

# Clinical Genetics

# Clinical genetics

- **Dept. of medical genetics**
- **Genetic diseases**
- **Rare diseases**
- **Patients on the departement of clinical genetics**
- **Genetic counselling**
- **Genetic prevention**
- **Chromosome abnormalities**
- **Prenatal diagnosis**
- **Neonatal screening**
- **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)

# Medical Genetics

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

# 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

# Rare diseases

- A disease is defined as rare if it affects less than 5 people out of 10 000, (i.e. less than 1 patient out of 2 000).
- We currently know of more than 8 000 various rare diseases.
- The number of patients with rare diseases is not small.

# **What are the major issues affecting people with rare diseases?**

- **Late or incorrect diagnosis**
- **Inaccessible expert health care**
- **Inaccessibility of so-called orphan drugs (i.e. drugs for rare diseases)**
- **Failures in the social support and benefits network due to lack of knowledge on the part of assessing doctors, social workers, etc.**
- **People with similar diseases who lack patient organizations have limited possibilities to share experiences**

# Rare diseases

- Rare disease often manifest soon after birth, affecting about 4-5% of newborns and infants (for example - some congenital defects, genetic metabolic disorders, genetically conditioned diseases and rare tumours). They can, however, occur during childhood or later in adulthood.
- **About 80% of rare diseases have a genetic origin.**
- In the case of incorrect or late diagnosis, especially in patients with a disease for which there is already a treatment option, there is irreversible damage to health. This leads to a psychic damage not only in the patients, but also their families, including the distrust to the quality health system.



# Rare diseases

- Centres of experts for rare diseases
- ERN – European Reference Networks
- Rare disease day – the last day in February from 2008



# Patients on genetic departments

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

# Patients on genetic departements

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

# 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

- **Intellectual disability**
- **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

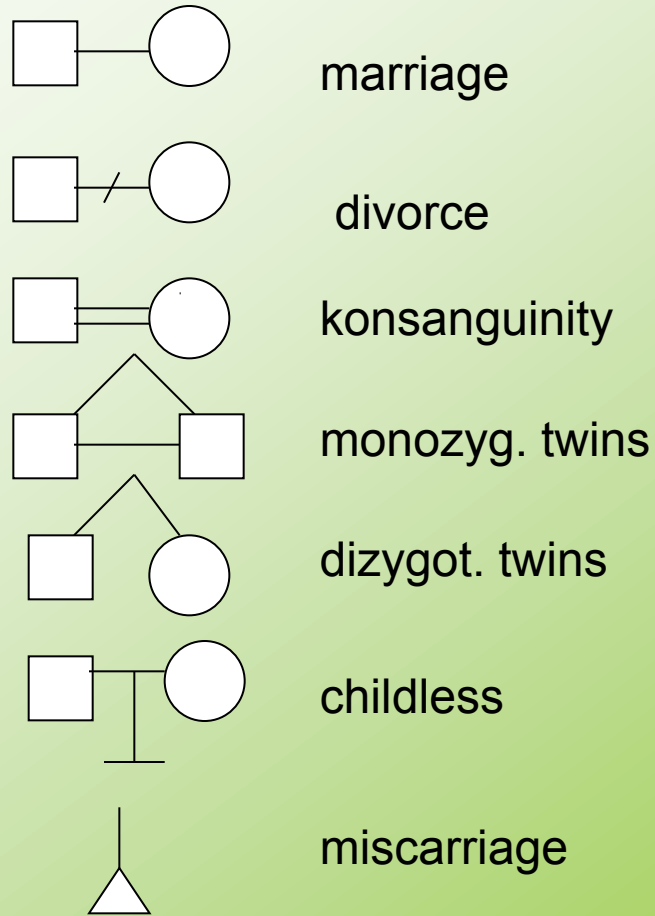
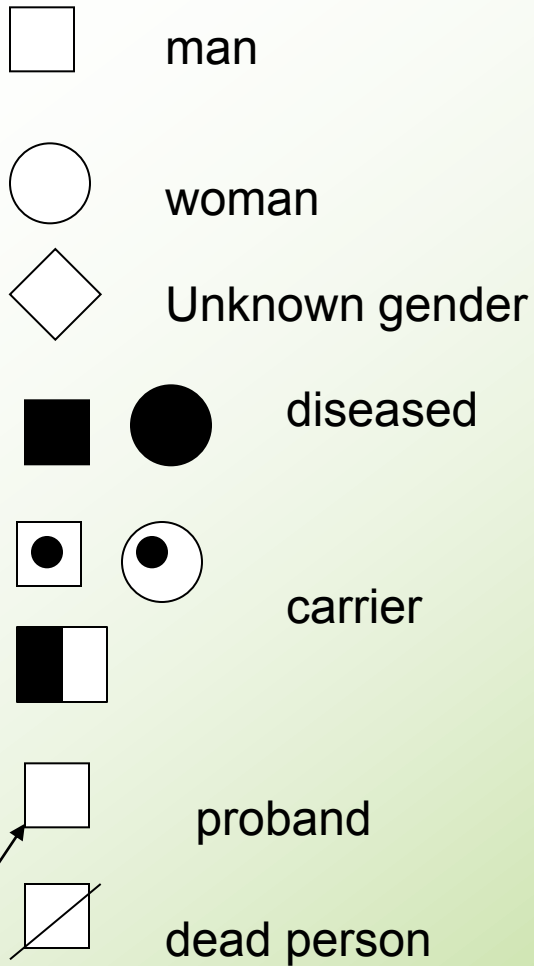
- **Ultrasound prenatal screening (pathological results)**
- **Congenital malformations in the fetus**
- **Risk of chromosomal abnormality in the fetus**

# Genetic counselling

- **Anamnesis**
- **Family history**
- **Pedigree analysis**
- **Examination of the patient**
- **Laboratory analysis (cytogenetic or DNA analysis)**
- **Other examinations (neurology, psychology, hematology, CT, MRI ...)**

# Three-generation pedigree

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



# 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, genetic prevention and prenatal analysis**

# 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**
- **Reduction 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

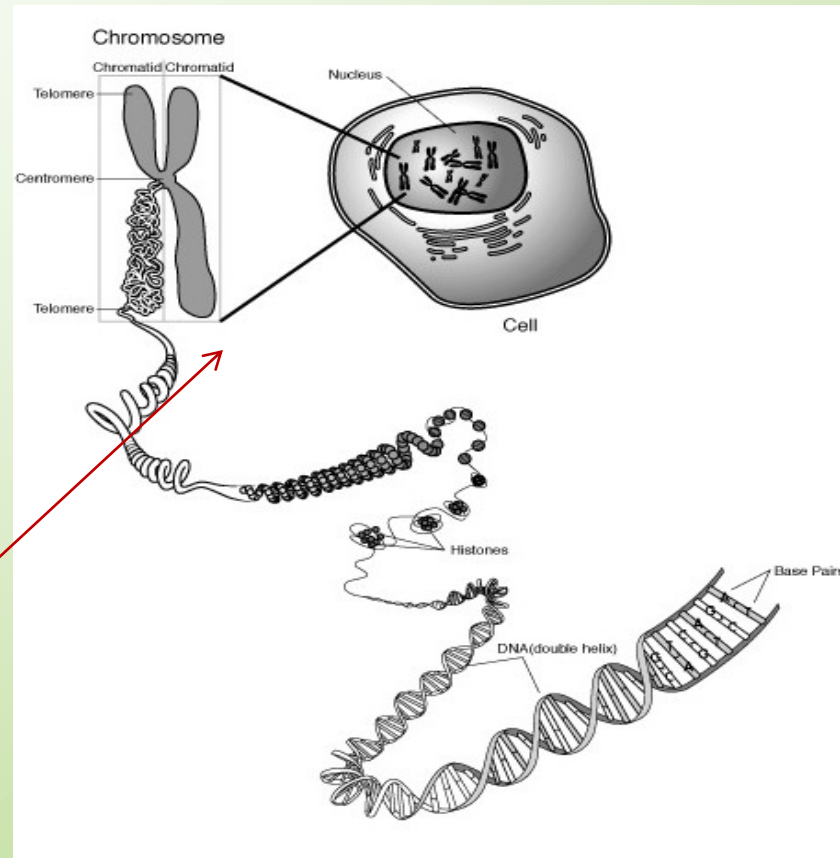
- of sperm, oocytes and embryos
- reduction in high genetic risk
- reproductive problems



# 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**

# Chromosome abnormalities



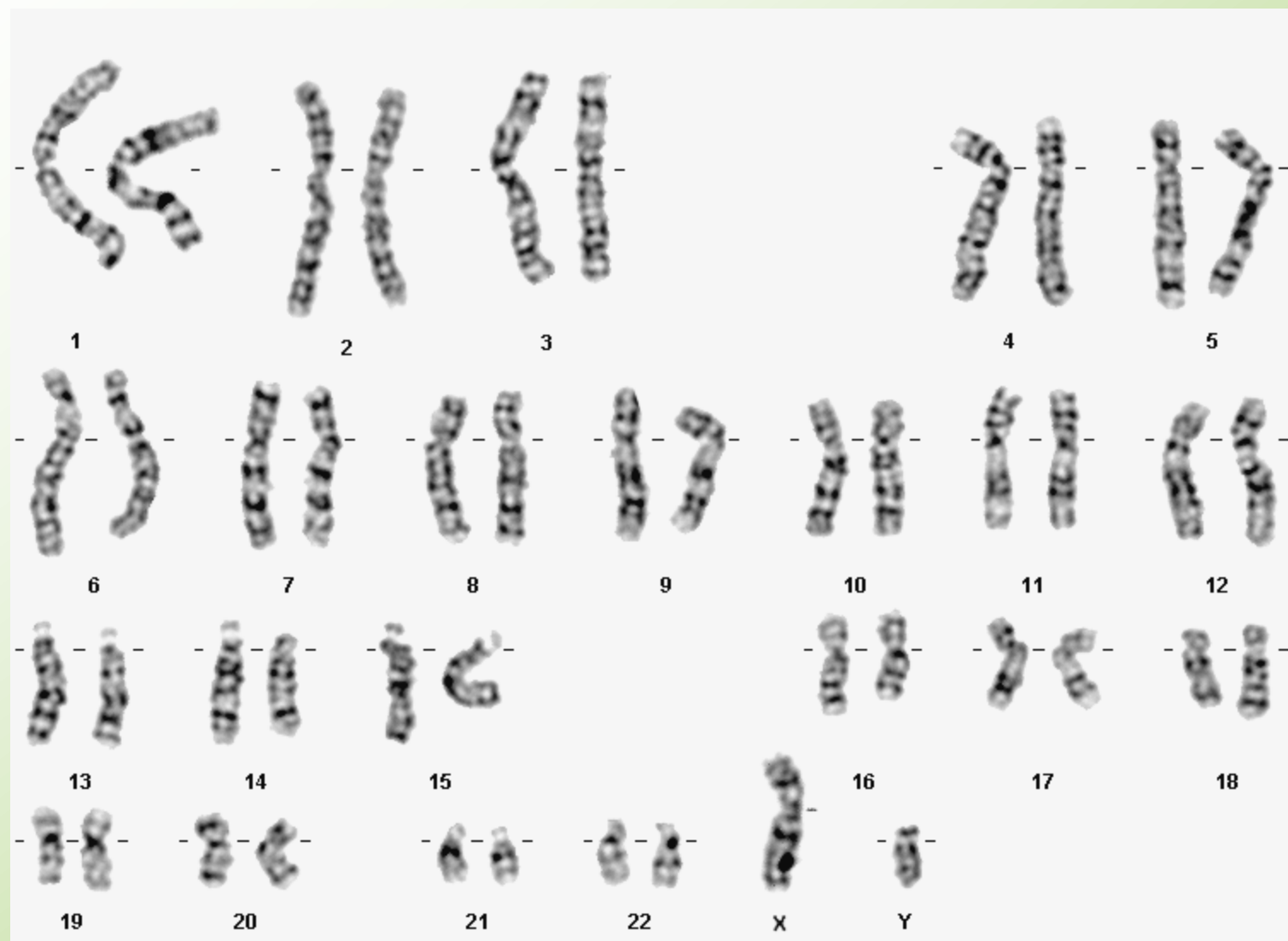
**0,6-0,7% live born**

# 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



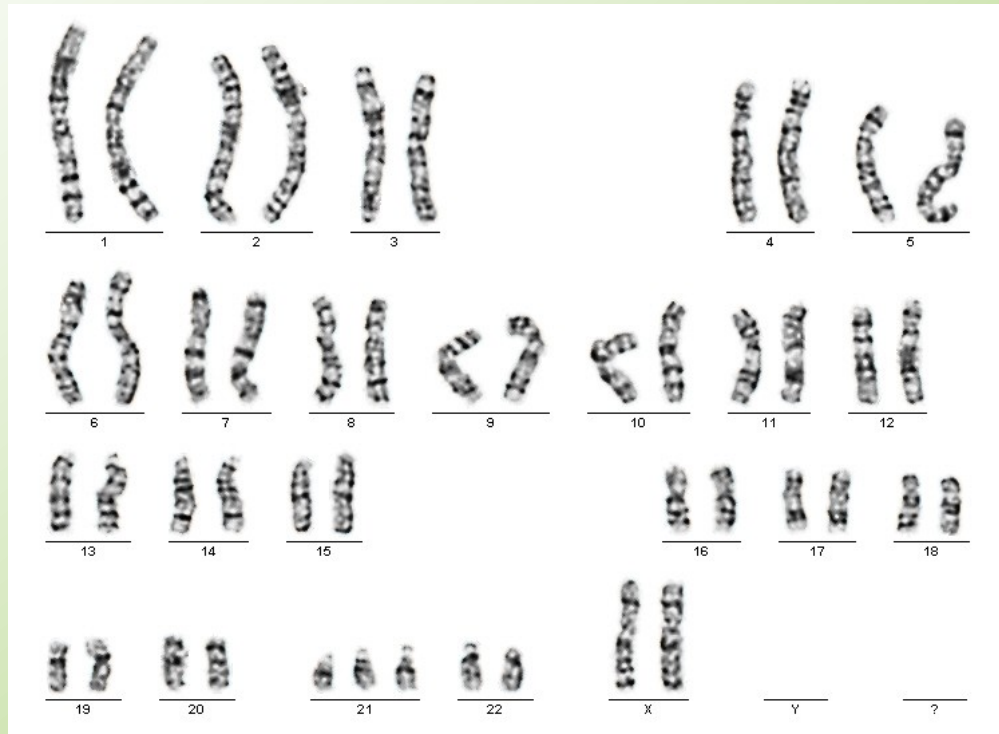
# Chromosome abnormalities in spont. abortions

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

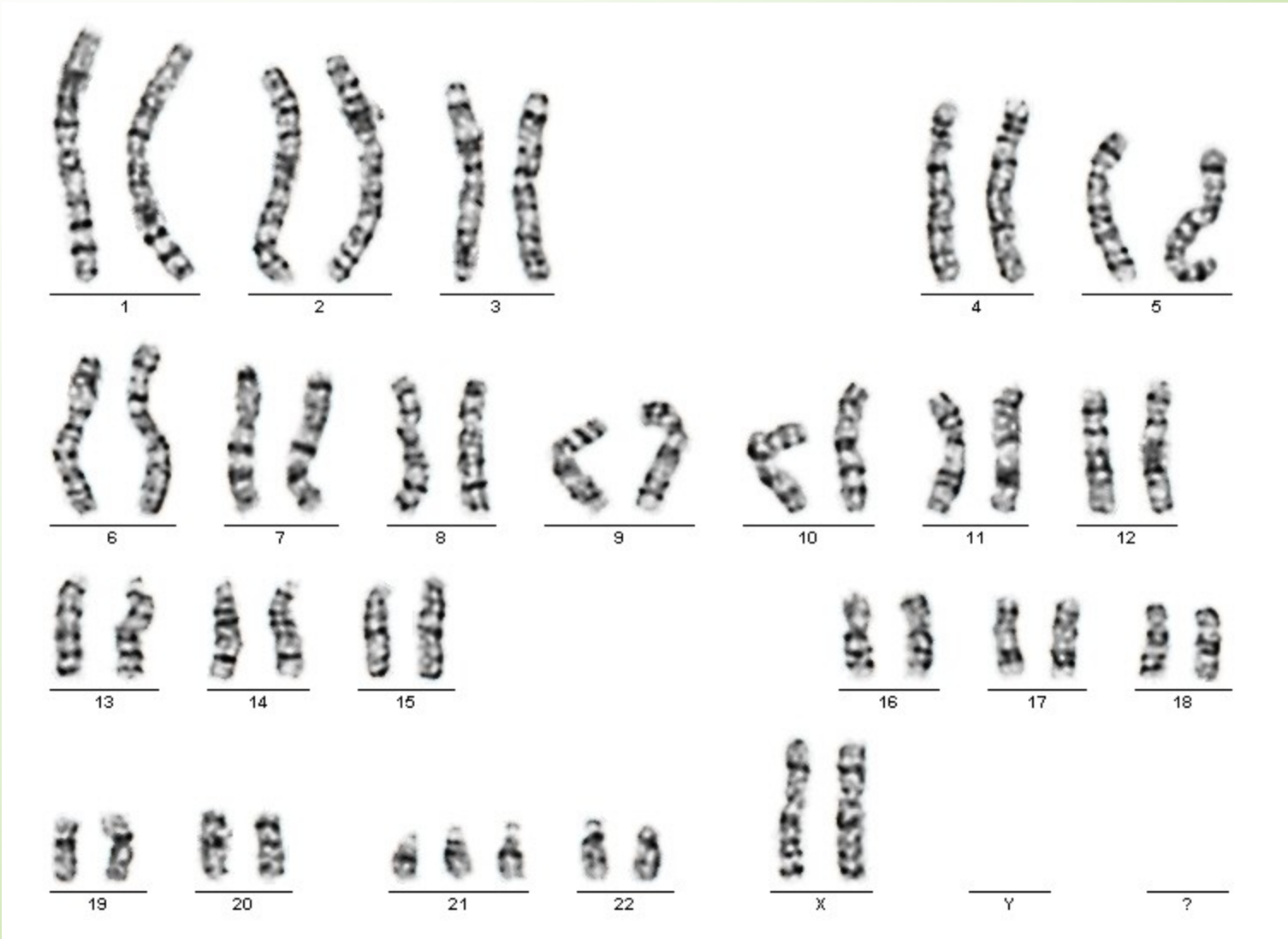
# Down syndrome








# Down syndrome

- Typical face
- Mongoloid position of the eye slits
- Small low set ears
- Short neck
- Hypotonia
- Brachydactylia
- Typical dermatoglyphs
- Transverse palm groove
- Small figure
- Congenital heart defect






**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 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

# Down syndrome- prenatal diagnosis

- non - invasive prenatal testing of fetal (placenta) DNA in the maternal plasma
- reliability of the tests is 98 - 99%
- also for +18, +13, 45,X, 47,XXY, microdeletions...

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

# Turner syndrom 45,X

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

# Klinefelter syndrom 47,XXY

# Others gonosome abnormalities

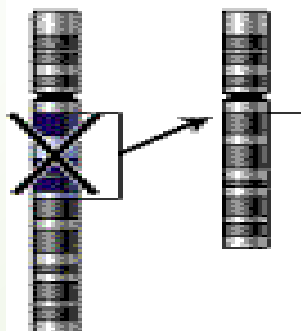
- **47,XXX**      **Infertility**
- **47,XYY**
  
- **48,XXXX**      **Intellectual disability,**
- **48,XXYY....** **congenital malformations,**  
**atypical face....**

# Structural chromosomal aberrations

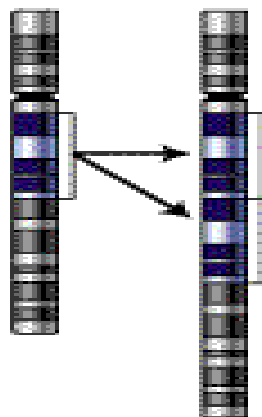
- deletion or a duplication of the genetic material of any chromosome, atypical structure - side by side to get the genetic material, which there normally is not - the effect of positional
- partial-partial deletions
- partial trisomy
- inversions, insertions, duplications ....

# Types of mutation

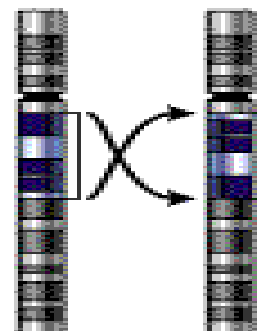
## Deletion



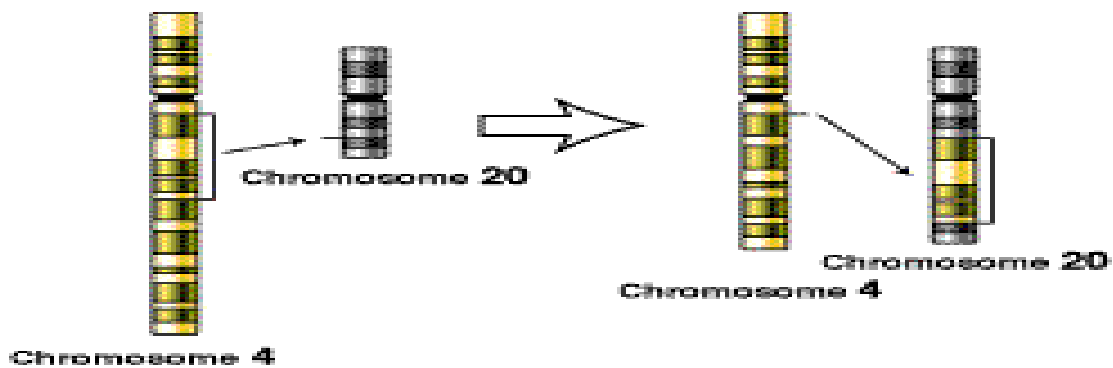
## Duplication



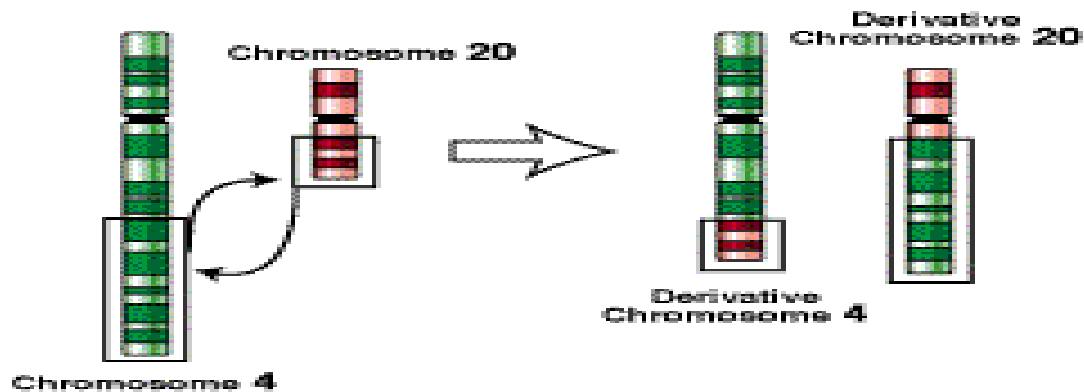
## Inversion



## Insertion



## Translocation



# **Wolf-Hirshorn syndrome**

## **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 syndrome (46,XX,4p-)

**Incidence?**

**IUGR**

**Hypotonia**

**Charakteristic face**

**Heart defects**

**Hypotonie**

**Hypotrophie**

**Severe mental  
retardation**



# **Cri du chat syndrome**

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

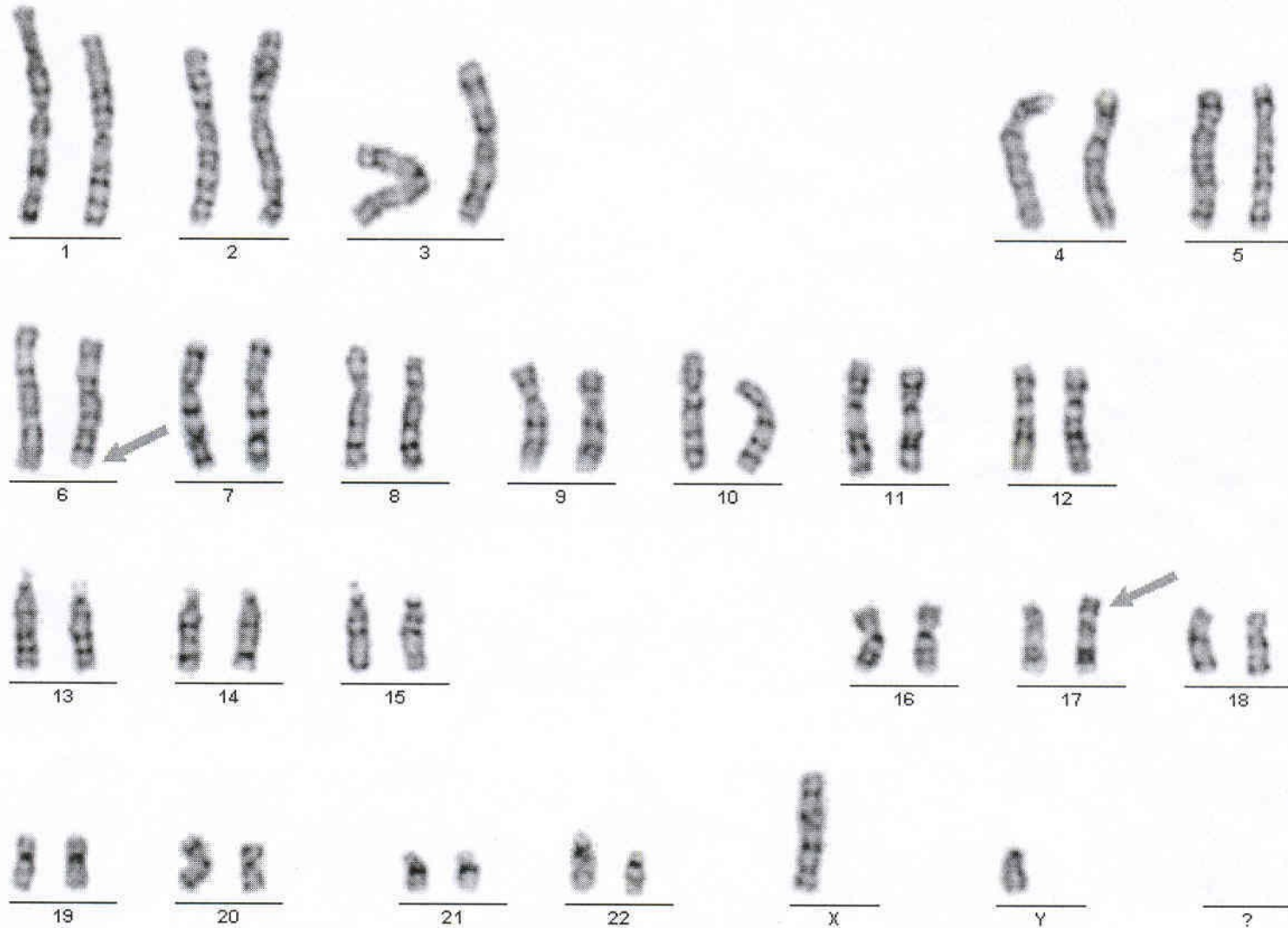
- **anomalies of the larynx causes the characteristic cry of a similar feline meow (only in infancy)**
- **low birth weight and length**
- **mental retardation, short stature, failure to thrive, small moon shaped face, the position antimongoloid eye slits, mikrocephalie**
- **other malformations and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

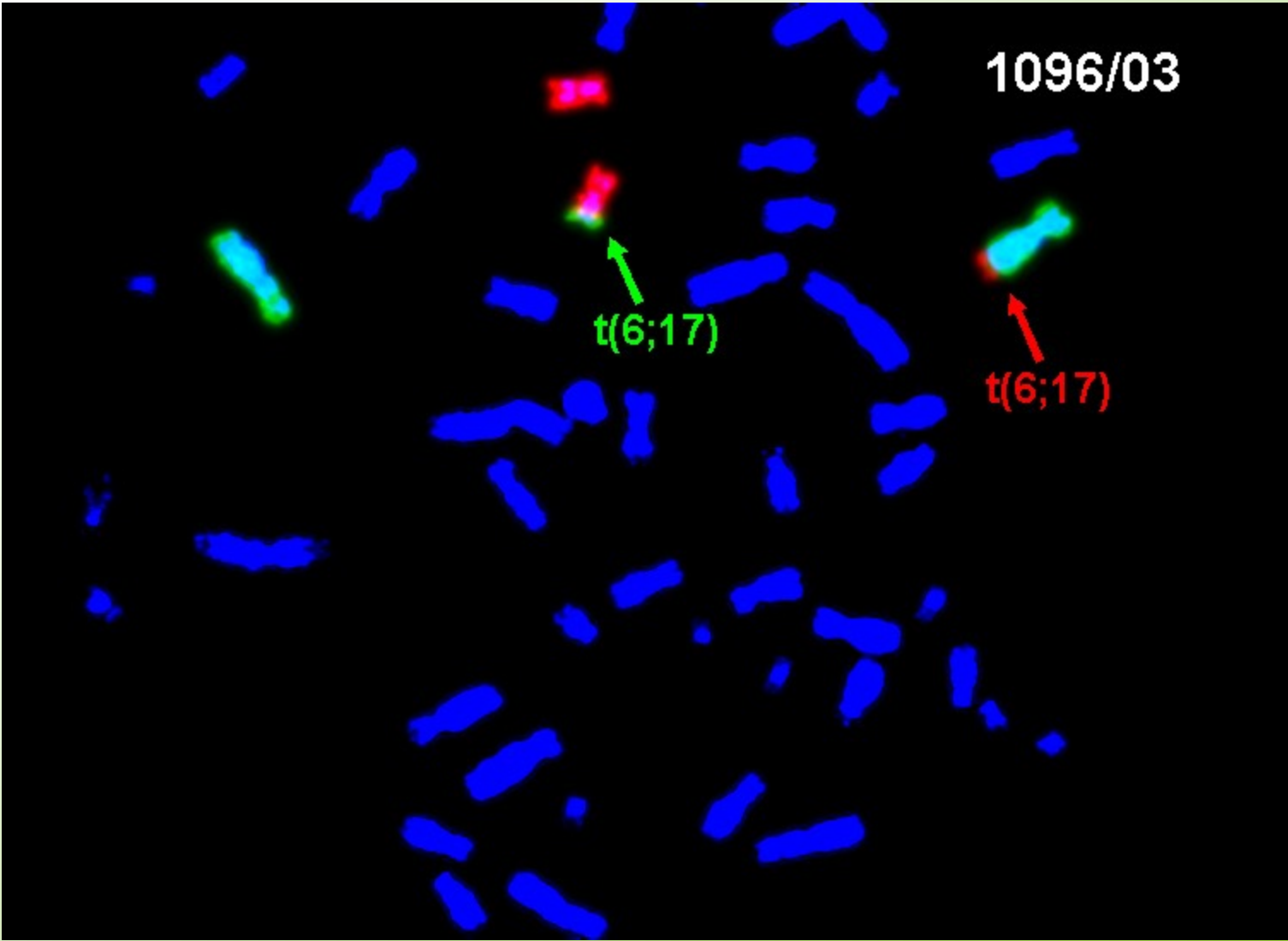
# **Cri du chat 46,XX(XY),5p-**

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

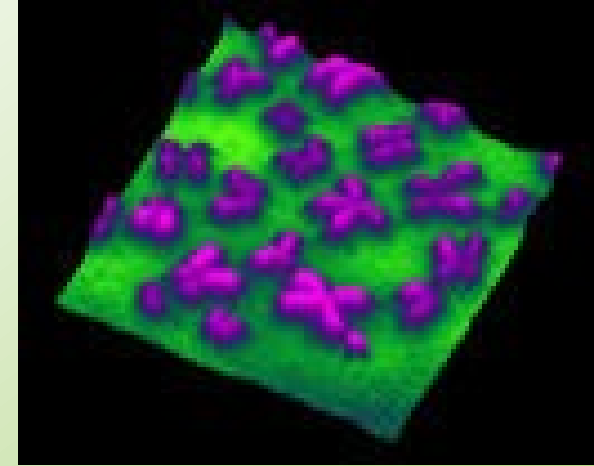
# Other structural chromosomal aberrations

46,XY,t(6;17) – balanced translocation in a men with sterility

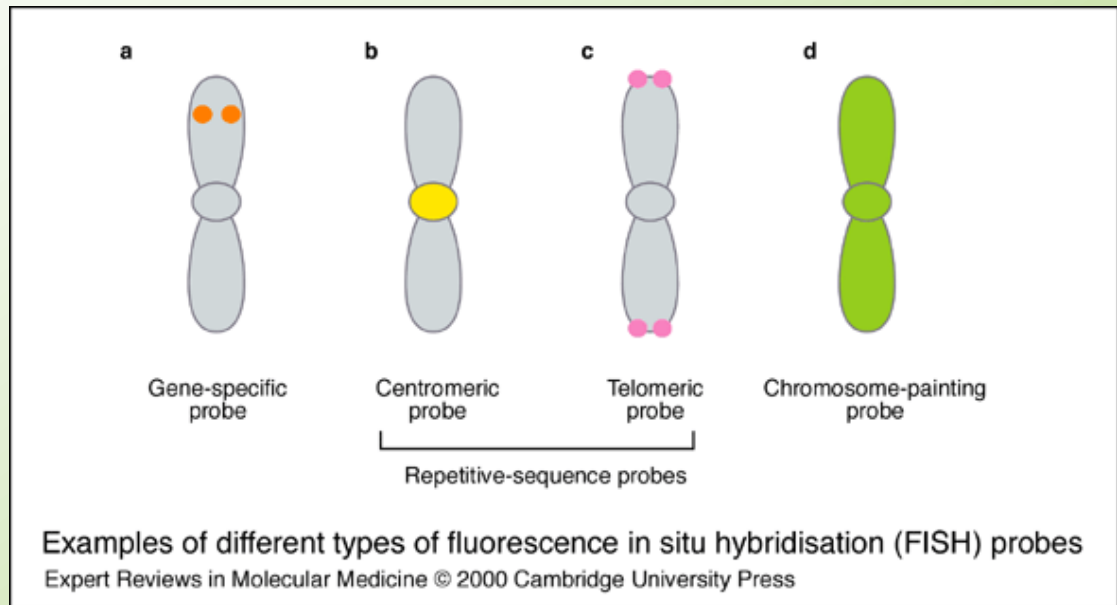




# Mikrocytogenetic Molekular cytogenetic

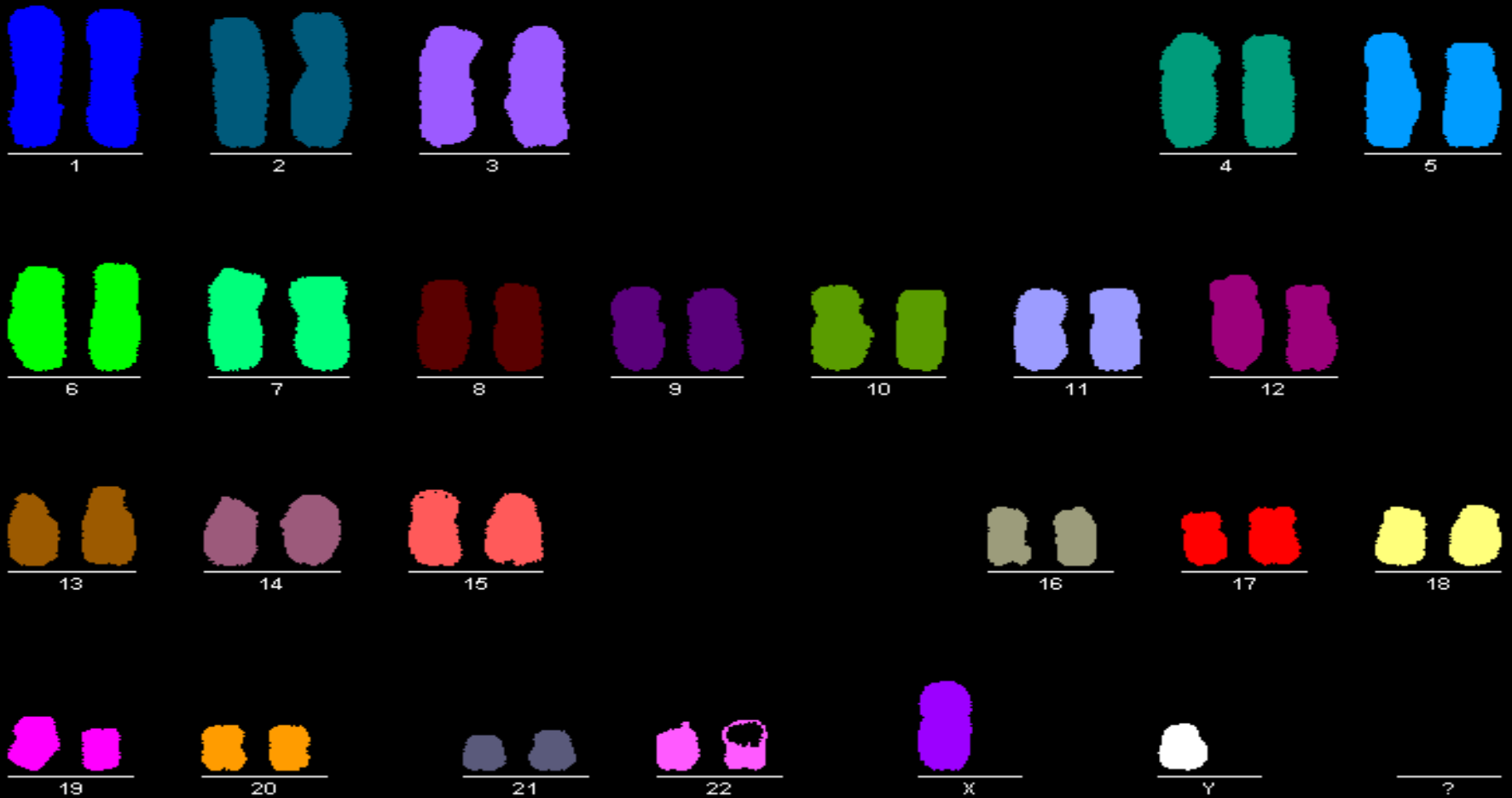


- FISH (fluorescenc in situ hybridisation), M-FISH, SKY (spektral karyotyping), CGH (comparativ genom hybridisation), MLPA, array-CGH
- mikrodeletions or mikroduplikations, marker chromosoms, complex rearegements, oncology – oncocyto-genetics, fast prenatal diagnostics ...)
- fast methods (possible for prenatal dg)
- metafase and intesfase examination



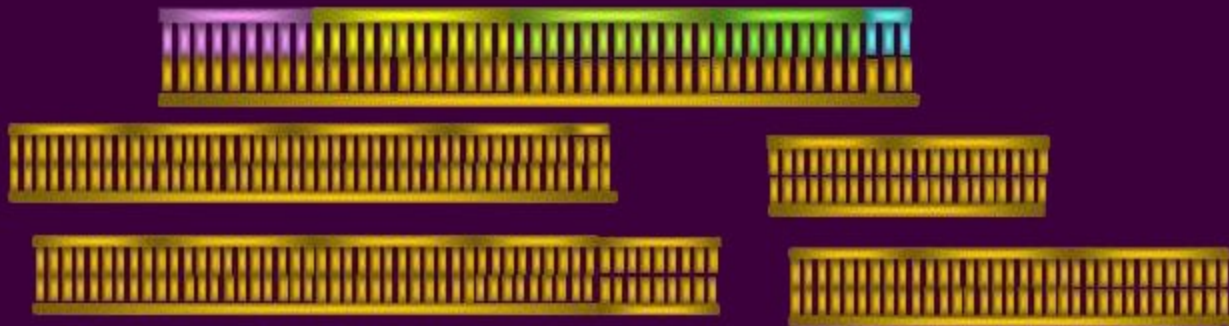
# FISH

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



# MLPA

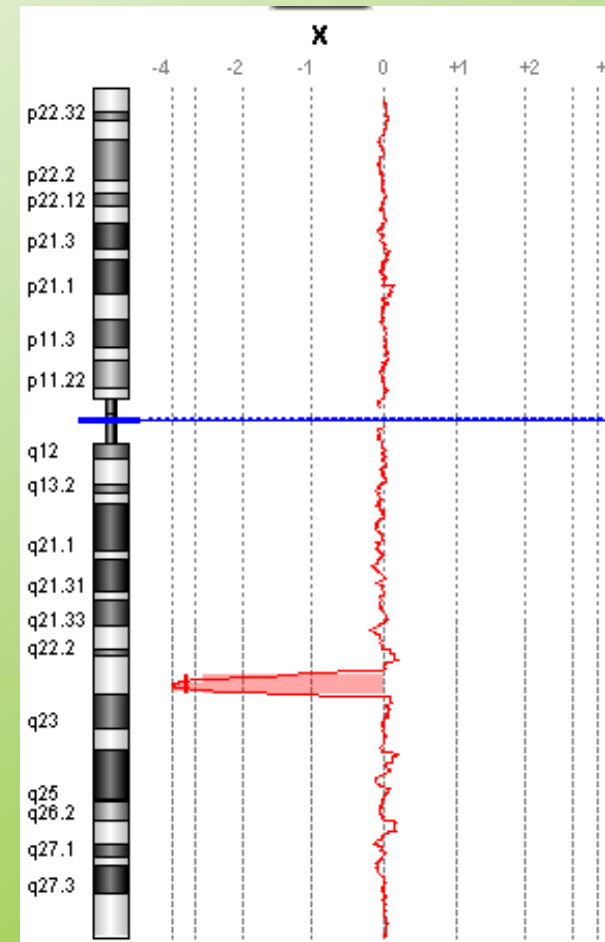
## Multiplex Ligation-Dependent Probe Amplification





# array CGH

- DNA mikroarray
- Chip technology



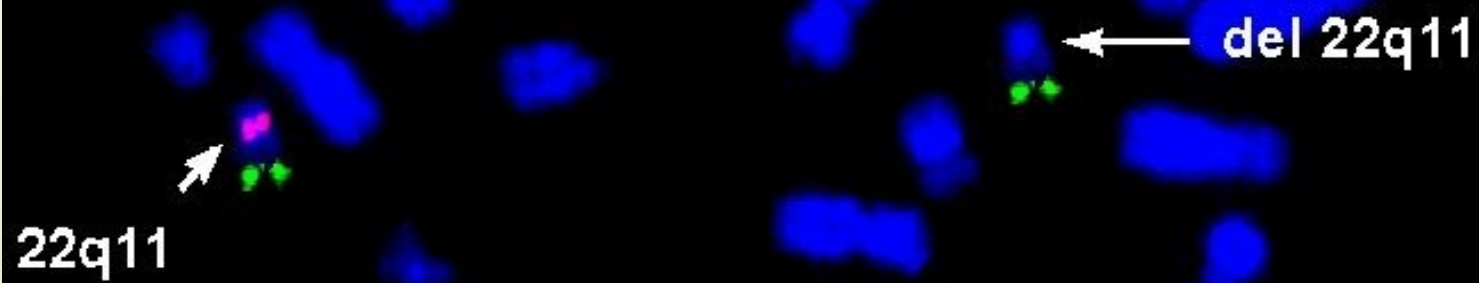
# Microdeletions

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

# Di George syndrome

- **Velo – Cardio - Facial syndrome**
- **CATCH 22**
- **Congenital heart defects (conotruncal), facial dysmorphism, thymus hypoplasia/aplasia, hypoparathyroidism, immunodeficiency**

# DiGeorge syndrom



# Williams - Beuren syndrom

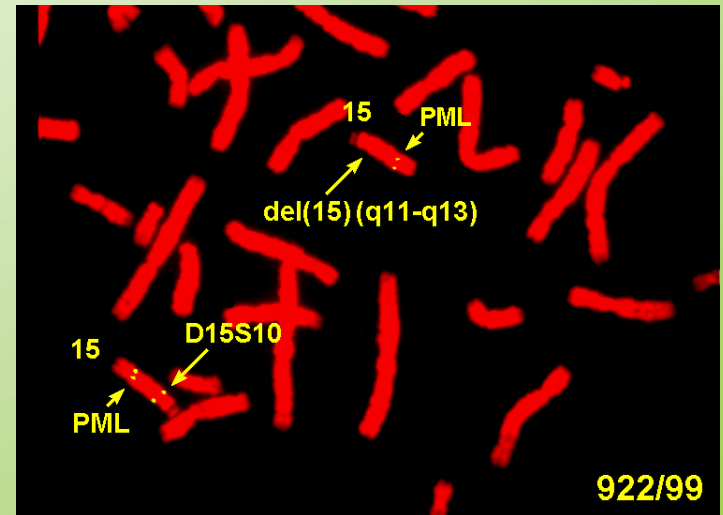
- del 7q11.23
- Facial dysmorfie - Elfin face, congenital heart disease, aortal or pulmonal stenosis, hypokalcemie, small statue, MR, hernie,...

# Prader-Willi syndrome

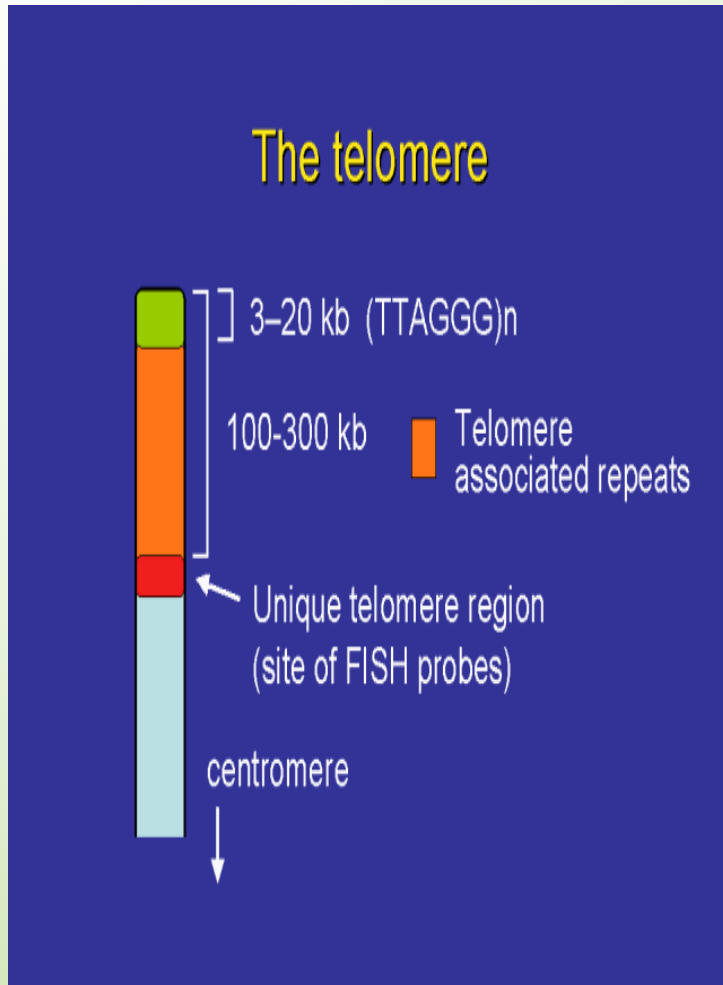
- Hypotonie, hypotrofie in small children
- PMR, small stature, obesity, hyperphagia, akromikrie, hypogonadismus
- mikrodeletion15q11-12 paternal

# Angelman syndrome

- severe mental retardation
- epilepsie
- laughter
- severely delayed speech development
- mikrodeletion 15q11-12 maternal



# The telomeres



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 during pregnancy**
- **Prenatal diagnosis and/or 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 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 microdetetions...)**
- **Rh in the fetus**
- **SRY in the fetus – in X linked diseases in the family**
- **Some mongenic 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

- **Patological 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

- 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, pojišťovna <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) - AAXXXX</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, jméno, podpis</small>	

CE IVD REF 10539735 Rev.0 LOT 6272207/51

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Hahnstraße 3,  
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# Screened diseases in CR from 10/2009

- **Kongenital hypothyreosis**
- **Kongenital adrenal hyperplasia – CAH**

# 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**
- **Izovaleric acidurie**

# Screened diseases in CR from 6/2016

1. argininémia (ARG)
2. citrulinémia I. type (CIT)
3. MCAD
4. VLCAD
5. biotinidasis deficiency(BTD)
6. LCHAD
7. deficit karnitinpalmityltransferasis I deficiencyI (CPT I)
8. karnitinpalmityltransferasisII def. (CPT II)
9. karnitinacylkarnitintranslokasis def. (CACT)
10. Phenylketonuria(PKU) a hyperúhenylalaninemia (HPA)
11. glutar aciduria type I (GA I)
12. homocystinuria ( cystathionin beta-syntázis def. (CBS), pyridoxin non-responziv form)
13. Homocystinuria (methyilentetrahydrofoltred. def.)(MTHFR)
14. izovaleric aciduria (IVA)
15. leucinosis (MSUD)

# Screened diseases

- **Cystic fibrosis**
- **cumulative risk of all screened diseases in CR about 1/1200**