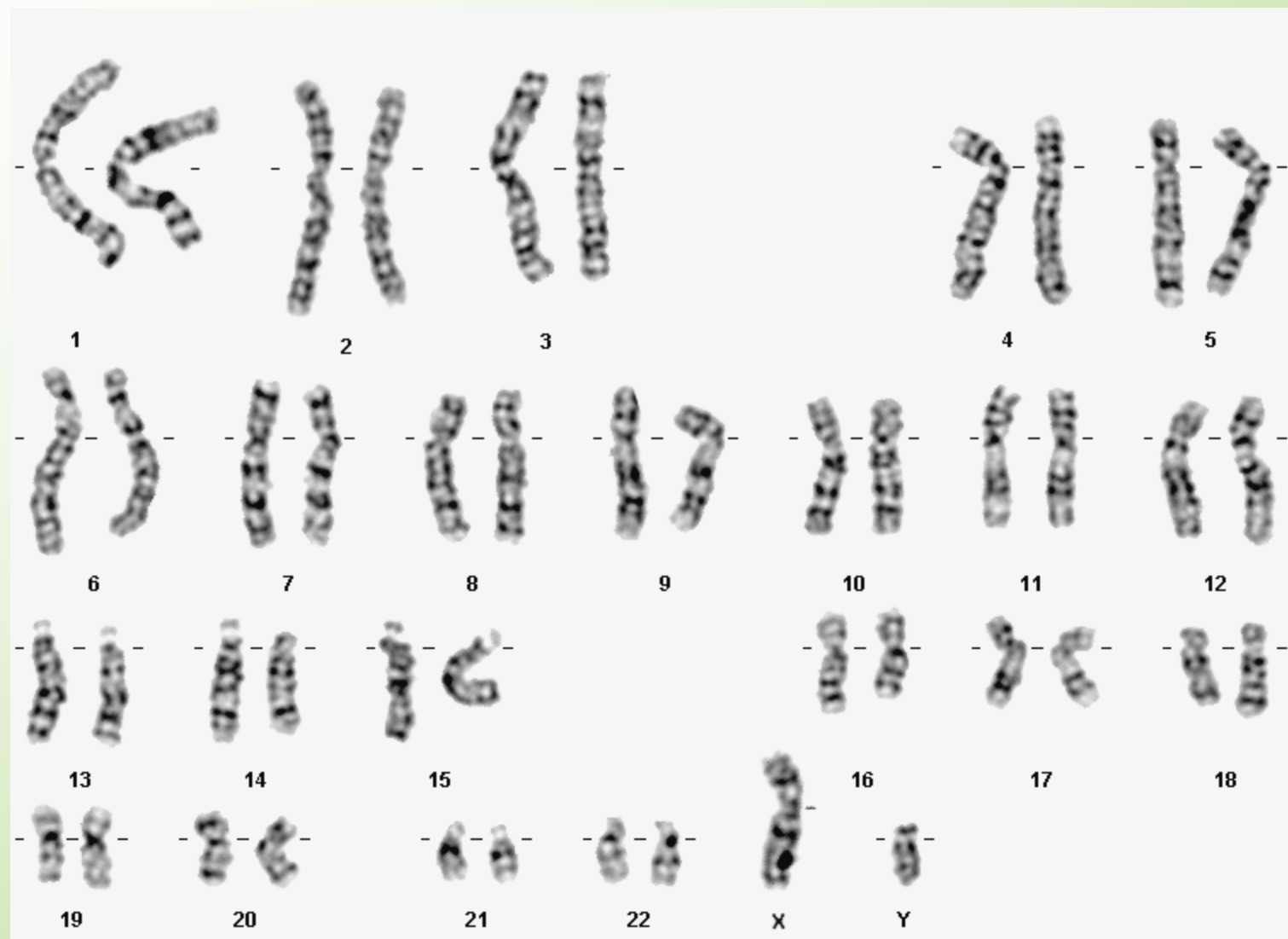
# Next steps

- Recommend the laboratory genetic testing
- Recommend other specialists if needed
- Require medical records
- Make photodocumentation

# The result of genetic counselling

- Specify exact diagnosis (if possible)
- Determine genetic prognosis
- Is the disease hereditary?
- Type of inheritance
- Genetic risks for other family members
- Possibilities of treatment, prenatal analysis

# Chromosome abnormalities



# 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)

<u>years</u>	<u>+21</u>	<u>+18</u>	<u>+13</u>	<u>XXY</u>	<u>All</u>
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)

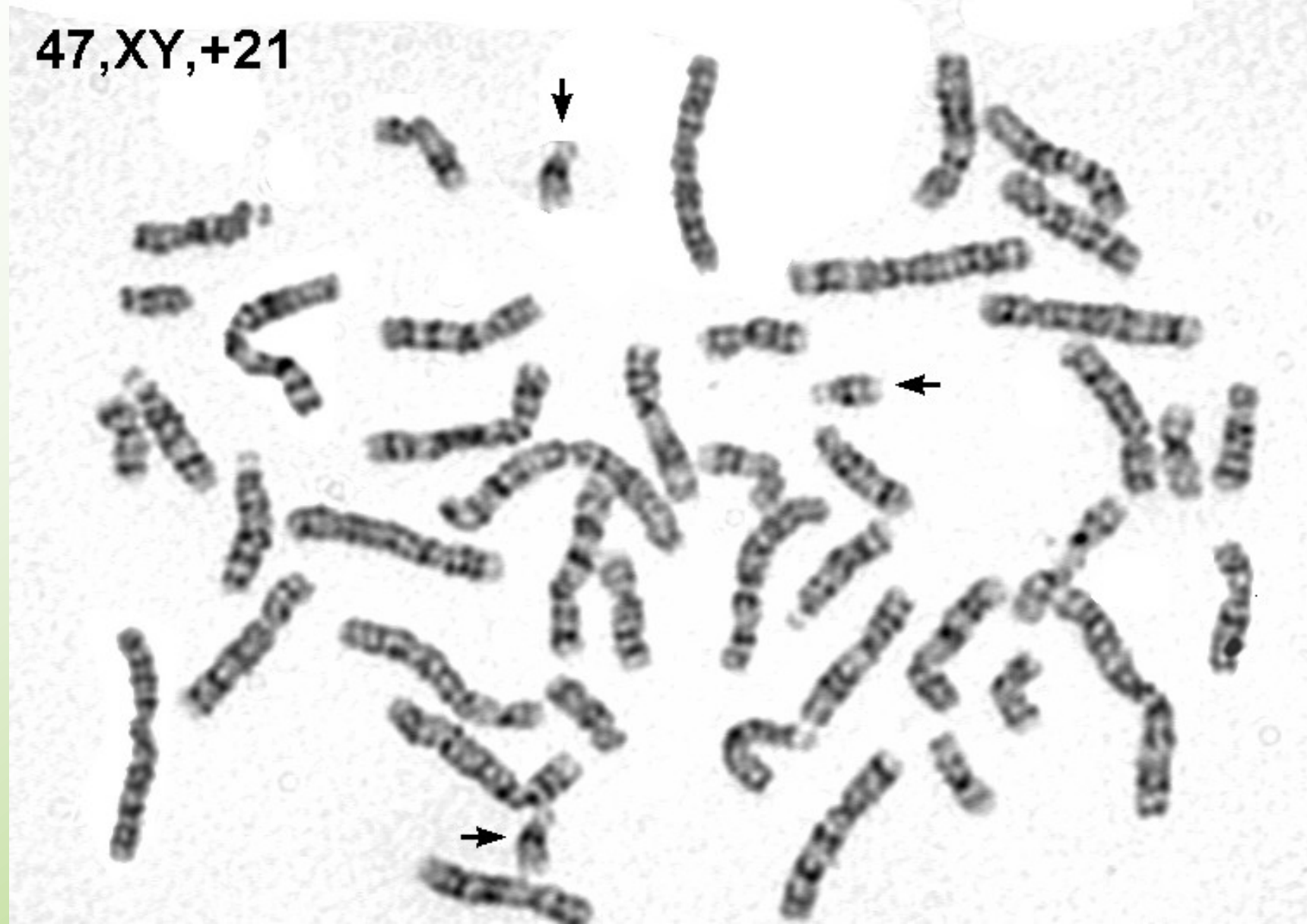
Maternal age (years)	Risk
15	1/1578
25	1/1351
35	1/384
40	1/112
45	1/28
50	1/6

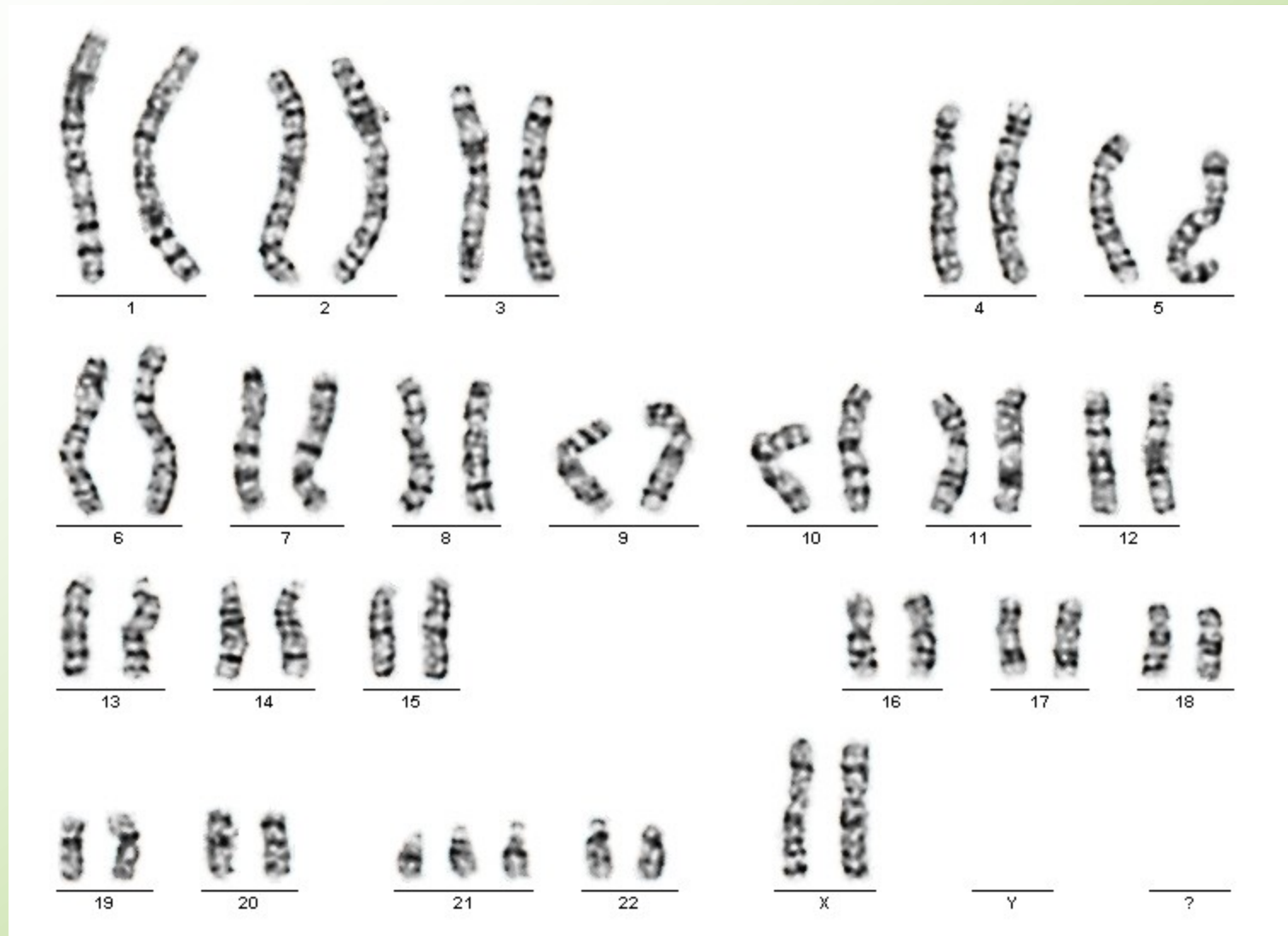
# Down syndrome

# 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, Brushfield's spots of the irides, small, down set ears, small nose, protruding tongue, simian crease in the hands (about 45%), short statue, mental retardation, congenital heart disease in about 50% of patients with DS, (atrioventricular canal)

# Down syndrome (G-banding)





47,XX,+21

# Down syndrome- prenatal diagnosis

- I. trimester screening - combined screening
- 10.-14. week of gestation
- **Ultrasound**
- Nuchal translucency - NT
- (Absence of nose bone)
- **Blood**
- PAPP-A, free-beta hCG
  
- Fals positive results less then 5%
  
- Reveals more then 95% of fetuses with Down syndrome



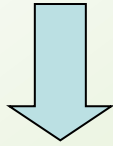
# Down syndrome- prenatal diagnosis

- II. trimester screening - biochemical screening
  - 16. -18. week of gestation
  - AFP - alpha-fetoprotein
  - total hCG - chorionic gonadotropin
  - uE3 - unconjugated estriol
- 
- Fals positive results about 5%
  - Reveals about 80% of fetuses with Down syndrome

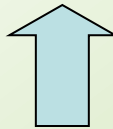
## II. Trimester screening

↑ risk for DS

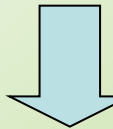
• AFP



• hCG



• uE3



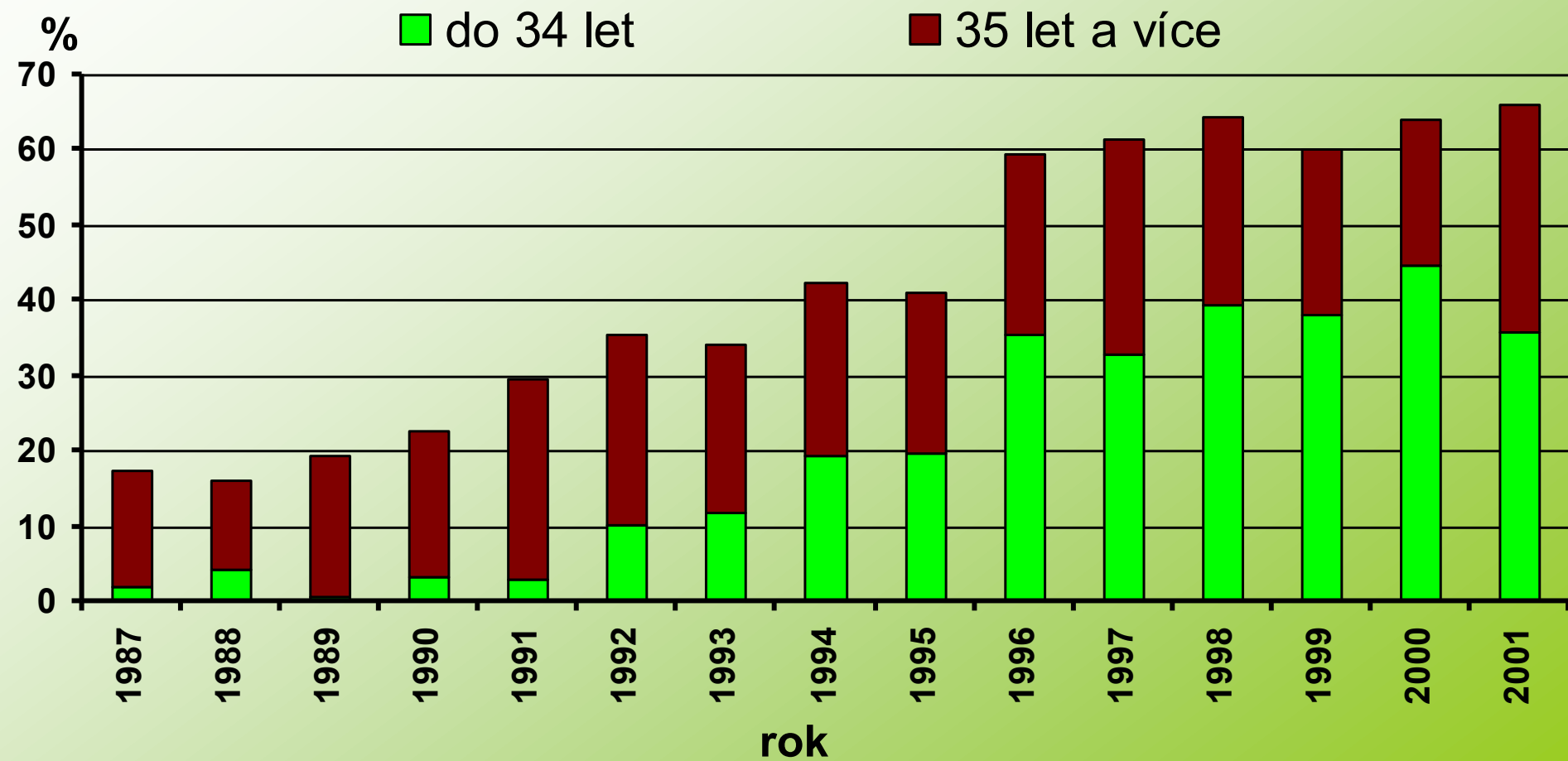
• The result:

- 1 child with +21 in XXX childer without +21
- Borderline - Risk 1 in 250
- Maternal age, week of gestation by US

# Down syndrome - prenatal diagnosis

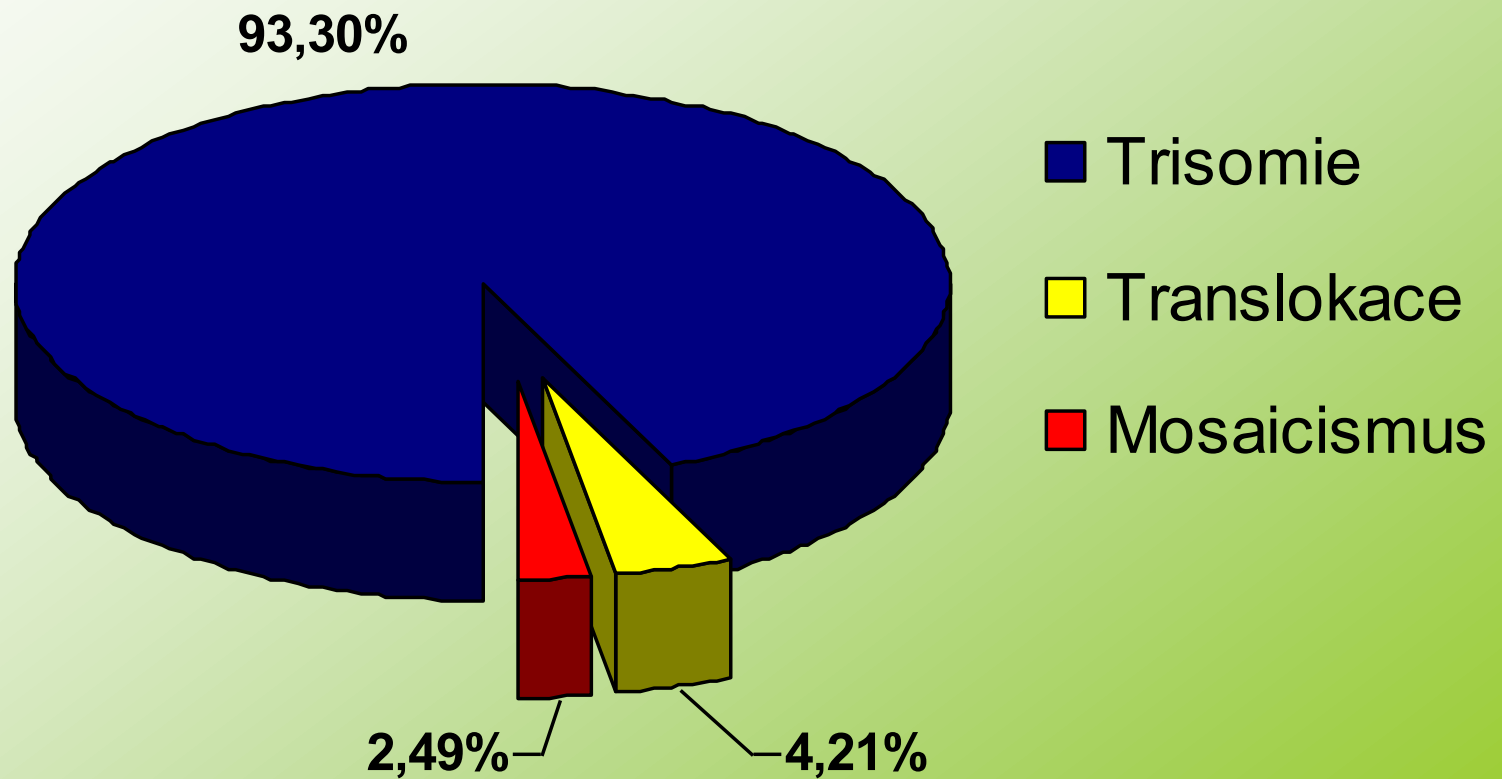
- Ultrasound
- 10.-14. week
- NT
- NB
- 20. week
- US- congenital heart disease and other malformations

# Prenatal dg. DS in Czech republic 1980 - 2001



# 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 feet, profil, prominent nose, small chin, congenital defects

# Edwards syndrome

- 1:5000
- IUGR, hypotrophie
- microcephalie
- dolichocephalie
- Cleft palate
- Down set ears
- micromandibula
- Hands, feet
- Other cong. malformations

# Prenatal dg. +18 - II. trimester

- 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 hexadactily...)

# Patau syndrome, + 13

- Microcephalie
- Trigenocephalie
- skin defects in the hairy part calva
- congenital defects of the brain  
(holoprosencephalie, arinencephalie)
- micro-anophthalmia
- Cleft lip, palate  
hexadactilie
- heart defects

# Turner syndrome

- 45,X ( in about 55% ), mosaicism, structural abnormalities of X chromosome
- 1/2500 newborn girls, min. 95% SA
- prenat.- hydrops foetus, hygroma coli
- postnatal lymphedema on feet, pterygium coli, congenital heart defect coarctation of aorta, small stature, other congenital defects, hypogonadism, hypergonadotropins, sterility-infertility

# 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, gynaecomastia
- sterility, infertility

# Others gonosome abnormalities

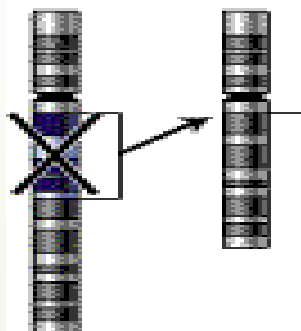
- 47,XXX
- 47,XY
- 48,XXXX
- 48,XXYY....

# Structural chromosomal aberrations

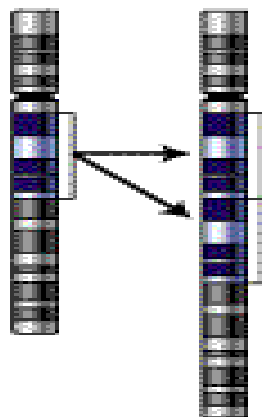
- deletion or a duplication of the genetic material of any chromosome, atypical structure - side by side to get the genetic material, which there normally is not - the effect of positional
- partial-partial deletions
- partial trisomy
- inversions, insertions, duplications ....

# Types of mutation

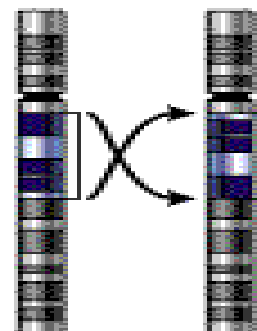
## Deletion



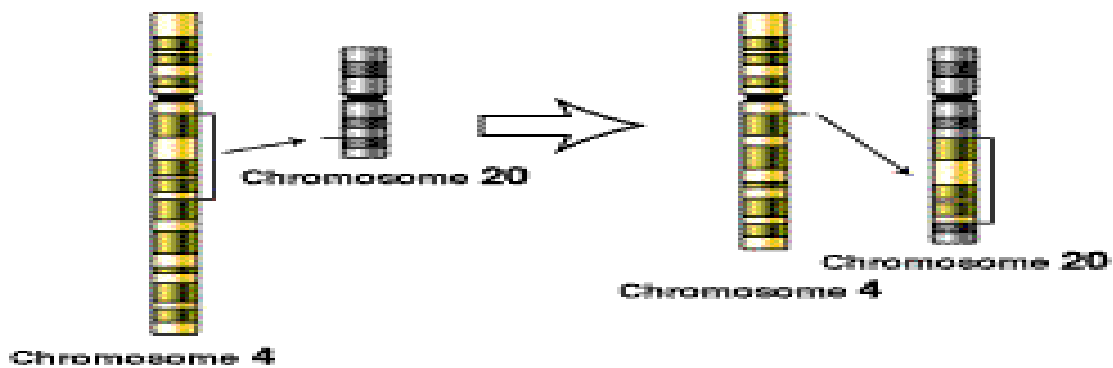
## Duplication



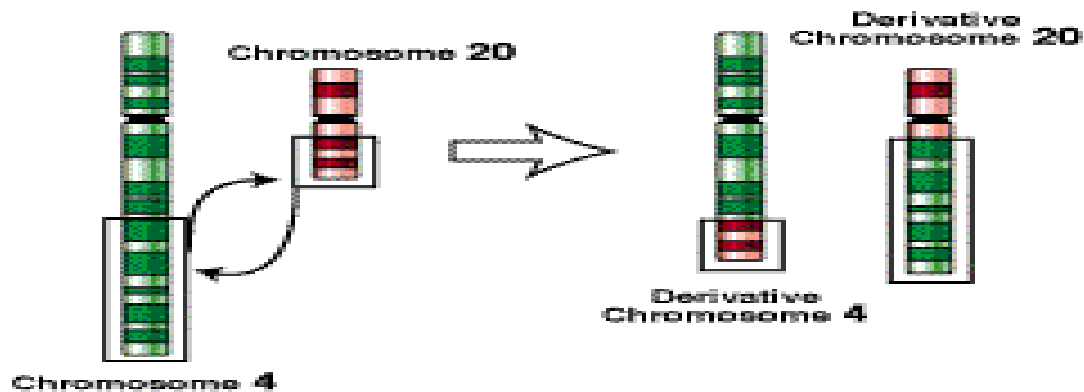
## Inversion



## Insertion



## Translocation





# Syndrom Wolf-Hirshorn

## 46,XX(XY),4p-

- severe mental retardation
- typical craniofacial dysmorphism - hypertelorism, pear nose, carp mouth,
- pre- and postnatal growth retardation,
- failure to thrive
- other associated developmental defects - heart, urogenital tract ...

# Wolf-Hirschhorn syndrom (46,XX,4p-)

Incidence?

IUGR

Hypotonia

Charakteristic  
face

Heart defects

Hypotonie

Hypotrophie

Severe mental  
retardation

# Syndrom Cri du chat

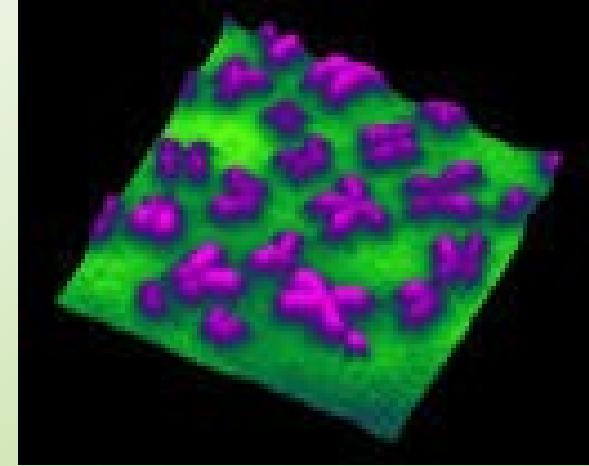
## 46,XX(XY),5p-

- anomalies of the larynx causes the characteristic cry of a similar feline meow (only in infancy)
- low birth weight and length
- mental retardation, short stature, failure to thrive, small moon shaped face, the position antimongoloid eye slits, mikrocephalie
- Other malformations and birth defects

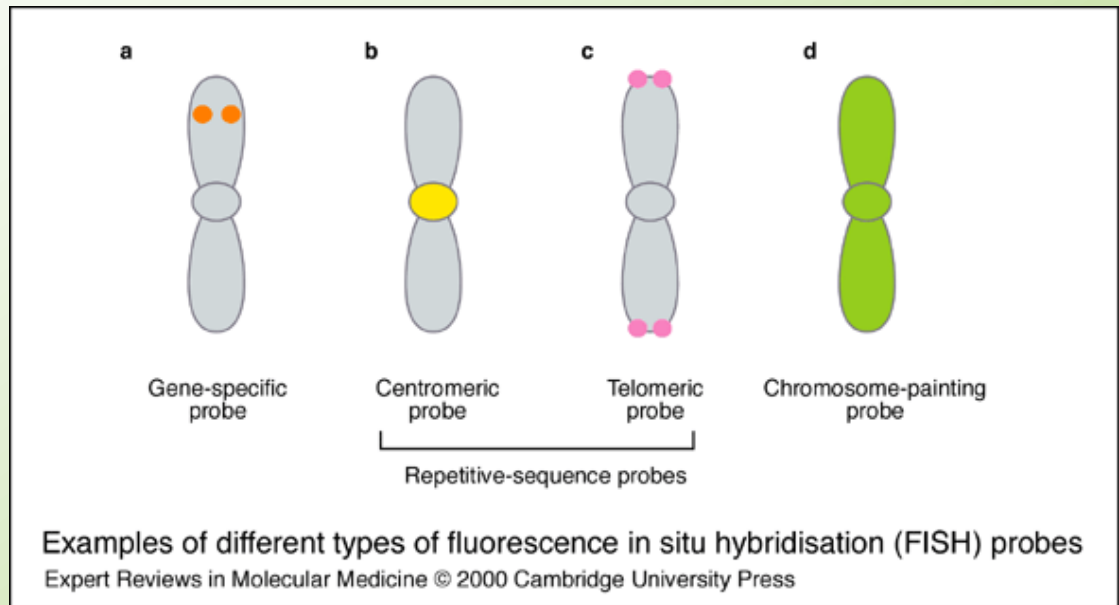
# Cri du chat 46,XX(XY),5p-

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

# Mikrocytogenetic Molekular cytogenetic

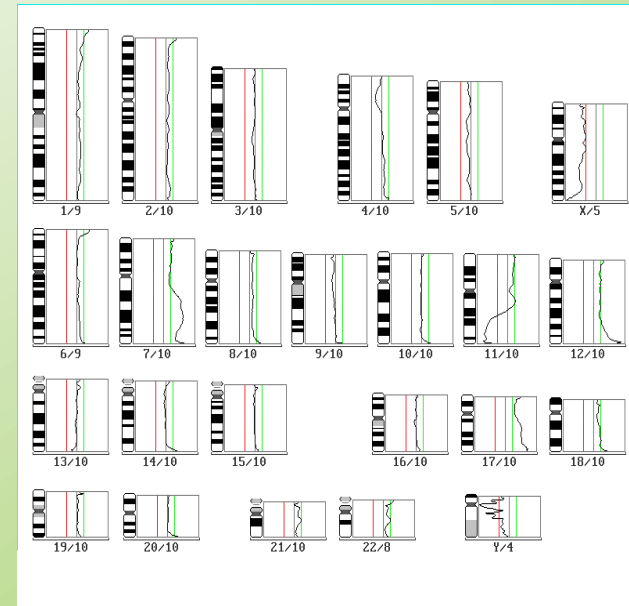
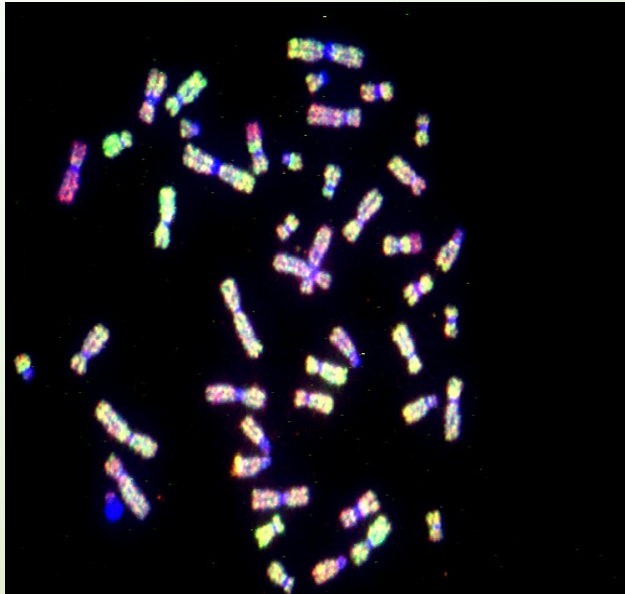


- FISH (fluorescenc in situ hybridisation), M-FISH, SKY (spektral karyotyping), CGH (komparativ genom hybridisation), MLPA
- mikroleletions or mikroduplikations, marker chromosomes, complex rearegements, oncology - oncocytogenetics, fast prenatal diagnostics ...)
- fast methods (possible for prenatal dg)
- metafase and intesfase examination



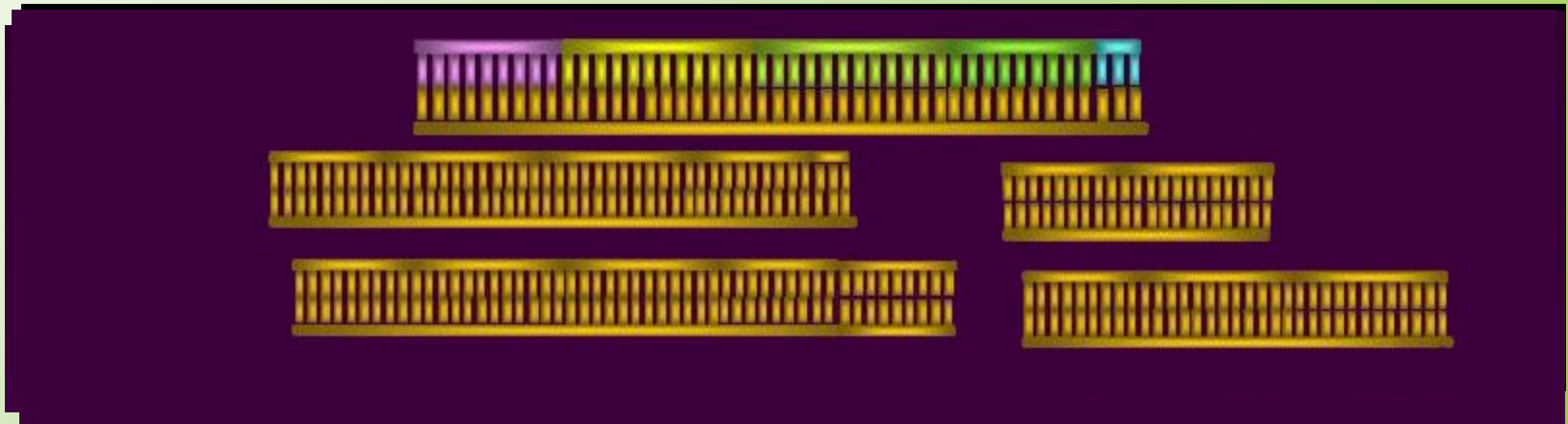
**FISH**

# Komparativ genom hybridisation



# MLPA

## Multiplex Ligation-Dependent Probe Amplification





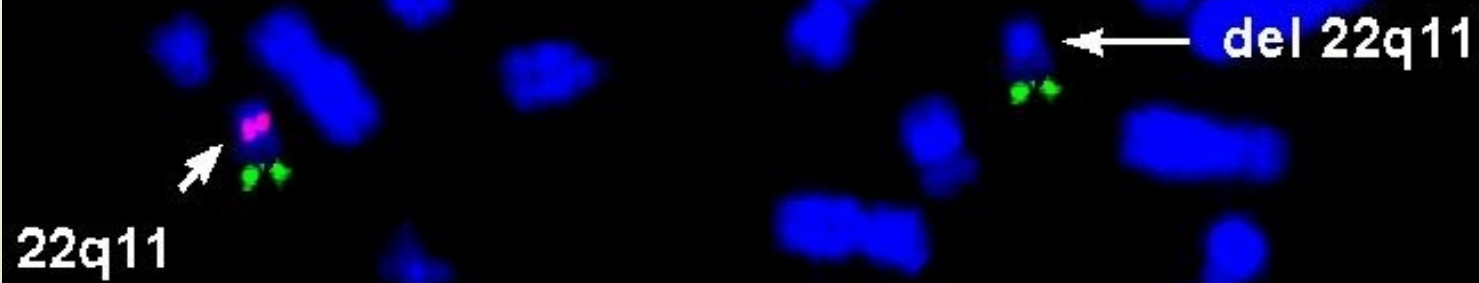
# Microdeletions

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

# Syndrom Di George

- Velo - Kardio- Facial syndrome
- CATCH 22
- Congenital heart disease - conotruncal, craniofacial dysmorfism, thymus aplasie, imunodeficient`cy, hypoparathyreoidismus

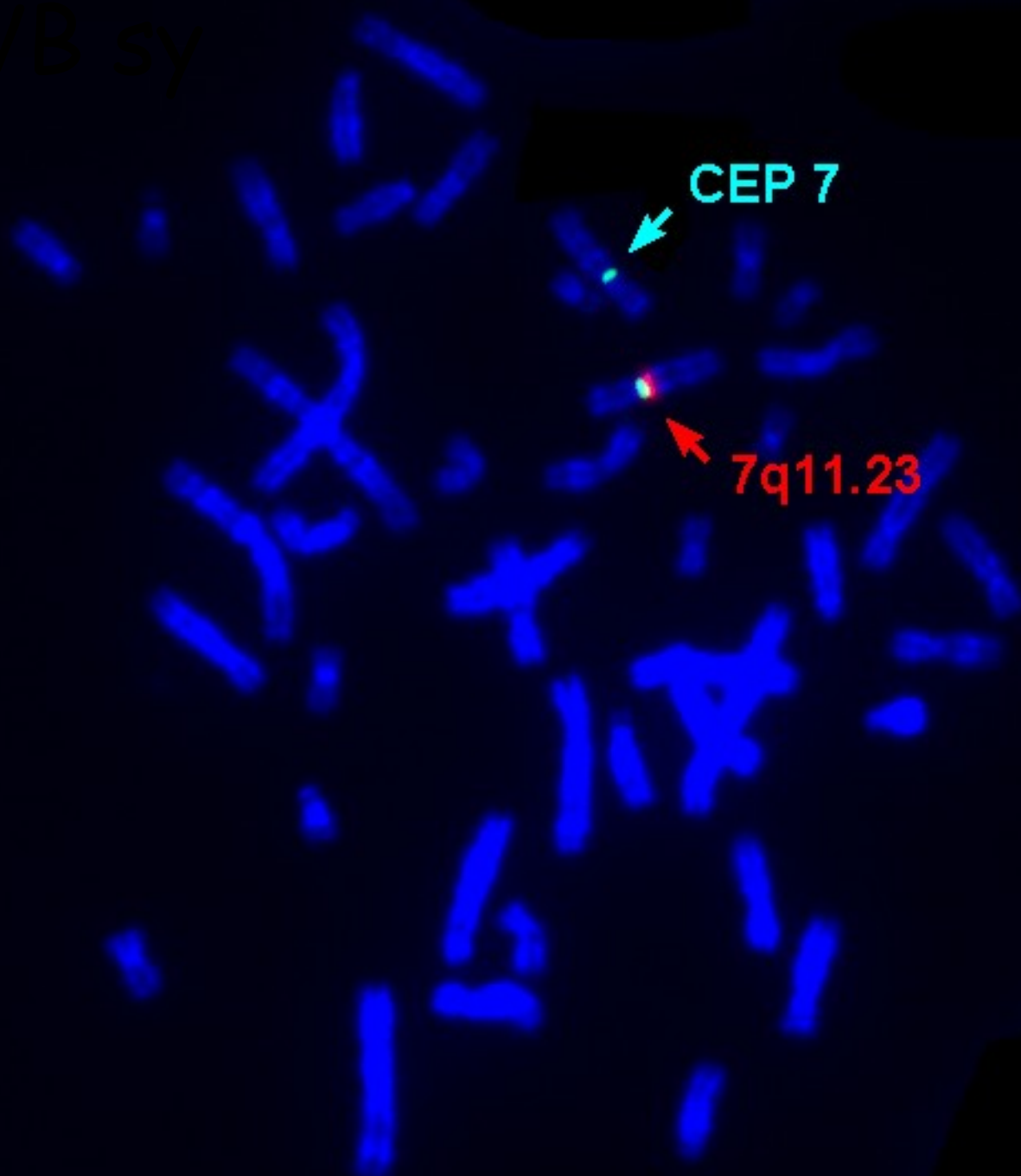
# DiGeorge syndrom



# Williams - Beuren syndrom

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

Photo WB sy



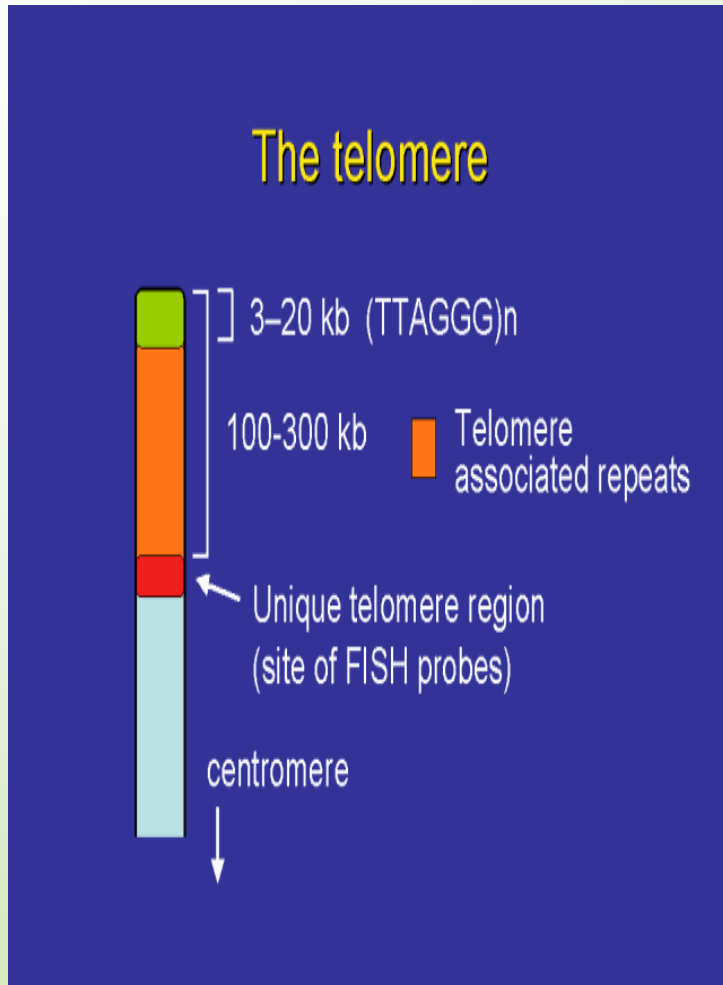
# Prader-Willi syndrom

- Hypotonie, hypotrofie in small children
- PMR, small statue, obesity, hyperfagie, akromikrie, hypogonadismus
- mikrodeletion15q11-12 paternal

# Angelman syndrom

- Severe mental retardation
- Epilepsie
- Laughter
- severely delayed speech development
- mikrodeletion 15q11-12 mat

# The telomere

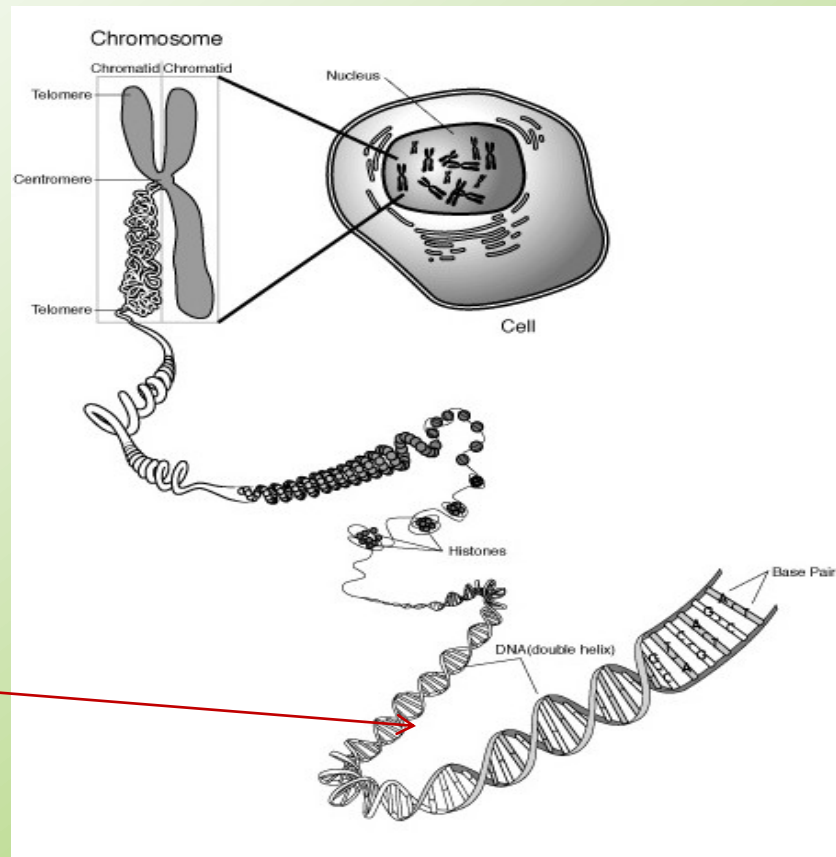


Rearrangement in about 6-8% children with mental retardation with or without congenital defect (FISH, HR-CGH, MLPA)



# Mendelian inheritance

# Monogenetic diseases

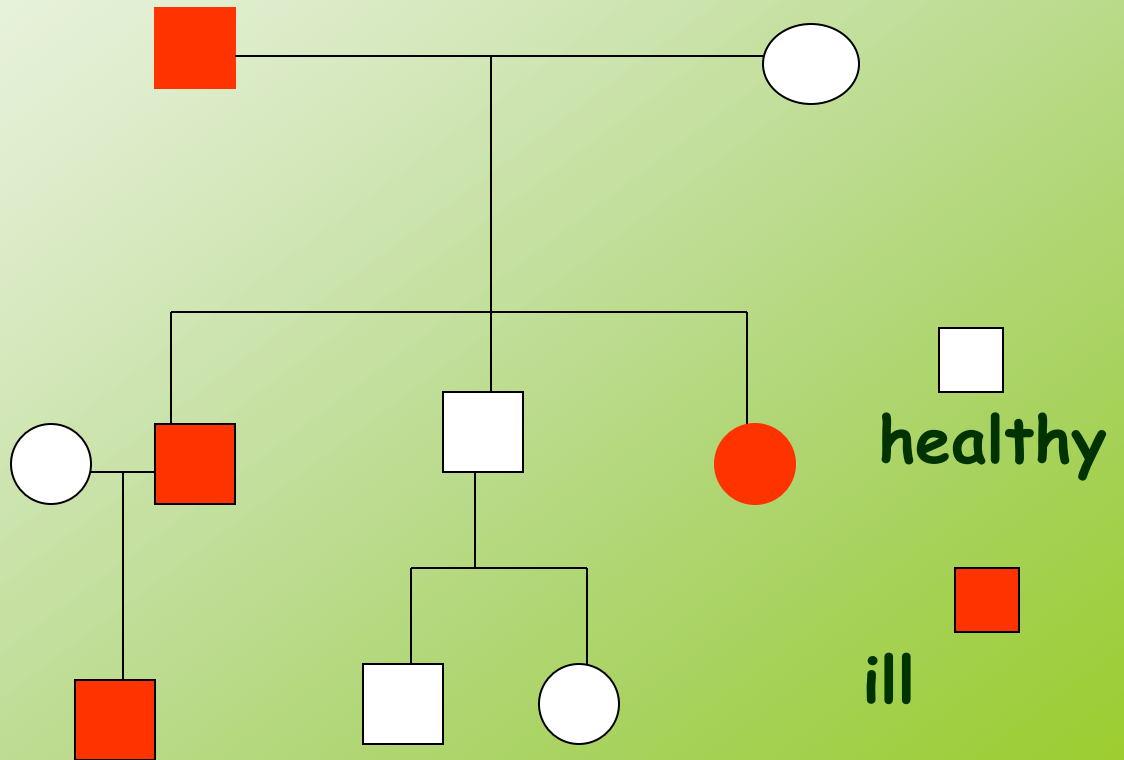


# Autosomal Dominant

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

# Pedigree AD inheritance

- the risk **50%**



# AD - diseases

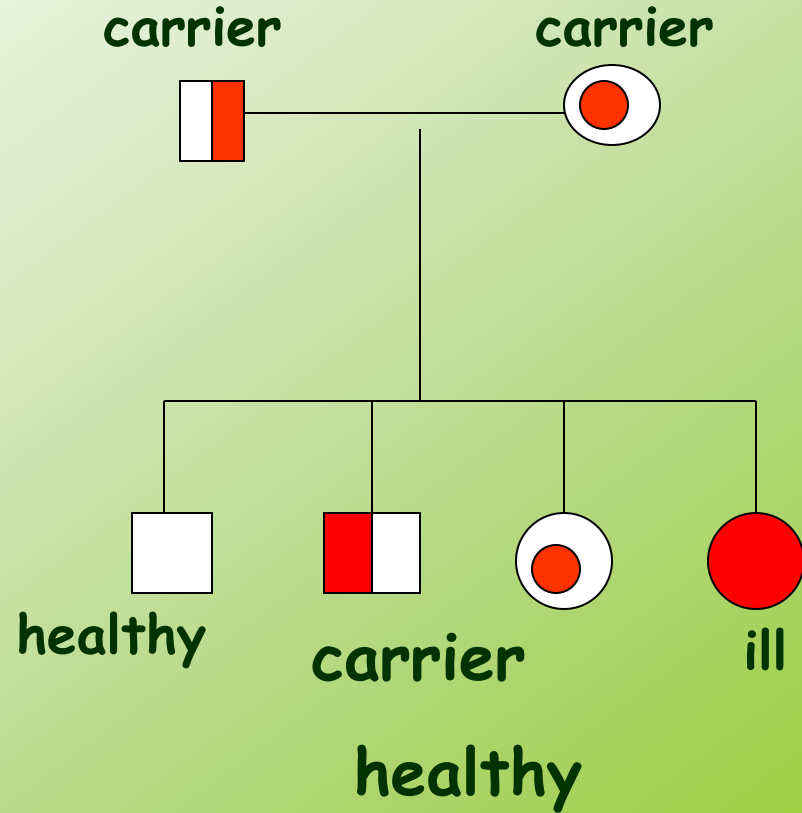
- Neurofibromatosis 1 and 2
- Achondroplasia
- Huntington disease
- Marfan syndrome
- Myotonic dystrophy

# Autosomal Recessive

- Heterozygotes are generally unaffected clinically
- The sexes are involved equally
- An individual manifesting a recessive disorder usually has heterozygous parents
- Once a homozygote is identified, the recurrence risk for other child of some parents is 25%

# Pedegree - AR inheritance

•The risk for next child 25%



# AR - diseases

- Cystic fibrosis  
(frequency of heterozygotes CR- 1/26)
- Phenylketonuria (1/40)
- Congenital adrenal hyperplasia (1/40)
- Spinal muscular atrophy (1/60-80)

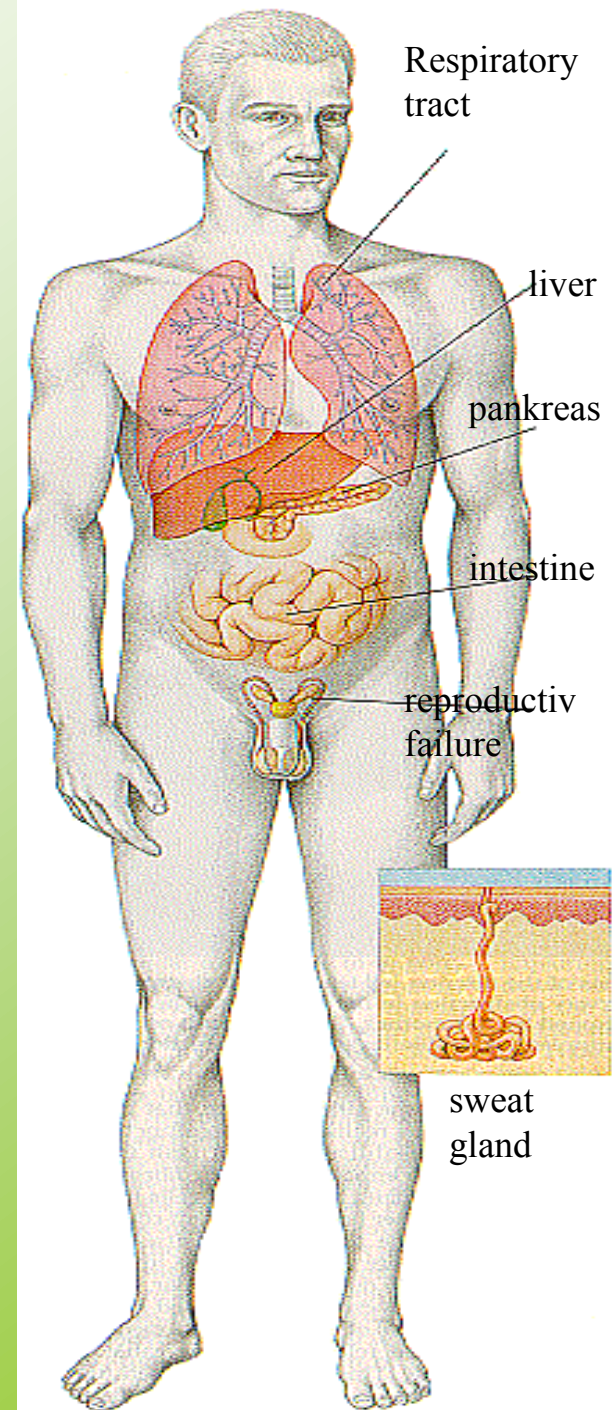


# Cystic fibrosis

- 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
- About 1600 mutations in CFTR gene were identified

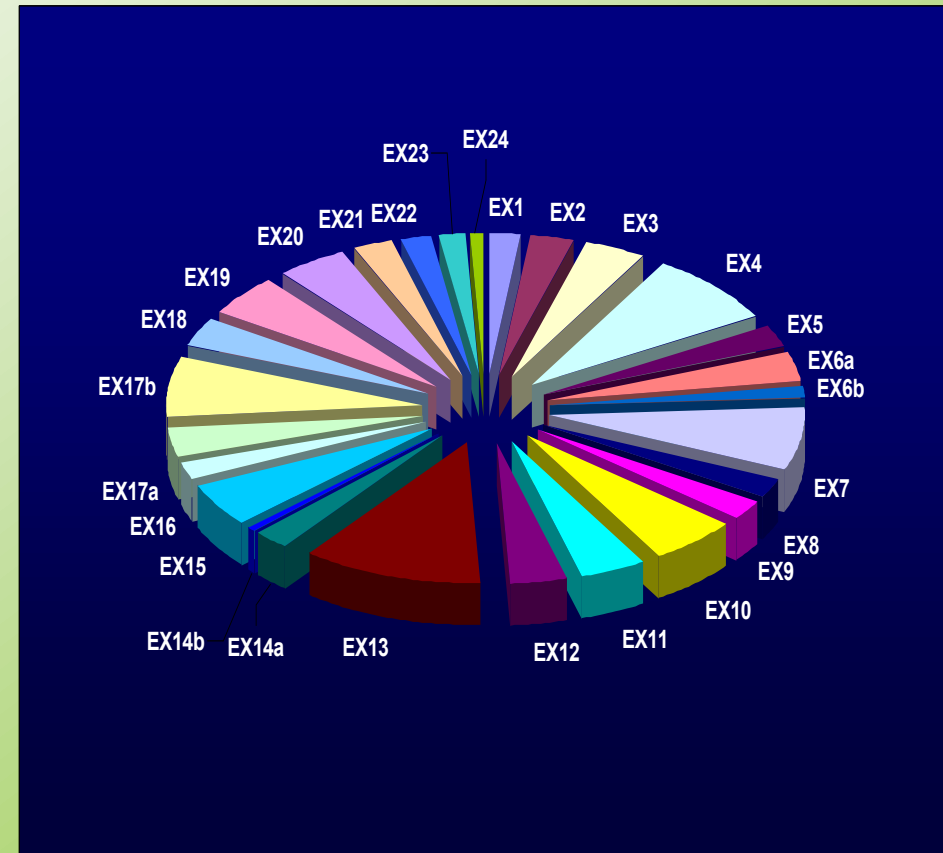
# Cystic fibrosis

- disease affecting multiple organs



# The reason for CFTR gene analysis

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



CFTR gene - distributions of mutations

# Most frequent CFTR mutations in Czech population

Mutation	Frequency in CR (%)
F508del	70,7
CFTRdele2,3(21kb)	6,4
G551D	3,7
N1303K	2,8
G542X	2,1
1898+1 GtoA	2,0
2143delT	1,1
R347P	0,74
W1282X	0,6

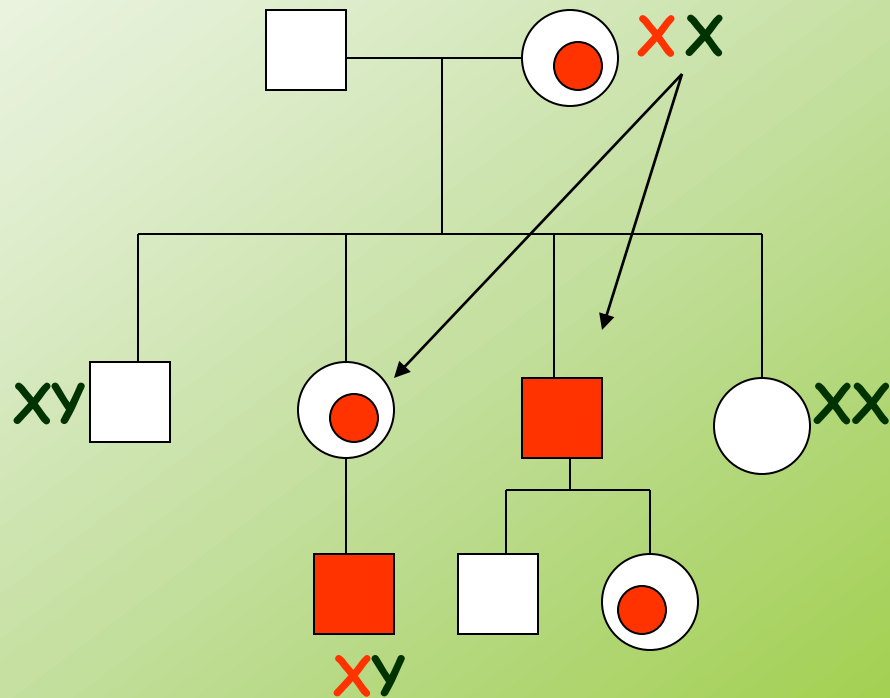
# X-linked Recessive

- Females are not affected as severely as males or are not affected
- An affected male cannot transmit the trait to his sons, because 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

# X-linked Recessive

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

# X- recessive inheritance

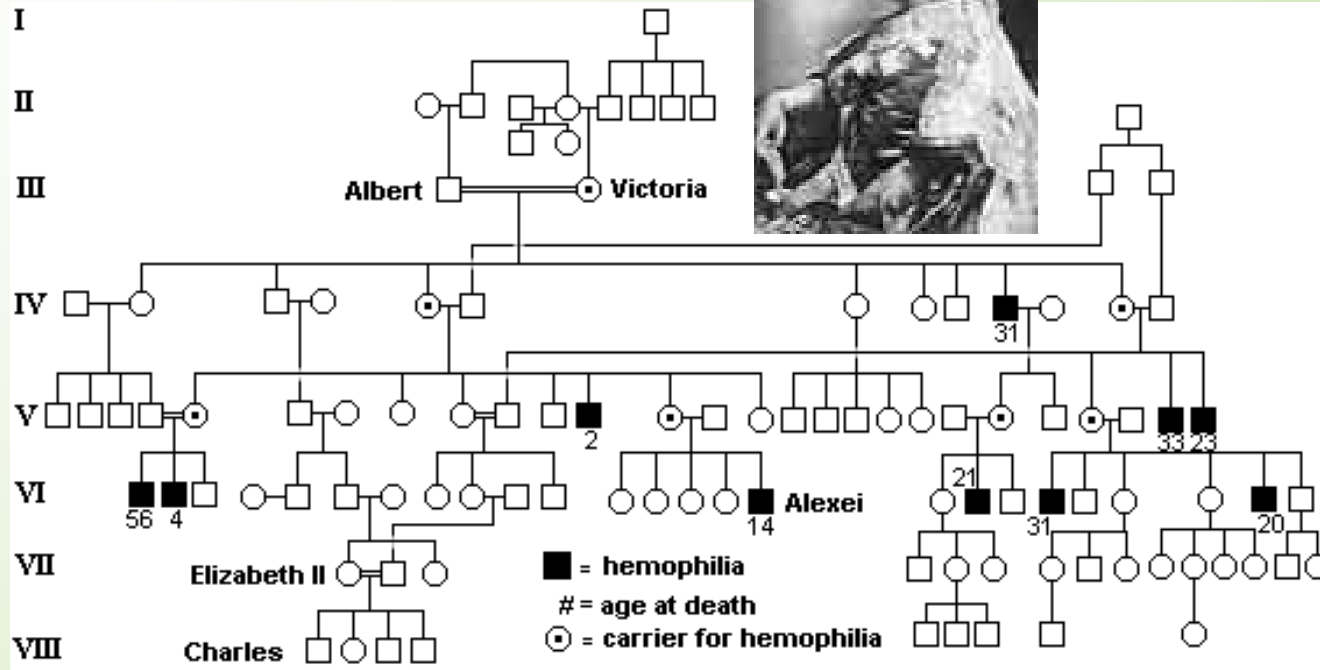


# XR - diseases

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



# Pedegree



**Multifaktorial -polygenic  
inheritance**

**Diseases with complex  
heritability**

**Teratogens**

# Charakterization

- disease with multifactorial inheritance include not mendelian types of inheritance
- diseases exhibit familial aggregation, because the relatives of affected individuals more likely than unrelated people to carry diseases predisposing predisposition

# Charakterization

- in the pathogenesis of the disease play a basic role non-genetic factors
- disease is more common among close relatives and in distant relatives is becoming less frequent

# Examples

- Congenital heart defects (VCC) 4-8/1000
- Cleft lip and palate (CL/P) 1/1000
- Neural tube defects (NTD, anencephalie, spina bifida,..) 0,2-1/1000
- Pylorostenosis
- Congenital hip dislocation
- Diabetes mellitus - most types
- Ischemic heart disease
- Essential epilepsy

# Common congenital defects

# Congenital heart diseases

- 0,5 - 1% in liveborn infants - 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

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

# 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

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

# Neural tube defects

- Multifactorial inheritance (risk for 1. 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

# Teratogens

- teratogen is a substance whose effect on embryo or fetus may cause abnormal development

action may be direct or through the maternal organism

# Human Teratogens

- Physical (radiation, heat (fever), mechanical impact)
- Chemical (chemicals, drugs)
- Biological (infection, fungus ...)
- Metabolic imbalance (disease mother)

# The effect of teratogens depends on :

- dose
- length of the action
- contact time
- genetic equipment of the fetus and the mother



# Critical period

- 14.-18. days after conception - the rule „all od nothing“
- 18.-90. day - organogenesis
- The most sensitive period for the emergence of developmental defects

# Drugs

- Distribution of medicines practice into categories
  - A
  - B
  - C
  - D
  - X
- Food and Drug Administration, 1980

# A

- in controlled studies have shown no evidence of risk to the fetus in the first trimester of fetal development or influence in the next period of pregnancy

product appears to be safe

# B

- Animal reproduction studies demonstrate a risk to the fetus, but there's no controlled studies in women

Animal reproduction studies have shown adverse effects, but in controlled studies in women have not been confirmed

# C

- Animal studies confirm the teratogenic embryotoxic or other adverse effects on the fetus,
- non-controlled studies in women
- lack of studies in animals and humans

product should be administered with caution and only in cases where the benefit for the woman of his administration exceeds the potential risk to the fetus

# D

- risk to the human fetus is known
- medicine may be administered in a situation where its use for a woman needed (lifesaving)
- no other safer drug is available



- studies in animals and in humans clearly demonstrate a teratogenic effect
- drugs absolutely contraindicated in pregnancy

# Drugs with teratogenic effect

- Thalidomid
- Hydantoin
- Valproic acid
- Anti coagulans - Warfarin
- Trimetadion
- Aminopterin
- Methotrexat
- Cyklophosphamid



# Drugs with teratogenic effect

- Retinoids
- Lithium
- Thyxreostatic drugs
- Androgens
- Penicilamin
- Enelapril, Captopril
- Antituberkulotics - Streptomycin

# Thalaidomid

- congenital heart defects
- limb reduction anomalies
- Other congenital defects  
(gastrointestinal, urogenital tract  
orofacial - ears anomalies, CNS  
defects..)

# Hydantoin

- Atypical face, growth retardation, mild mental retardation, behavioral problems, hypoplastic nails and fingers

# Aminopterin a Methotrexat

- folic acid antagonist  
facial dysmorfism, cleft lip and/or  
palate, small mandible, ears  
anomalies, hydrocephaly, growth  
and mental retardation, miscarriage

# Warfarin

- coumarin antikoagulans
- facial dysmorfism - nasal cartilage hypoplasia, CNS - defects

# Retinoids

- Cleft lip and palate, mikrognatia, eyes anomalies, ears dysplasia
- Defects of CNS
- Thymus hypoplasia
- Limb defects

# Infection

- Toxoplasmosis
- Rubella
- Cytomegalovirus
- Herpesvirus
- Others (parvovirus, antroprozoonosy, chlamydia..)

• TORCH

# Toxoplasmosis

- chorioretinitis
- hydrocephaly or microcephaly
- intracranial calcification, mental retardation
- icterus, hepatosplenomegalia, carditis
- prematurity
  
- positiv IgM in the mother - treatment with Rovamycin
- Prenatal dg.: serology, DNA-PCR)



# Rubella

- hearing and vision impairment (cataract, glaucoma, mikroftalmia, blidness)
- mental retardation
- Cong. heart defects
- icterus, hepatosplenomegalia
  
- prevention- vaccination

# Cytomegalovirus

- Intrauterin growth retardation
- mikrocephaly, calcification in the brain, mental retardation,
- hepatosplenomegaly
  
- Repeated maternal infection is possible
- Prenatal dg.: serology, DNA-PCR

# Varicella zoster

- Skin lesions and defects
- Brain damage, mental retardation
- Eye defects
  
- Prenatal dg. - serology, DNA-PCR

# Metabolic dysbalance

- Fetal alcohol syndrom (FAS)
- Maternal Phenylketonuria
- Maternal Diabetes mellitus
- Maternal Hypothyreosis

# Fetal alcohol syndrom

- Hypotrophy, growth retardation, mental retardation
- facial dysmorphism
- Congenital heart defects
- Limb defekts
  
- Abuse of 60g pure alcohol / day (longterm)
- Combine with malnutrition, folic acid deficit...

# Maternal Phenylketonuria

- Low birth weight
  - hypertonia
  - mikrocefaly, mental retardation
  - Cong. heart defects
  - hyperaktivity
- 
- newborn screening
  - (frequency 1/10 000 newborns
  - inheritance - AR)
  - initiation of treatment within three weeks to prevent mental retardation in the child

# Reproductive Genetics

Preconceptional testing  
Genetic counselling and analysis  
in couples with reproductive disorders  
Prenatal diagnosis  
Preimplantation genetic diagnosis  
Examination of potential donor gametes

# Secondary prevention of genetic

- The procedures in pregnancy - prenatal diagnosis and early postnatal diagnosis



# Prenatal diagnosis

- Non invasive methods- screening
- Invasive methods
- **CVS** - after the 10. week of gestation
- **AMC** - 15.-18. week of gestation
- **Kordocentesis** - after the 20. week of gestation

# Prenatal diagnosis results

- CVS - karyotype - about 5 days
- AMC - karyotype - about 14-21 days
- DNA analysis (monogen diseases)
- About 5-15 days
- DNA from amniocytes after cultivation - exclusion contamination by maternal tissues

# Prenatal screening (CR)

- Ultrasound (12. - 20. - 33. week)
- Ultrasound 20.week - cong. defect
- Ultrasound 20-22. week - cong. heart defect
- 10-14. week of gestation
- Free beta hCG, PAPP-A, US-NT, NB..
- 16.-18.week of gestation
- AFP, hCG, uE3

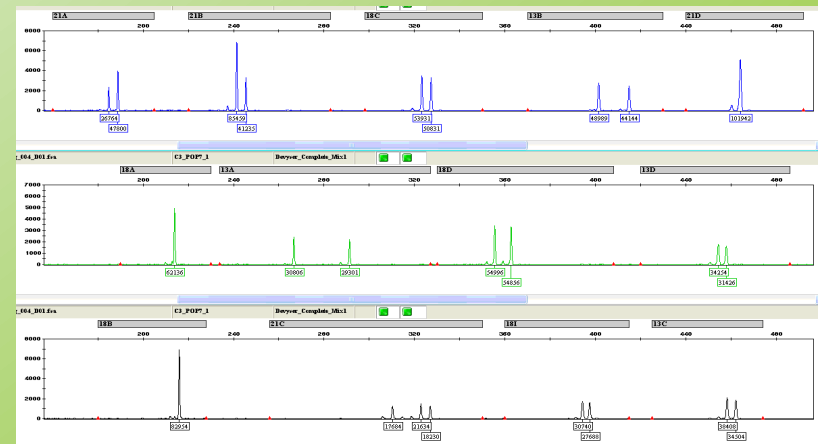
# Indications for prenatal diagnosis / counselling

- Advanced maternal age (35-38 years)
- Risk factors - US - congenital defects
- Family history of known conditions for which diagnosis is possible (DNA analysis)
- Known chromosomal abnormality (de novo finding in previous child, structural change in parents)
- Positive prenatal screening for chromosomal abnormalities

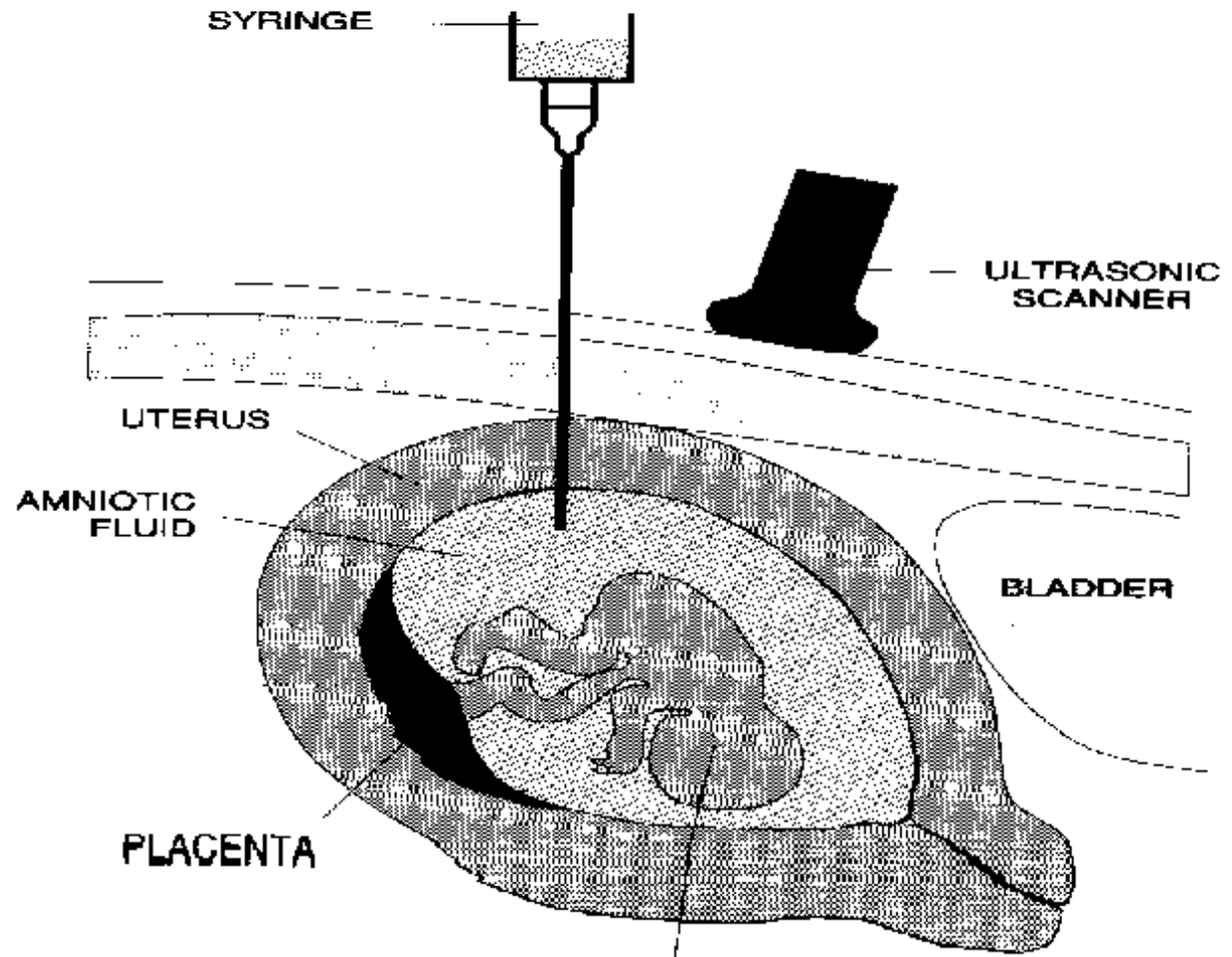
# Prenatal analysis of most frequent aneuploidias

## QF PCR

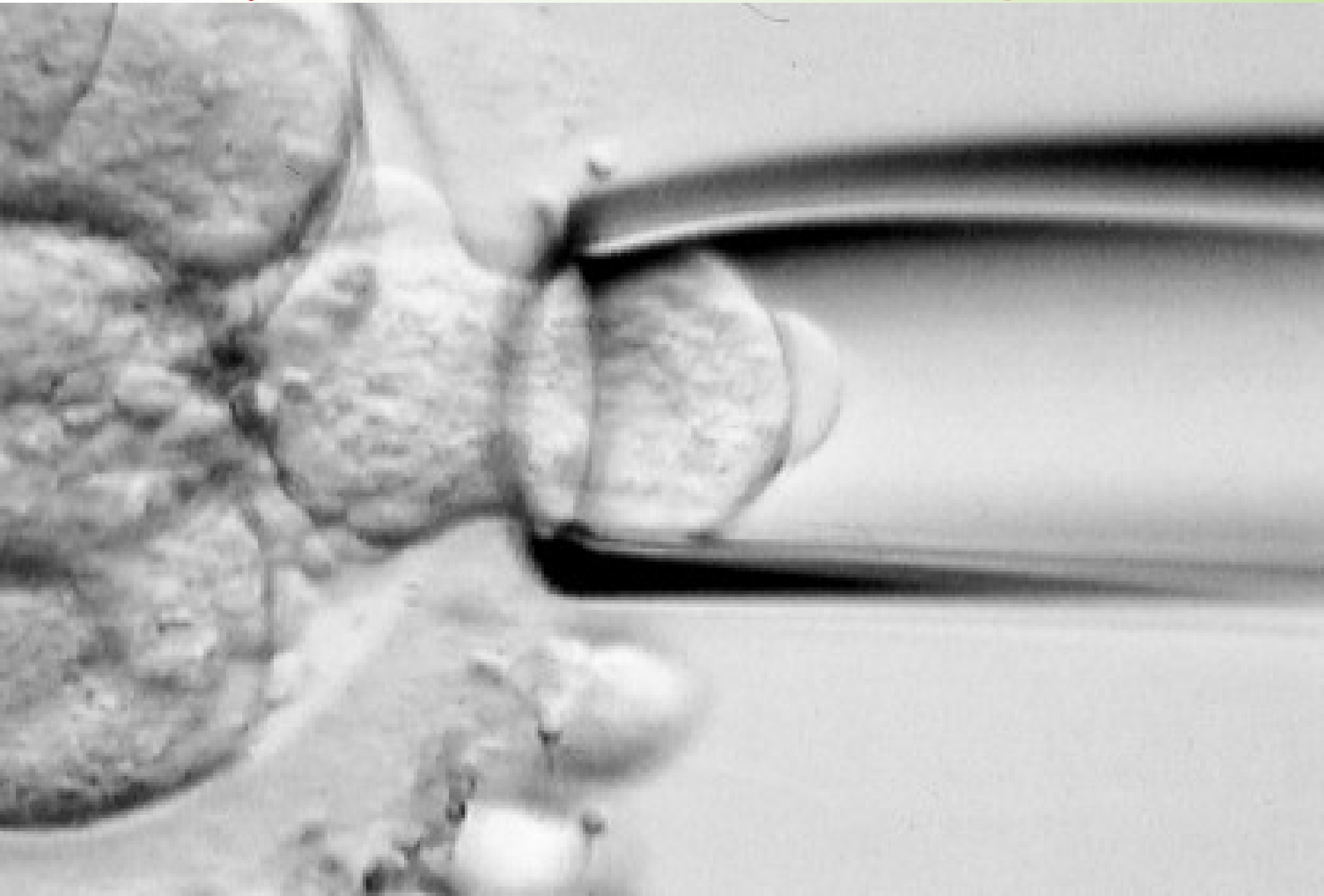
- Examination of the most common numerical changes in chromosomes 13, 18, 21, X and Y
- The result for 24-48 hours



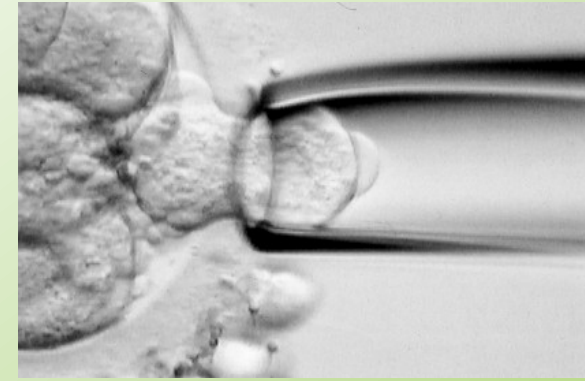
# Amniocentesis



# Preimplantation Genetic Diagnostics



# Preimplantation Genetic Diagnostics



- IVF
- Preimplantation genetic screening
- most common aneuploidias  
chr.13,18,21,X,Y, 15,16,22
- Preimplantation Genetic Diagnostics  
Structural chromosomal aberrations
- (parents are carriers of balanced rearrangement)
- Monogenic diseases (known in family history)



# PG Diagnostic

X

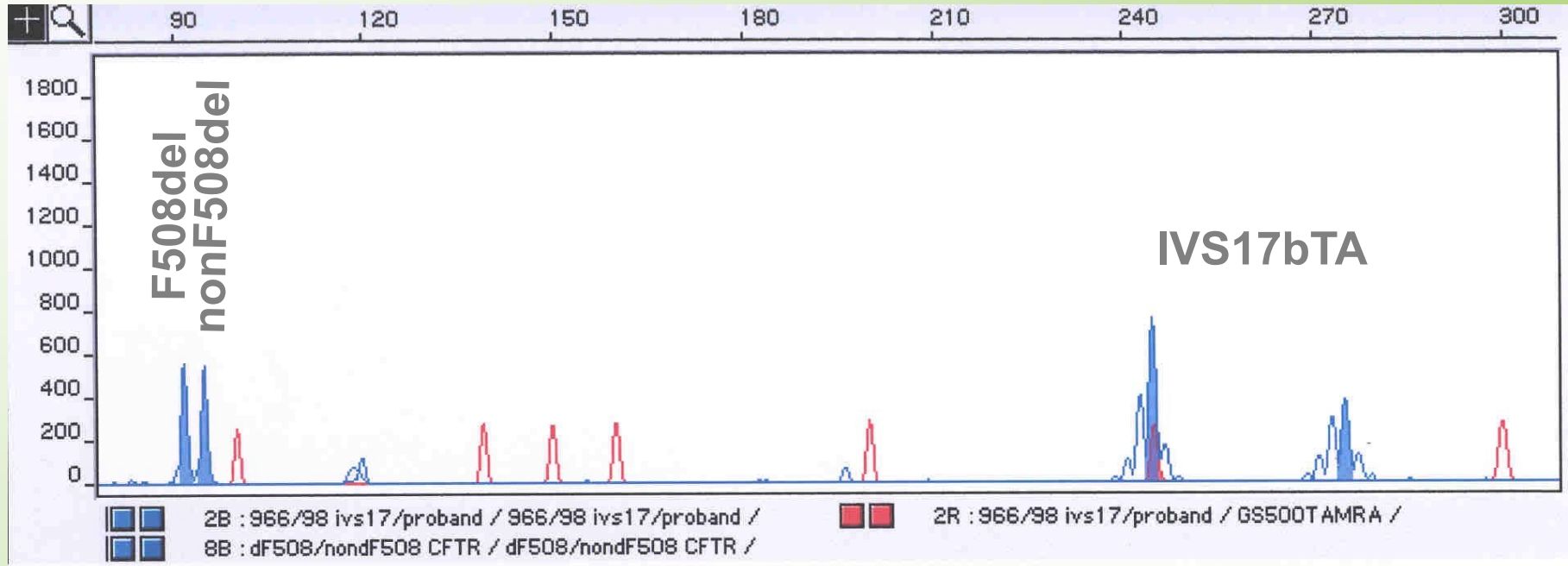
# PG Screening

- 
- PGD high genetic risk
  - PGS most common aneuploidies

# PGD - Cystic fibrosis

## Detection of the mutation F508del in CFTR gene

Fragmentační analýza - ABI PRISM 310



Multiplex PCR - koamplifikace mutace F508del s intragenním mikrosatelitem IVS17bTA

Genotyp blastomery: [F508del]+[nonF508del]

# Genetic counselling in infertility

# Infertility

- Is the infertility one aspect of a genetic disorder that might be transmitted?
- Will correction of infertility give an increased risk of malformations in the offspring?
- Genetic testing before use of methods of assisted reproduction.

# Infertility

- Pathological examination of the abortus where possible, this may identify major structural malformations.
- **Cytogenetic study of parents**, this is especially 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 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)

# Factor V - Leiden

- frequency in the white European population of about 5 - 9%
- AD inheritance
- increased risk of thromboembolism in homozygots for FVL 50-100x, in heterozygots 5-10x
- increased risk of fetal loss after the 10. week of gestation

# Sterility in male

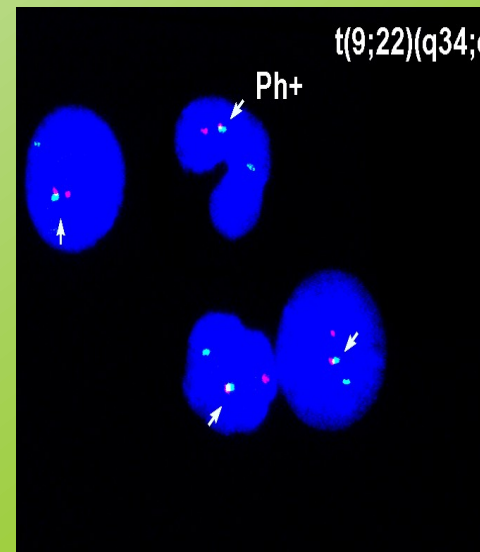
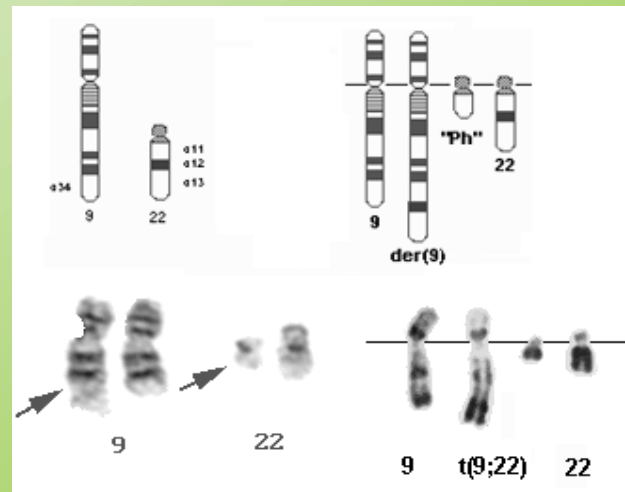
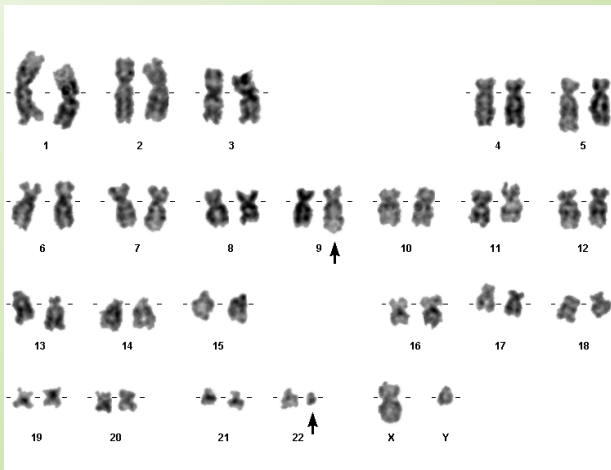
- AZF (azoospermia factor) deletions of the DAZ gene **Yq** (deleted in azoospermia)
- Infertile man - 4-5%
- Men with azoospermia - about 15%
- CFTR mutations and polymorphisms



# Genetic risk in cancer

# Genetic testing in oncologic patients

- Specification of the:
- Diagnosis
- Therapy
- Prognosis
- Monitoring of minimal residual disease



# Genetic risks in cancer

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

# Hereditary cancer syndromes

- AD inheritance
- Preventive, pre-symptomatic testing
- Prevention
- Associated problems

# Hereditary cancer syndromes following AD inheritance

- Breast cancer - BRCA 1 and BRCA 2
- Familial Adenomatous Polyposis coli - FAP
- Von Hippel - Lindau syndrome - VHL
- Retinoblastoma
- Neurofibromatosis - NF1, NF2
- Li-Fraumeni syndrome
- Lynch syndrome - hereditary non polypous colon cancer - HNPCC

# Genetic testing in Hereditary cancer syndromes

- 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

# Postnatal care and neonatal screening

- Early diagnosis

Dispensary

Specialized Care

# Prenatal and perinatal management of pregnancies with malformation or genetic disease in the fetus

- Consultation with experts, who will continue to take care of the pregnant woman - ultrasound specialist, gynecologist, obstetrician, psychological support ..

Consultations with specialists, who will care after the birth of newborns with disabilities

The planned delivery of specialized care workplace - kardiocentrum, pediatric surgery, cardiology...



# Newborn screening

## Sampler card

0004305

Whatman 903<sup>®</sup> Lot 6272207/51 2009-05 SN

SN 0004305

**Kartičku vyplnit před odběrem  
Nedotýkat se oblasti pro kapky krve  
Při poškození kartičku nepoužít**

Požadavek (zaškrtnout): SKH  CAH  Jiný (vypsat):  Odběr: První:   
Opakovaný:

Jméno novorozence	
Jméno	Příjmení
Rodné číslo, pojišť'ovna <small>(dítě nebo matka)</small>	Porodní hmotnost g
Datum a čas narození <small>DD.MM.RRRR – HH.MM</small>	Datum a čas odběru <small>DD.MM.RRRR – HH.MM</small>
Kódové číslo odběru <small>Kód oddělení (AAA) • pořadí odběru (XXX) - AAAXXX</small>	Praktický dětský lékař Jméno, telefon
Jméno matky	
Jméno	Příjmení
Telefon matka (rodina) <small>Mobil i pevná linka</small>	Adresa matky (pobytu)
Odesílatel vzorku <small>Čitelné razítko, jménovka, podpis</small>	

CE IVD REF 10539735 Rev.0 LOT 6272207/51

Whatman GmbH  
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37586 Dassel Germany

# Screened diseases in CR from 10/2009

- Kongenital hypothyreosis
- Kongenital adrenal hyperplasia - CAH

(cumulative risk 1/2900)

# Screened diseases in CR from 10/2009

- Inborn errors of metabolism
- Fenylketonuria (PKU, HPA)
- Leucinosis
- MCAD
- LCHAD
- VLCAD
- Def.karnitinpalmitoyltransferasis I a II
- Def.karnitinacylkarnitintranslocasis
- Glutaric aciduria
- Izovaleric acidurie

(cumulative risk 1/4000)

# Screened diseases

- Cystic fibrosis

(1/4000)

- cumulative risk of all 13 screened diseases in CR - 1/1200