

# 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
- Prenatal diagnosis
- Reproductive genetics

# 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, possibilities of testing, prenatal analysis)
- Voluntary choice for patients
- Informed agreement

# Primary genetic prevention

- **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 some monogenic diseases (Neurofibromatosis I, 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, ...)

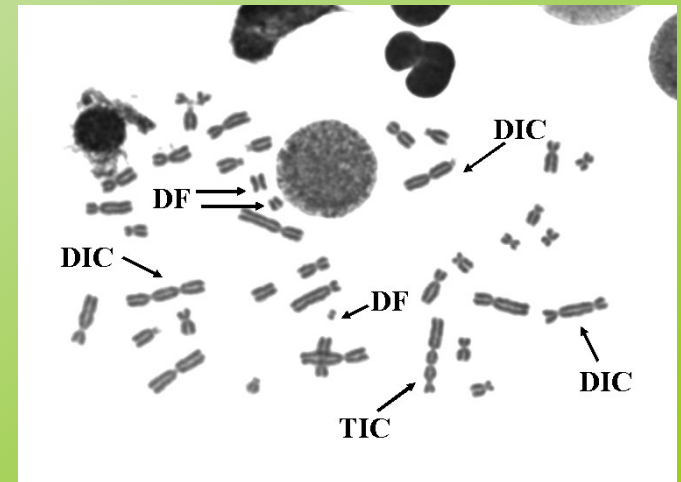
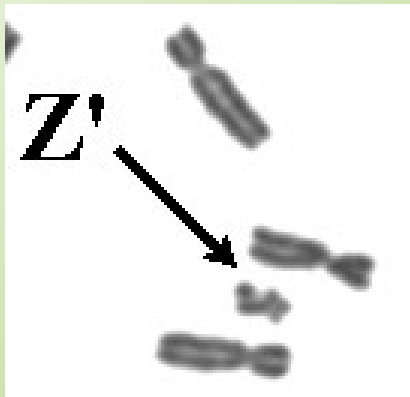


# Vitamin prevention of neural tube defects, anterior abdominal wall defects, clefts

- 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

# 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)

# Adoption

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

# Donation

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

# Secondary genetic prevention

- 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

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

# 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

- Donors of gametes  
(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  
(Pathological results)

# Pregnant women

- Ultrasound prenatal screening  
- pathological results
- Congenital malformations in the fetus
- Risk of chromosomal abnormality in the fetus

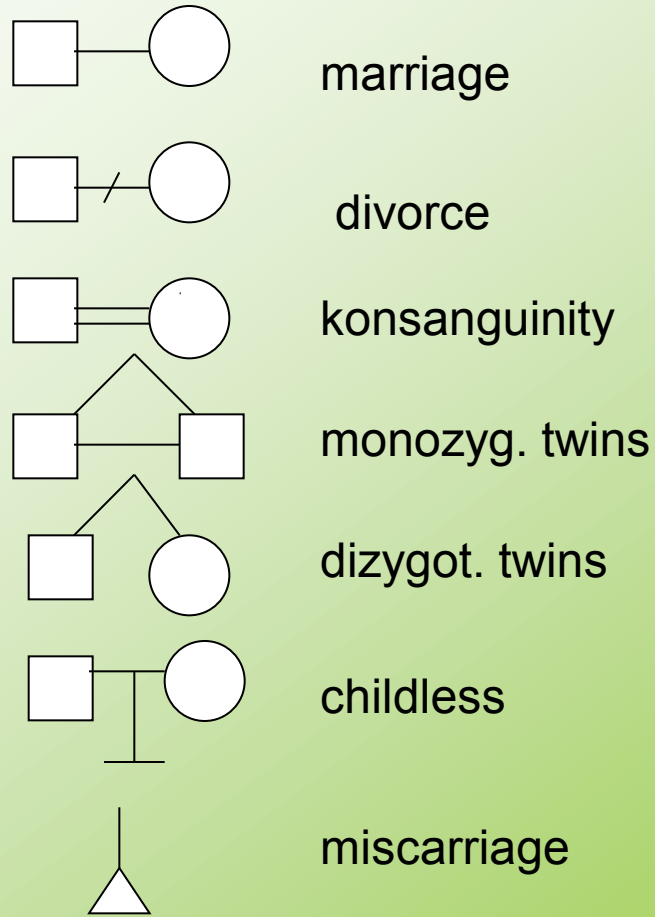
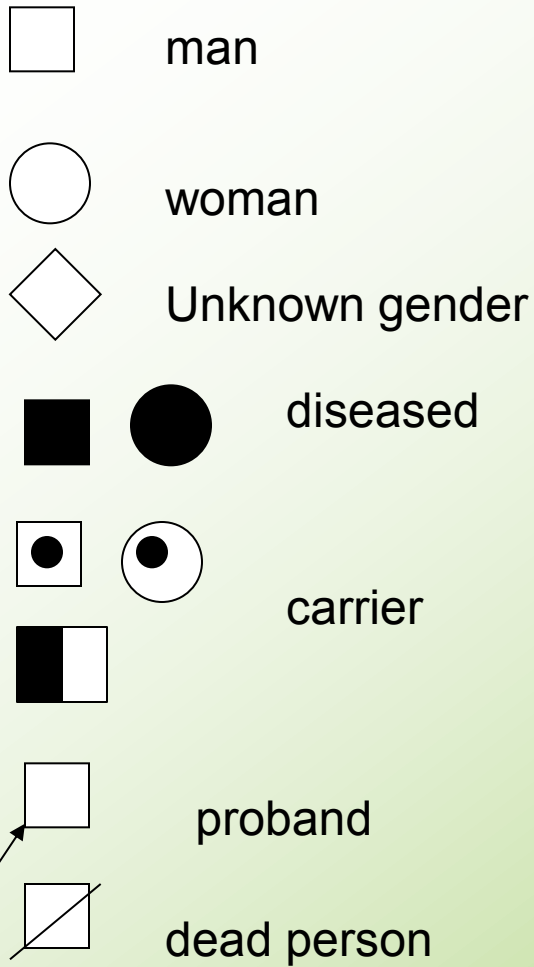


# Genetic counselling

- Anamnesis
- Family history
- Pedigree analysis
- Examination of the patient
- Laboratory analysis
- Other examinations - neurology, psychology, hematology, CT, MRI ...

# Three-generation pedigree

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



# Clinical examination

**Atypical ears**

**Dermatoglyfy** - grooves on the palms  
and soles

**Hexadactylie**

# Atypical holding of fingers in trisomy 18



**Atypical shape of the foot  
in trisomy 18**

**small  
figure**

# Anomalies of teeth

# Status eye slits

**Atypical face, skin**

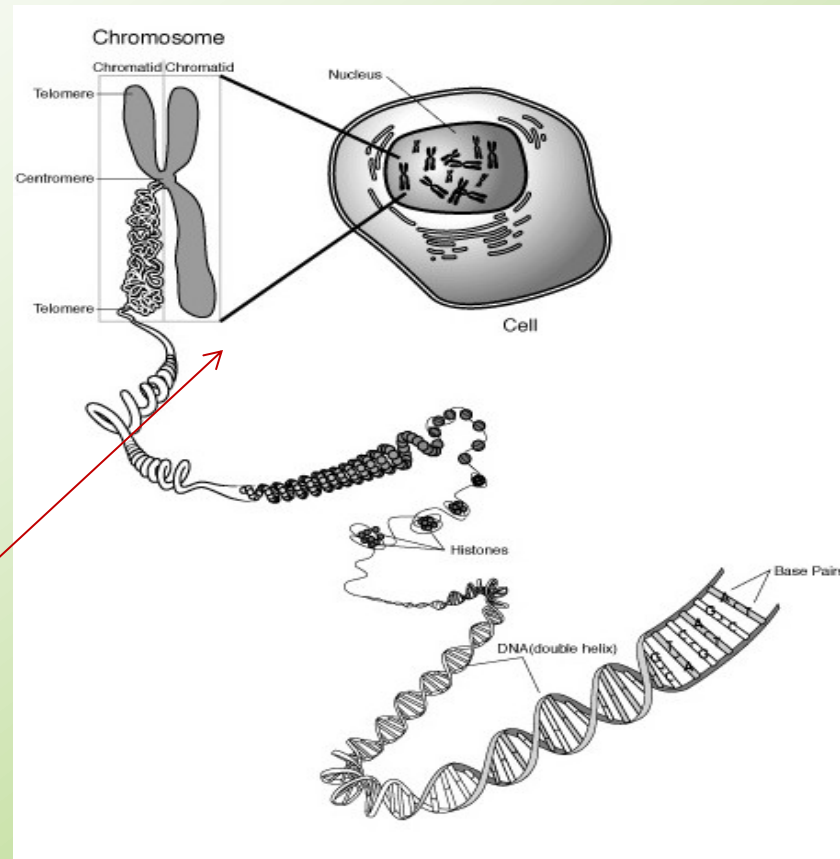
# Next steps

- 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



0,6-0,7% live born



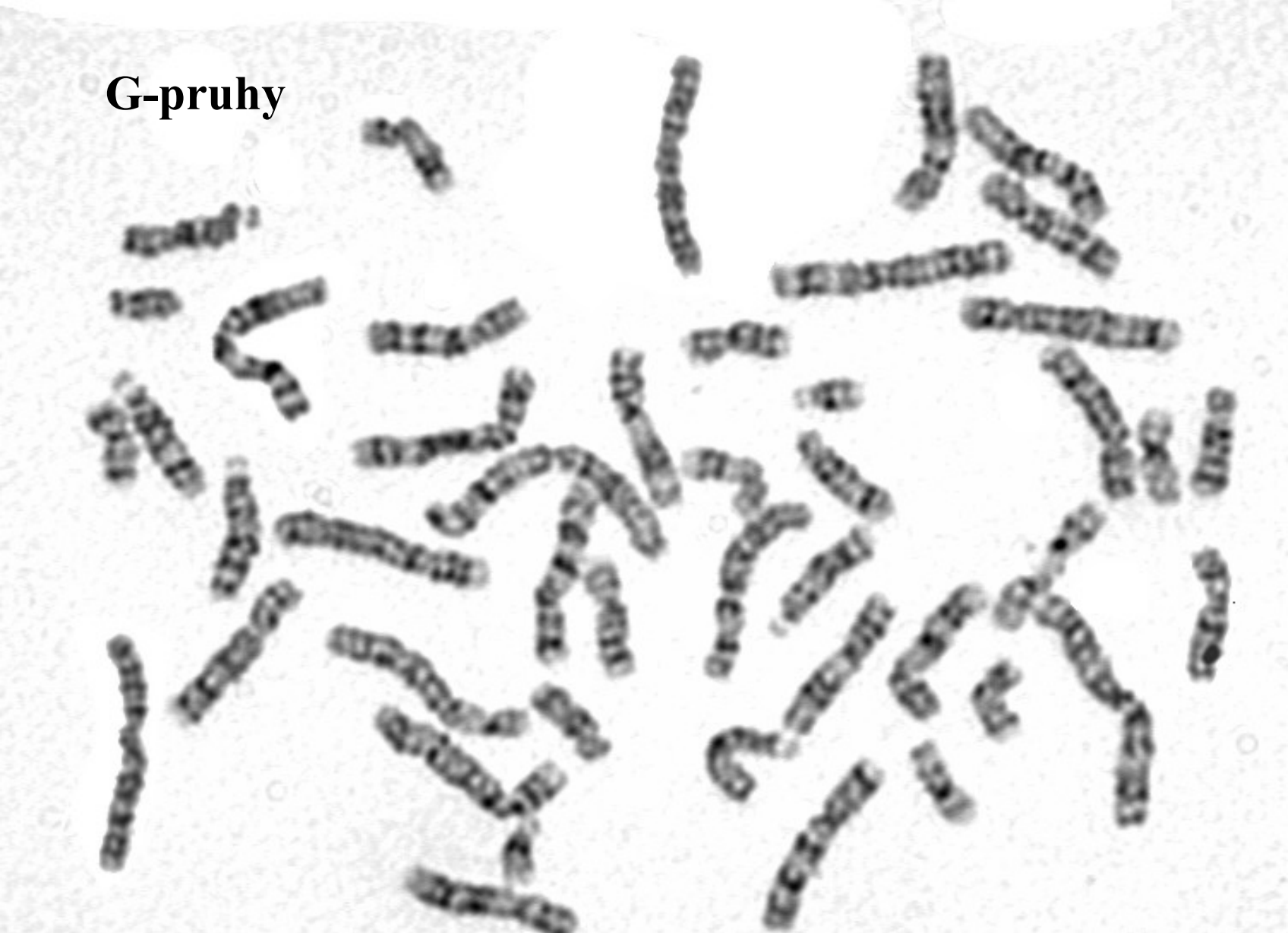
# Congenital chromosome abnormalities

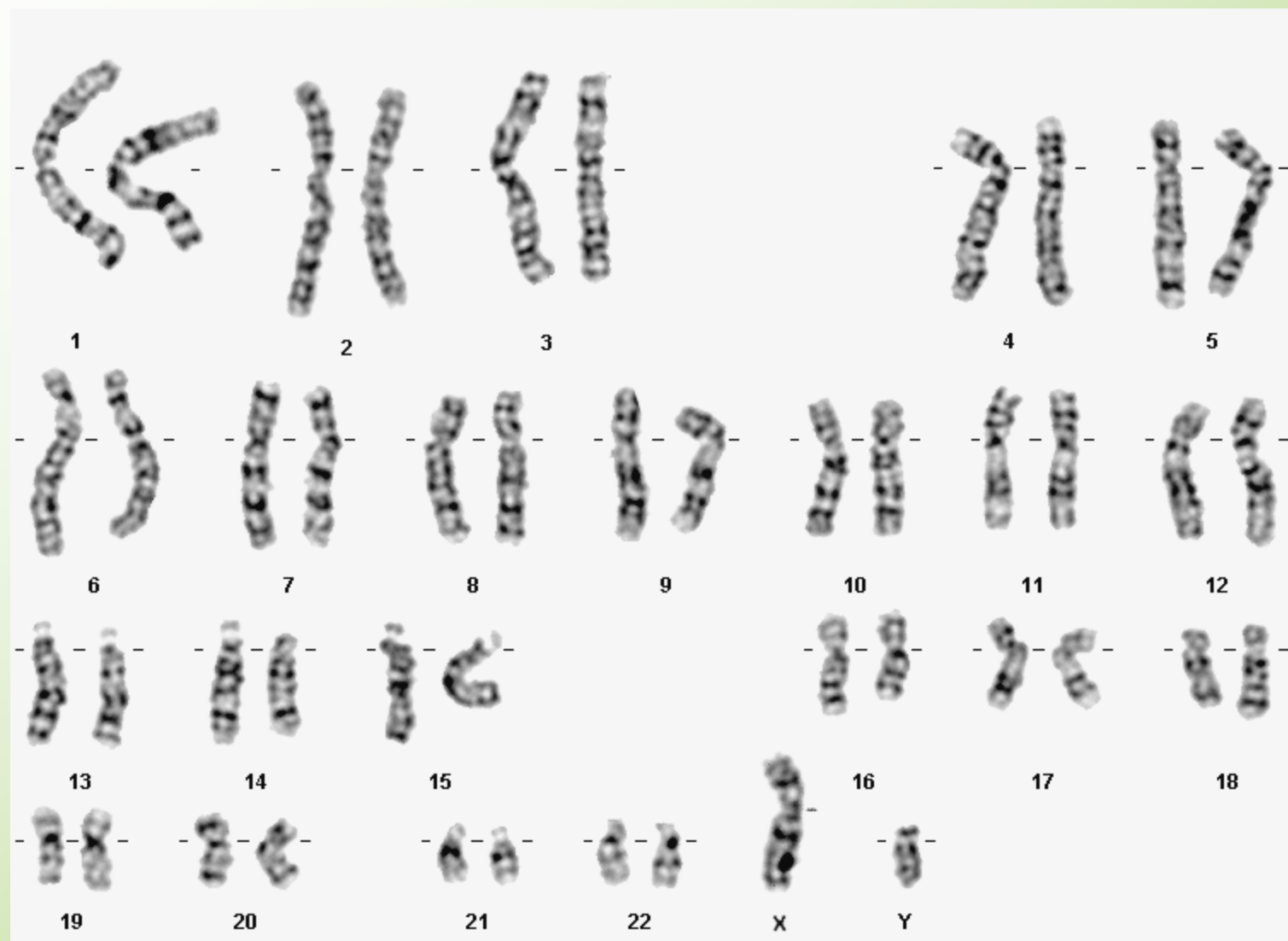
- **Autosomes**
- **Gonosomes**
  
- **Numerous**
- **Structural**
  
- **Balanced**
- **Unbalanced**

# 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

**G-pruhy**





# 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

- 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)



**Happy nature**

**Vision and hearing  
disorders**

**Hypothyroidism**

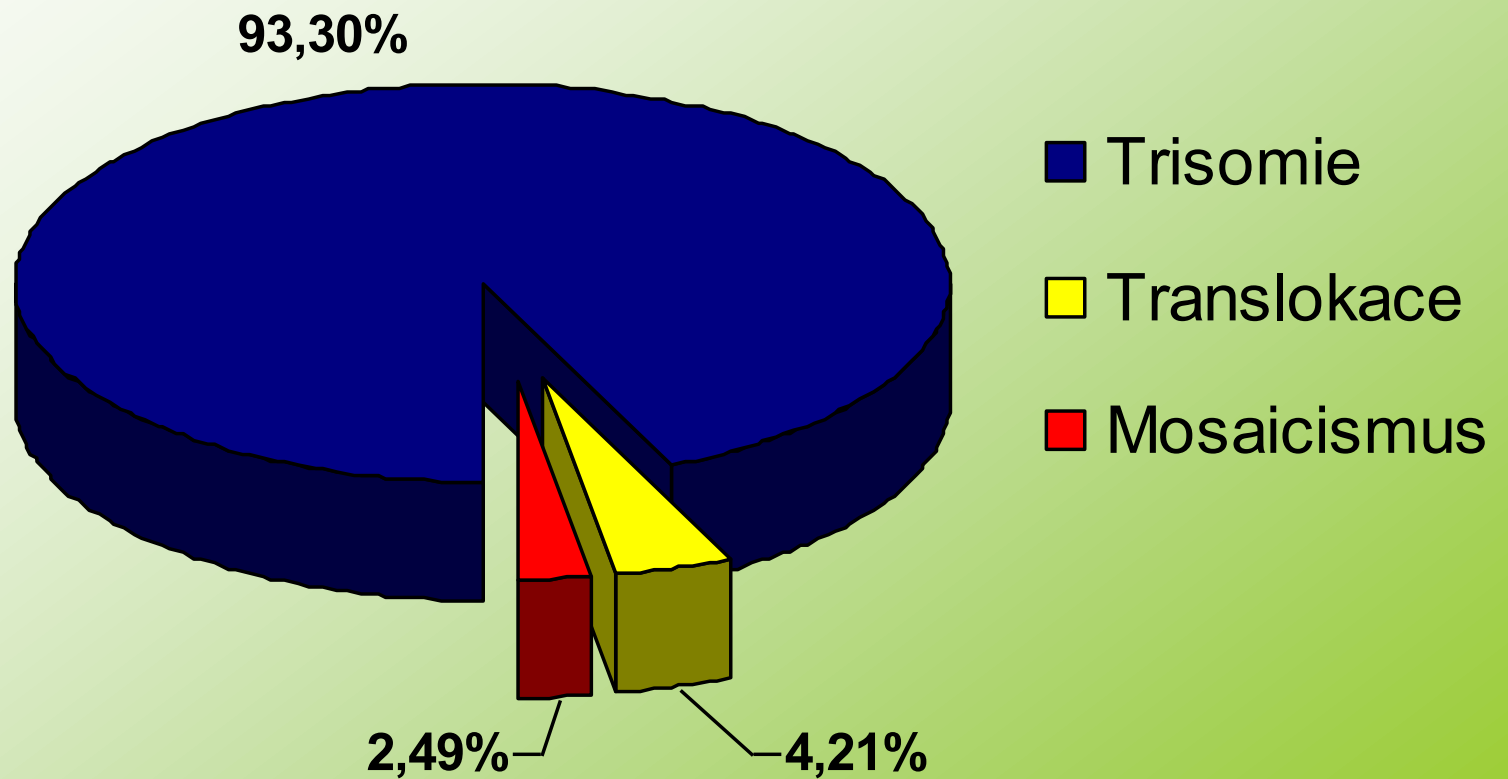
**Correlation between  
positive stimulation and  
height IQ**

**Male sterility**




**Alzheimer-like symptoms  
in 40**

# Cytogenetic findings in DS in Czech republic

1994 - 2001



# 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 about 95% of fetuses with Down syndrome
- 1/100 - positiv - genetic counselling and karyotyping
- 1/100-1/1000 - US and genetic counselling
- 1/1000 - negativ - US

# Down syndrome - prenatal diagnosis

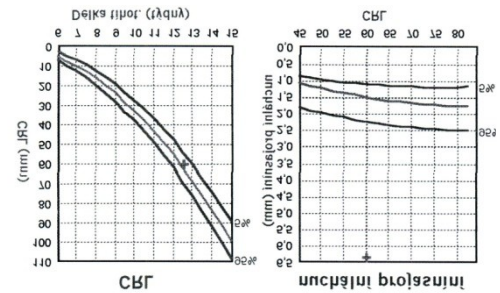
- II. trimester screening - biochemical screening
- 16. -18. week of gestation
- AFP - alpha-fetoprotein (↓)
- total hCG - chorionic gonadotropin (↑)
- uE3 - unconjugated estriol (↓)
  
- Fals positive results about 5%
  
- Reveals about 70% of fetuses with Down syndrome
  
- 1/250 - positiv
- 1/250-1/350 - border
- 1/350 - negativ

# Down syndrome - prenatal diagnosis

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



# NT+



# 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



# 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

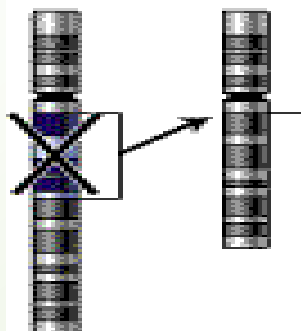
- 47,XXX
- 47,XY
- 48,XXXX
- 48,XXYY....

# Structural chromosomal aberrations

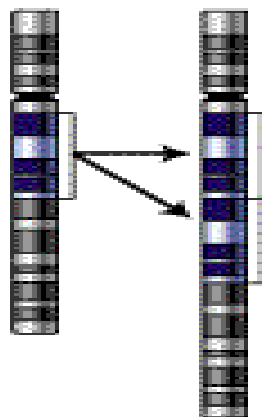
- deletion or a duplication of the genetic material of any chromosome, atypical structure - side by side to get the genetic material, which there normally is not - the effect of positional
- partial-partial deletions
- partial trisomy
- inversions, insertions, duplications ....

# Types of mutation

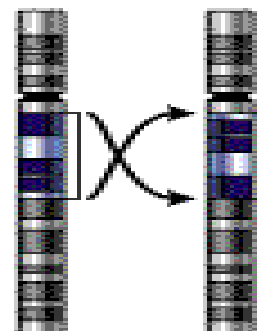
## Deletion



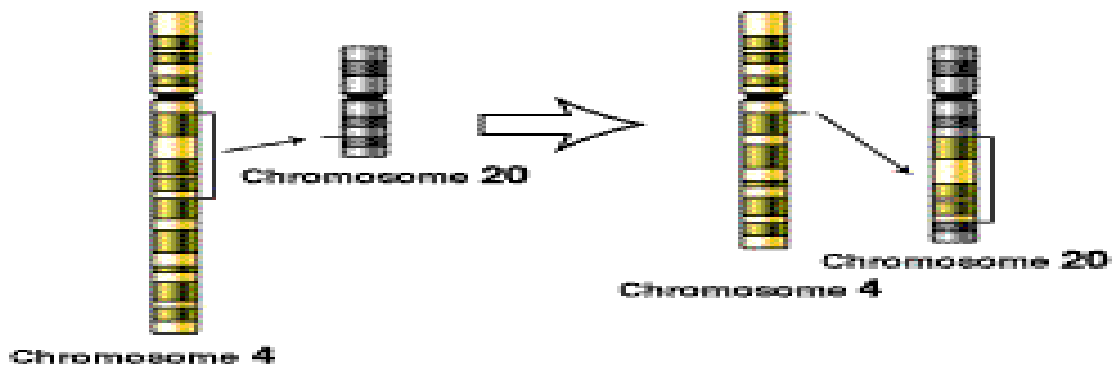
## Duplication



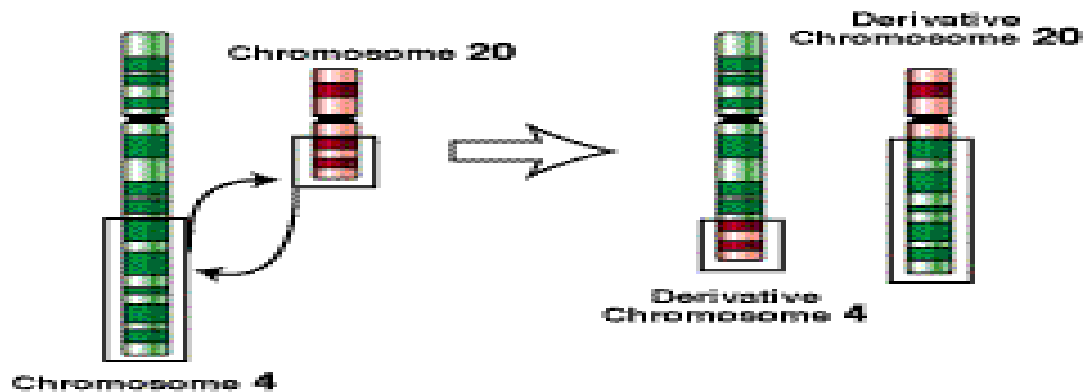
## Inversion



## 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



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





# Syndrom Cri du chat

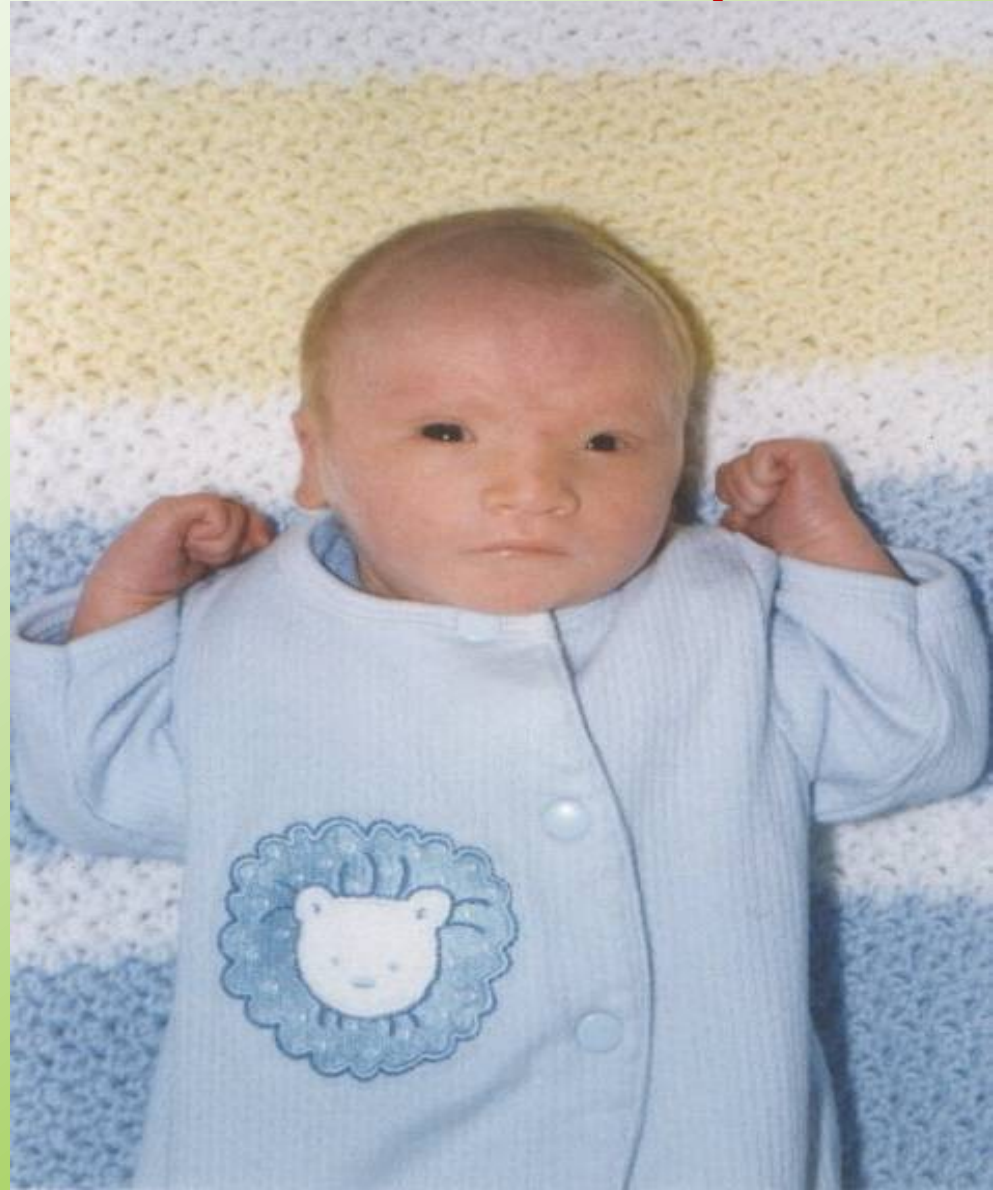
## 46,XX(XY),5p-

- 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

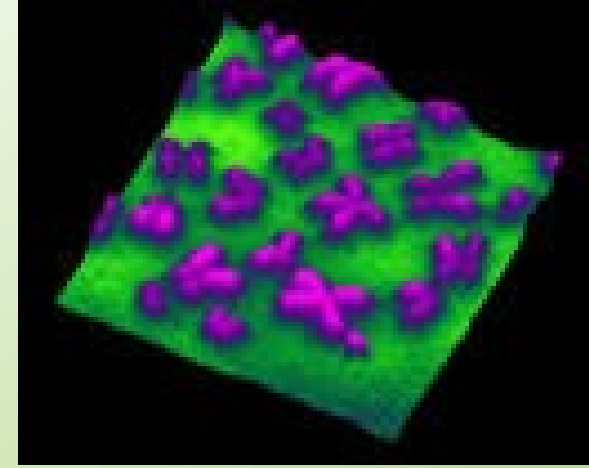


# Cri du chat 46,XX(XY),5p-

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

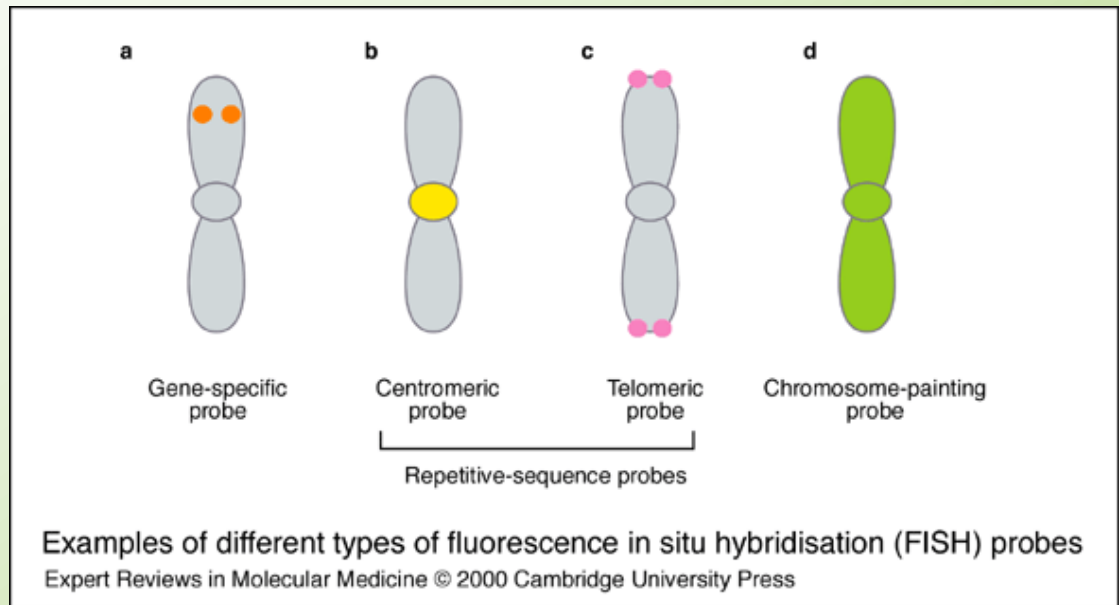


# Mikrocytogenetic Molekular cytogenetic

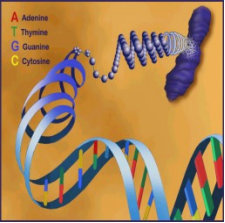


- FISH (fluorescenc in situ hybridisation), M-FISH, SKY (spektral karyotyping), CGH (komparativ genom hybridisation), MLPA
- mikroleletions or mikroduplikations, marker chromosomes, complex rearegements, oncology - oncocytogenetics, fast prenatal diagnostics ...)
- fast methods (possible for prenatal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

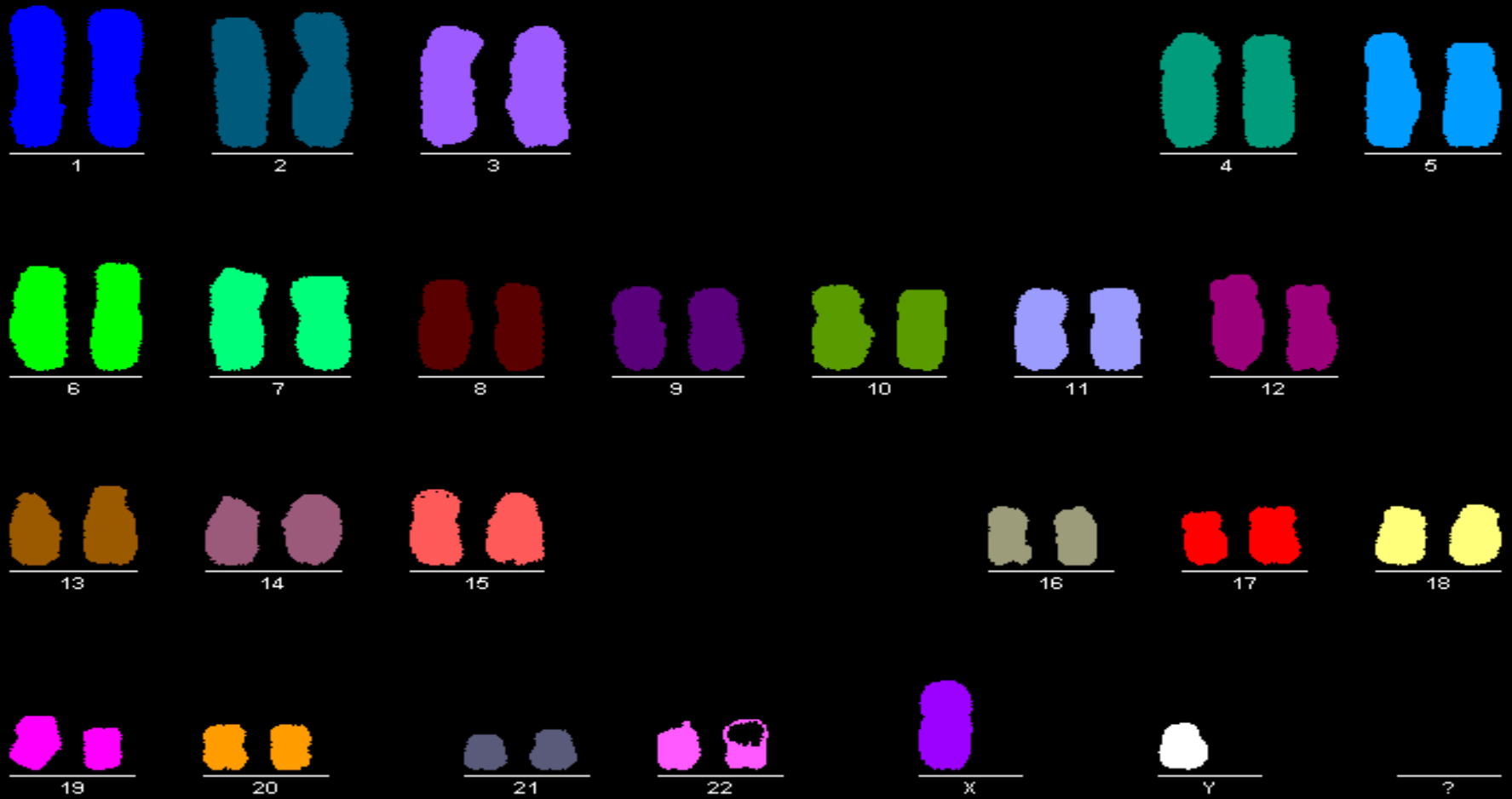




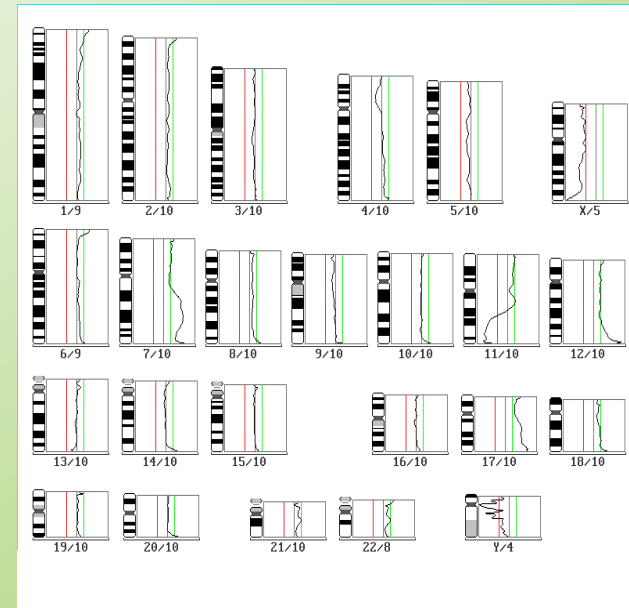
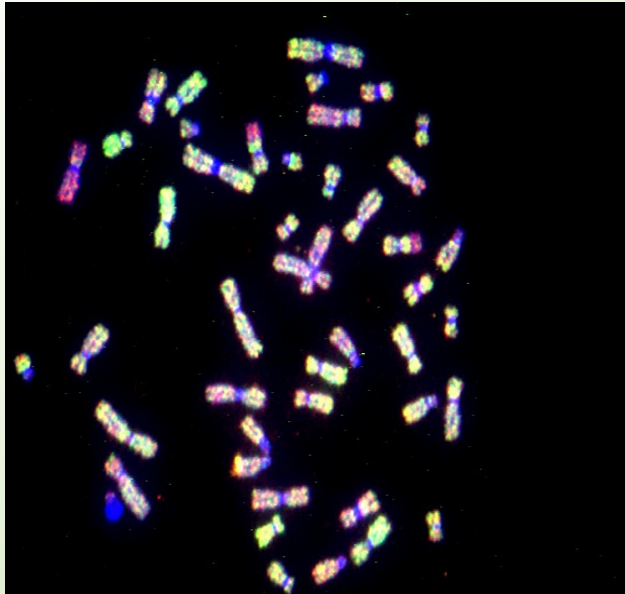
# FISH



# M-FISH (multicolor) Spektral karyotyping (SKY)

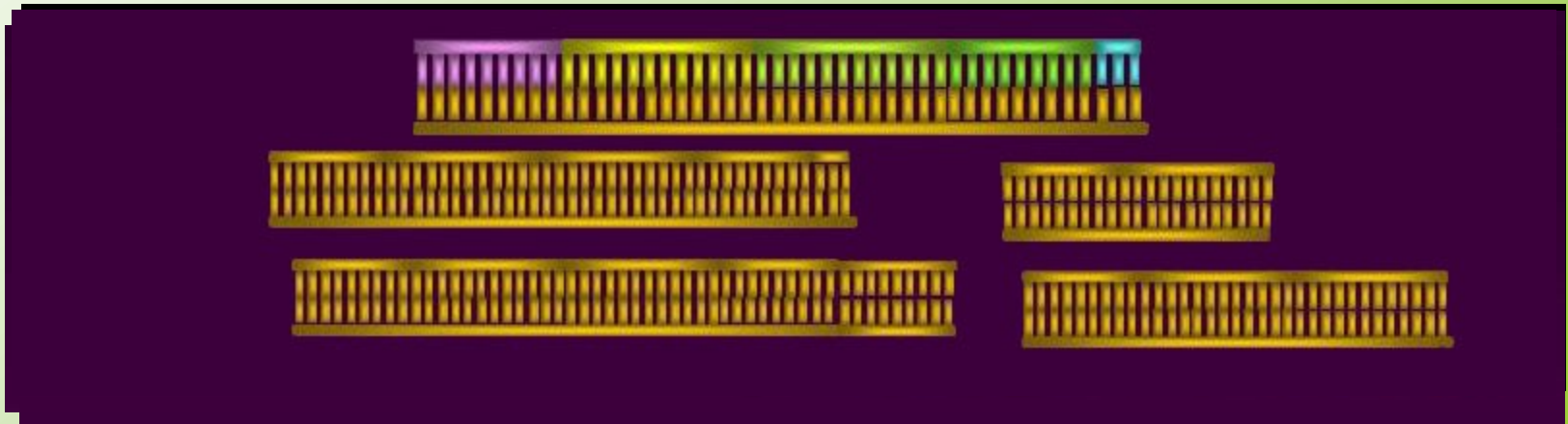


# Comparativ genom hybridisation



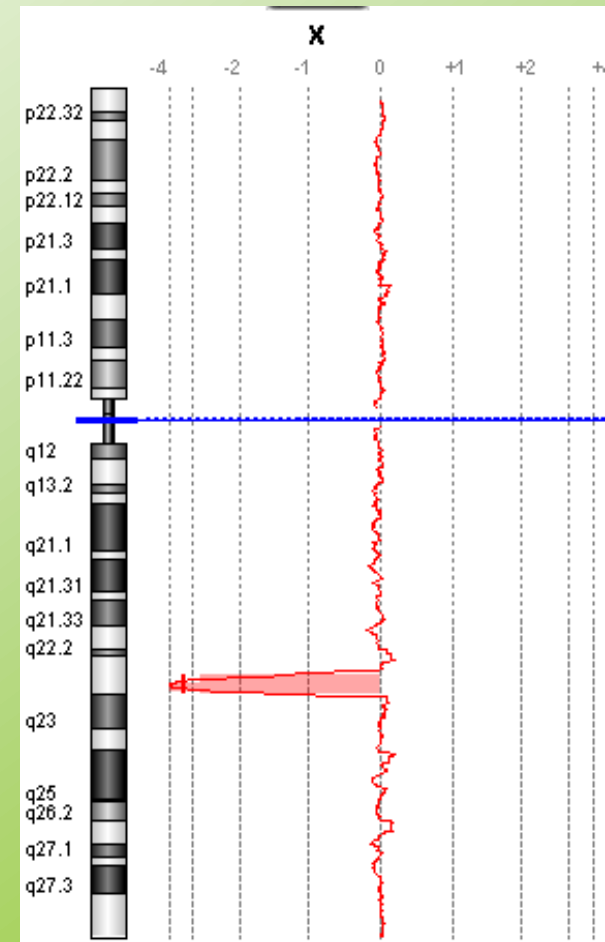
# MLPA

## Multiplex Ligation-Dependent Probe Amplification



# array CGH

- DNA mikroarray
- Chip technology



# 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

# Williams - Beuren syndrom

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



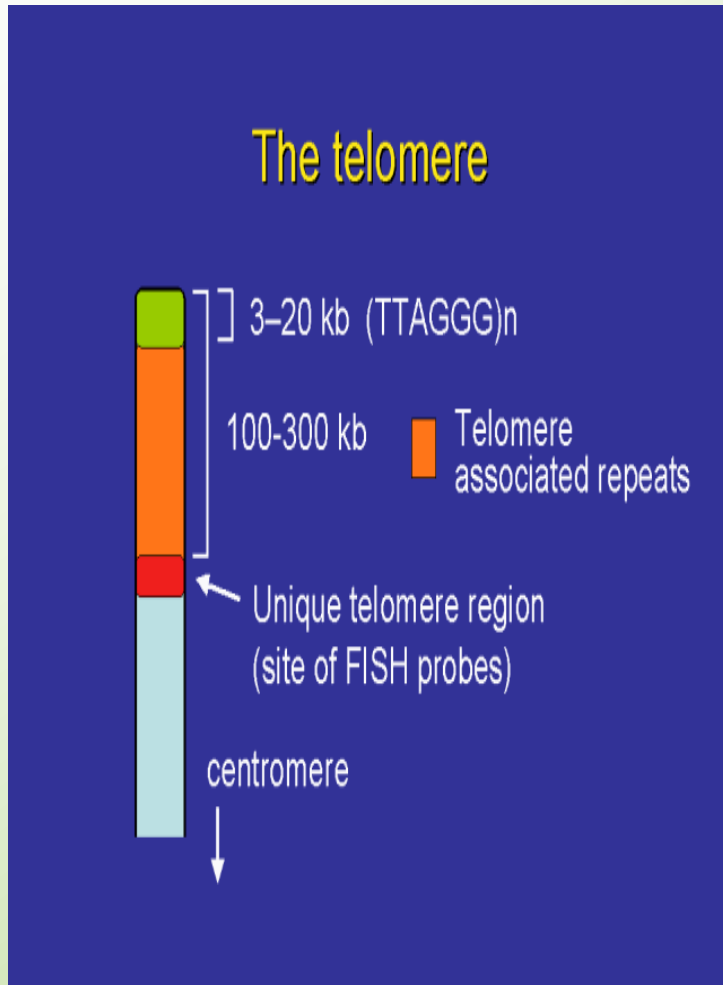
# Prader-Willi syndrom

- Hypotonie, hypotrofie in small children
- PMR, small statue, obesity, hyperfagie, akromikrie, hypogonadismus
- 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)

# 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
- Screening
  
- Invasive methods
- **CVS** - after the 10. week of gestation
- **AMC** - 15.-18. week of gestation
- **Cordocentesis** - 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 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



# 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

# NIPT - non-invasive prenatal testing

examination of fetal DNA in maternal plasma

- aneuploidy (21, 13, 18, X/Y and others - microdeletions...)
- Rh in the fetus
- SRY in the fetus - in X linked diseases in the family
- Some monogenic diseases in the fetus (achondroplasia)

# Indications for prenatal examination / genetic counselling

- US screening - 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
- Advanced maternal, paternal age

# Preimplatation Genetic Diagnostics

# Preimplantation Genetic Diagnostics

- IVF - assisted reproduction
- **Preimplantation genetic screening**
- aneuploidy - array- CGH, chip technology
- (FISH -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

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- PGD high genetic risk
- PGS (most common)  
aneuploidies

# 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

# Mutation G20210A factor II (Prothrombin)

- increased risk of fetal loss after the 10. week of gestation
- frequency in the white European population of about **2-3%**

# Sterility in male

- Klinefelter syndrome and other chromosomal aberrations
- 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

# 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  
Hahnstraße 3,  
37586 Dassel Germany



# Newborn screening in CR

- From Phenyketouria tu 18 diseases
- 2009: 3 → 13
- 2016: 13 → 18

# Screened diseases in CR from 6/2016

- Kongenital hypothyreosis
- Kongenital adrenal hyperplasia - CAH

(cumulative risk 1/2900)

# Screened diseases in CR from 10/2009

- **Inborn errors of metabolism**
- **Fenylketonuria (PKU, HPA)**
- **Leucinosi**
- **MCAD**
- **LCHAD**
- **VLCAD**
- **Def.karnitinpalmitoyltransferasi I a II**
- **Def.karnitinacylkarnitintranslokasi**
- **Glutaric aciduria type I**
- **Izovaleric aciduria**
- **Argininemia (ARG)**
- **Citrulinemia type I (CIT)**
- **Biotinidasi defisiensi (BTD)**
- **Homocistinuria (cystathionin beta-sintasi defisiensi (CBS), piridoksin non-responsif)**
- **Homocistinuria (metilena tetrahidrofolat reduktase defisiensi -MTHFR)**

**(cumulative risk 1/4000)**

# Screened diseases

- Cystic fibrosis

(1/4000)

- cumulative risk of all 13 screened diseases in CR - 1/1200
- (9/2009-5/2016)