Clinical Genetics

Clinical genetics

- **Genetic counseling**
- **Neonatal screening**
- **Reproductive genetics**
- **Prenatal screening, prenatal diagnostics, preimplantation genetic diagnostics.**

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, posibilities 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 domage 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 Refernece Networks**
- **Rare disease day – the last day in February from 2008**

Patients on genetic departements

- 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

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

Children

- **Suspition on congenital chromosom aberations (children with congenital malformations, abnormal face, atipical 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 adulds

- 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

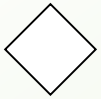
- Anamnesis
- Family history
- Pedigree analysis
- Examination of the patient
- Laboratory analysis (cytogenetic or DNA analysis)
- Other examinations (neurology, psychology, hematology, CT, MRI …)

Three-generation pedigree

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

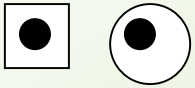
man

woman

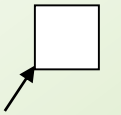


Unknown gender

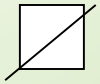
diseased



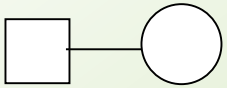
carrier



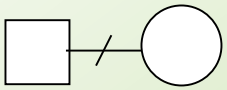
proband



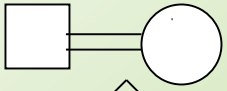
dead person



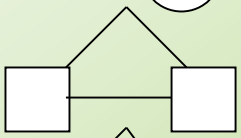
marriage



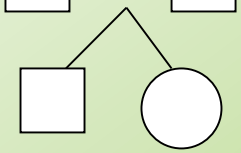
divorce



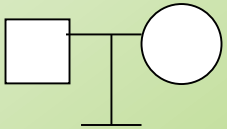
konsanguinity



monozyg. twins



dizygot. twins



childless

miscarriage

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**
- **Posibilities 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**

Vacctination, 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 environmetal 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**

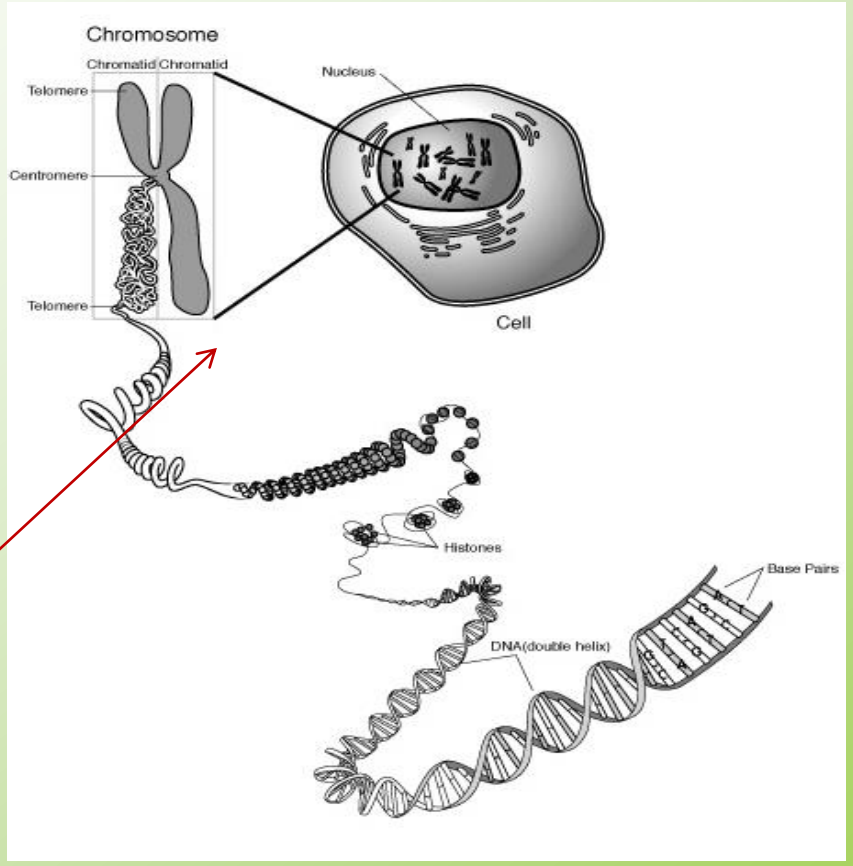
Donation

- 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

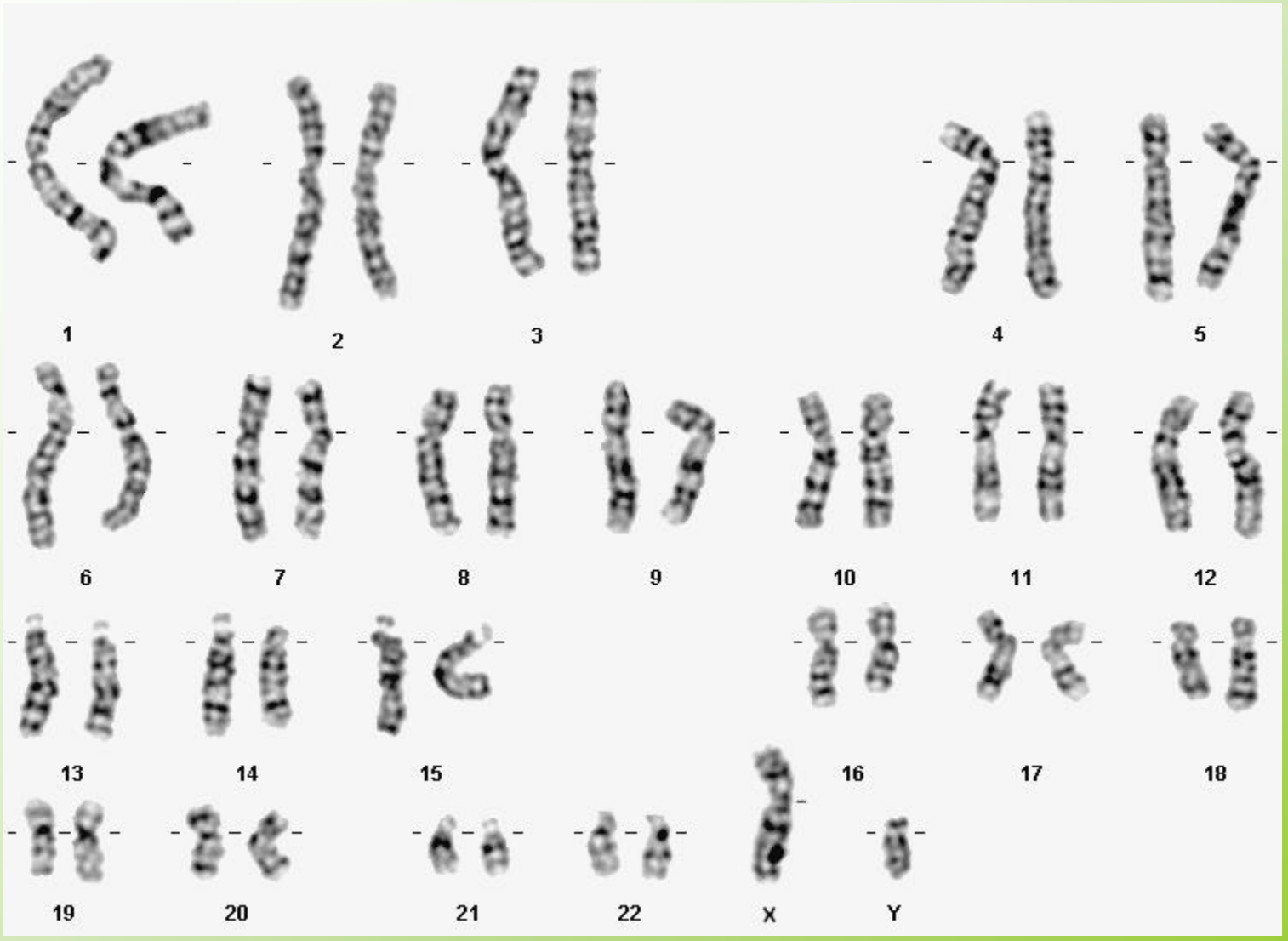
- Autosomes
- Gonosomes

- 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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X
Y

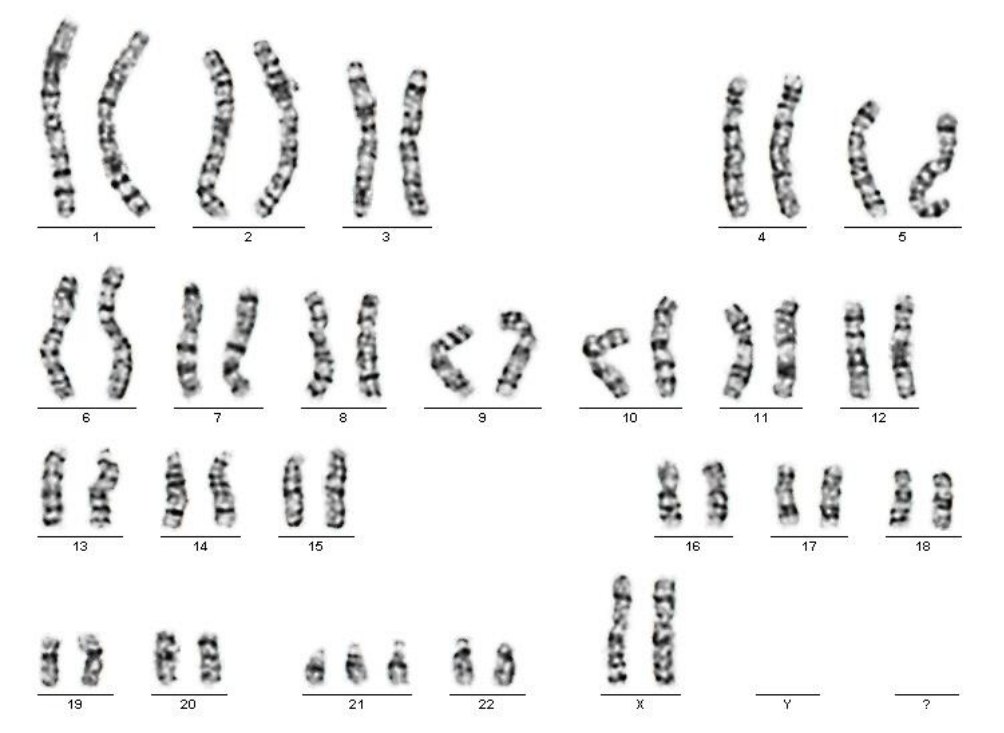
Chromosome abnormalities in spont. abortions

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

Maternal age and chromosome abnormalities in AMC (per 1000)

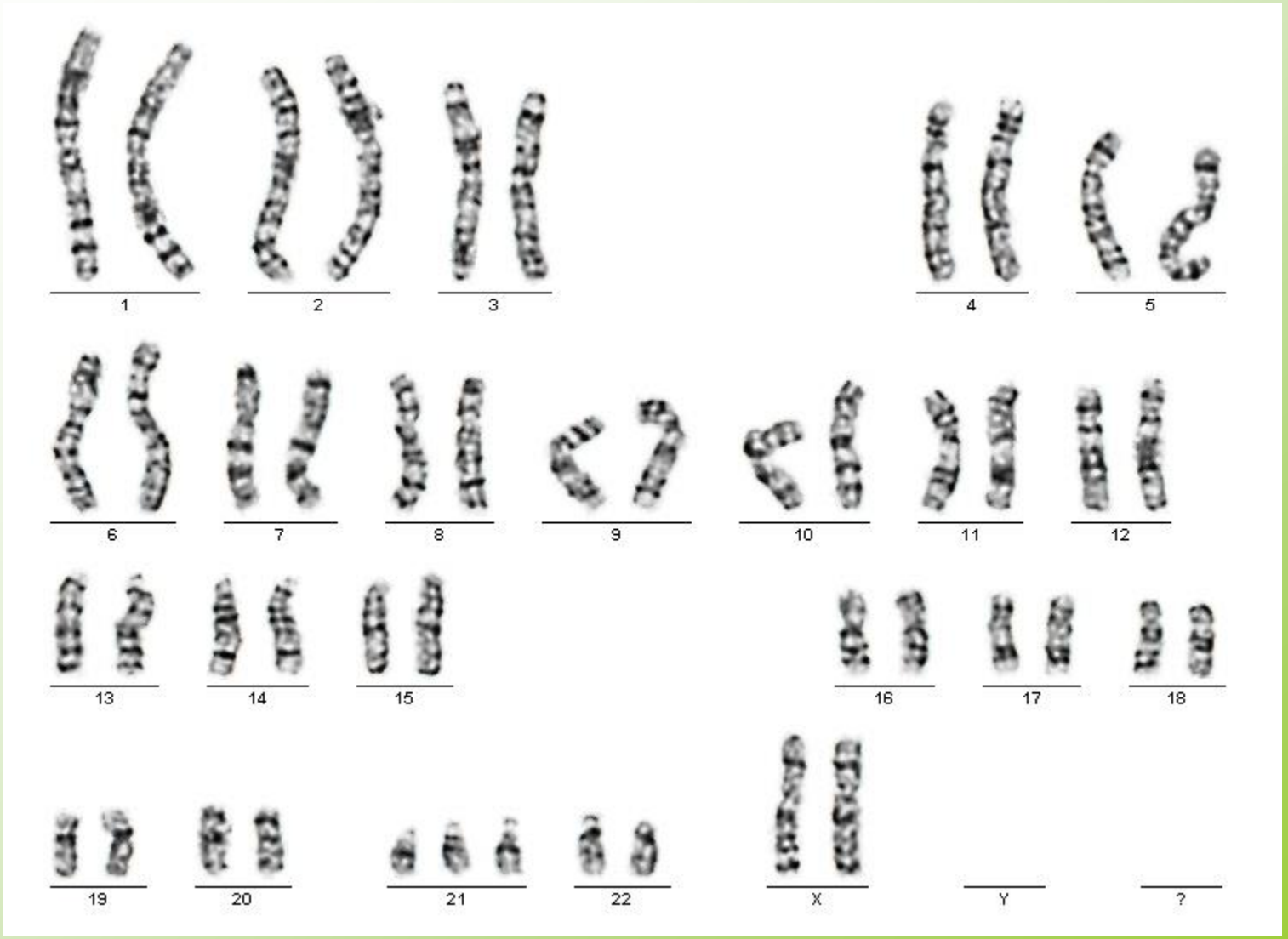
years	+21	+18	+13	XXY	All
35	3,9	0,5	0,2	0,5	8,7
37	6,4	1,0	0,4	0,8	12,2
40	13,3	2,8	1,1	1,8	23,0
43	27,4	7,6		4,1	45,0
45	44,2			7,0	62,0
47	70,4			11,9	96,0

Down syndrome



Down syndrome

- Typical face
- Mongoloid position of the eye slits
- Small low set ears
- Short neck
- Hypotonia
- Brachydactylia
- Typical dermatoglyphs
- Tranverse 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 karyotiping
- 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 mothernal plasma
- reliability of the tests is 98 - 99%
- also for +18, +13, 45,X, 47,XXY, microdeletions…

Edwards syndrome

- 1:5000
- IUGR, hyopotrophie
- microcephalie
- dolichocephalie
- Cleft palate
- Down set ears
- micromandibula
- Hands, feets
- 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

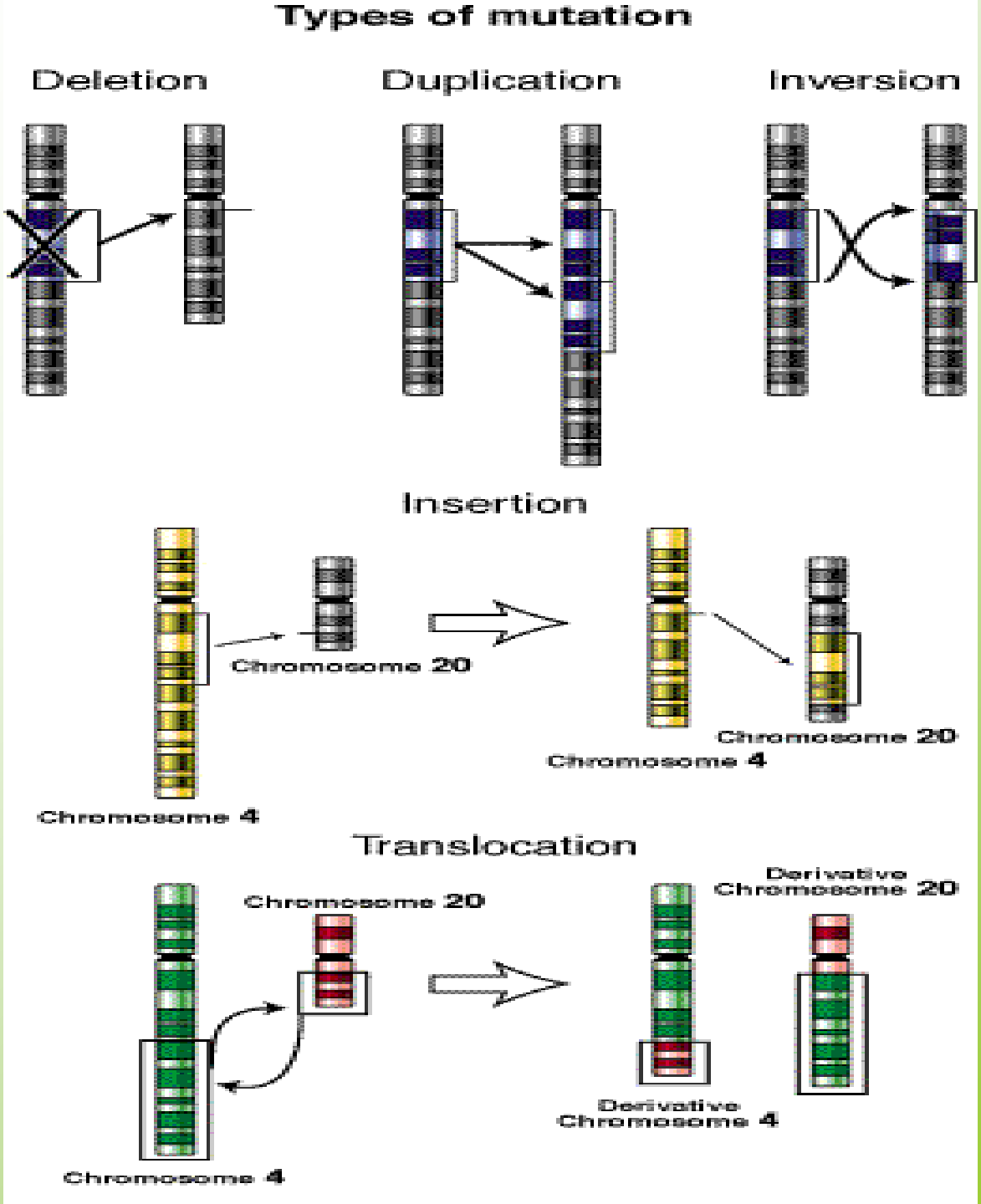
Others gonoseme abnormalities

- **47,XXX** — **Infertility**
- **47,XYY**

- **48,XXXX**
- **48,XXYY….** — **Intellectual disability, congenital malformations, atyical 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
Chromosome 20
Chromosome 4
Chromosome 20
Chromosome 4
Translocation
Chromosome 20
Derivative Chromosome 20
Chromosome 4
Derivative Chromosome 4

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

- severe mental retardation
- typical craniofacial dysmorphia - 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-

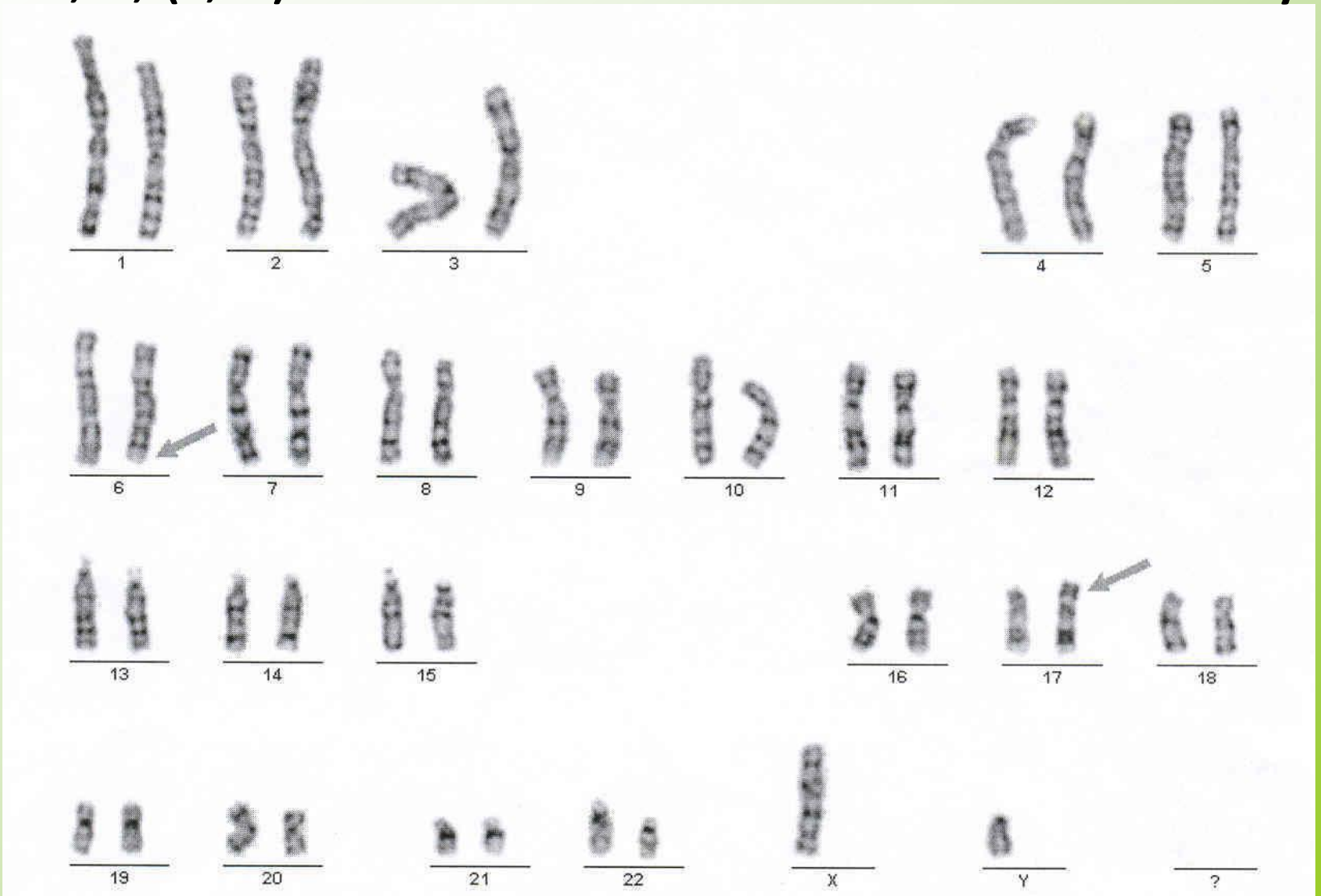
- anomalies of the larynx causes the characteristic cry of a similar feline meow (only in infancy)
- low birth weight and length
- mental retardation, short stature, failure to thrive, small moon shaped face, the position antimongoloid eye slits, mikrocephalie
- other malformations and birth defects

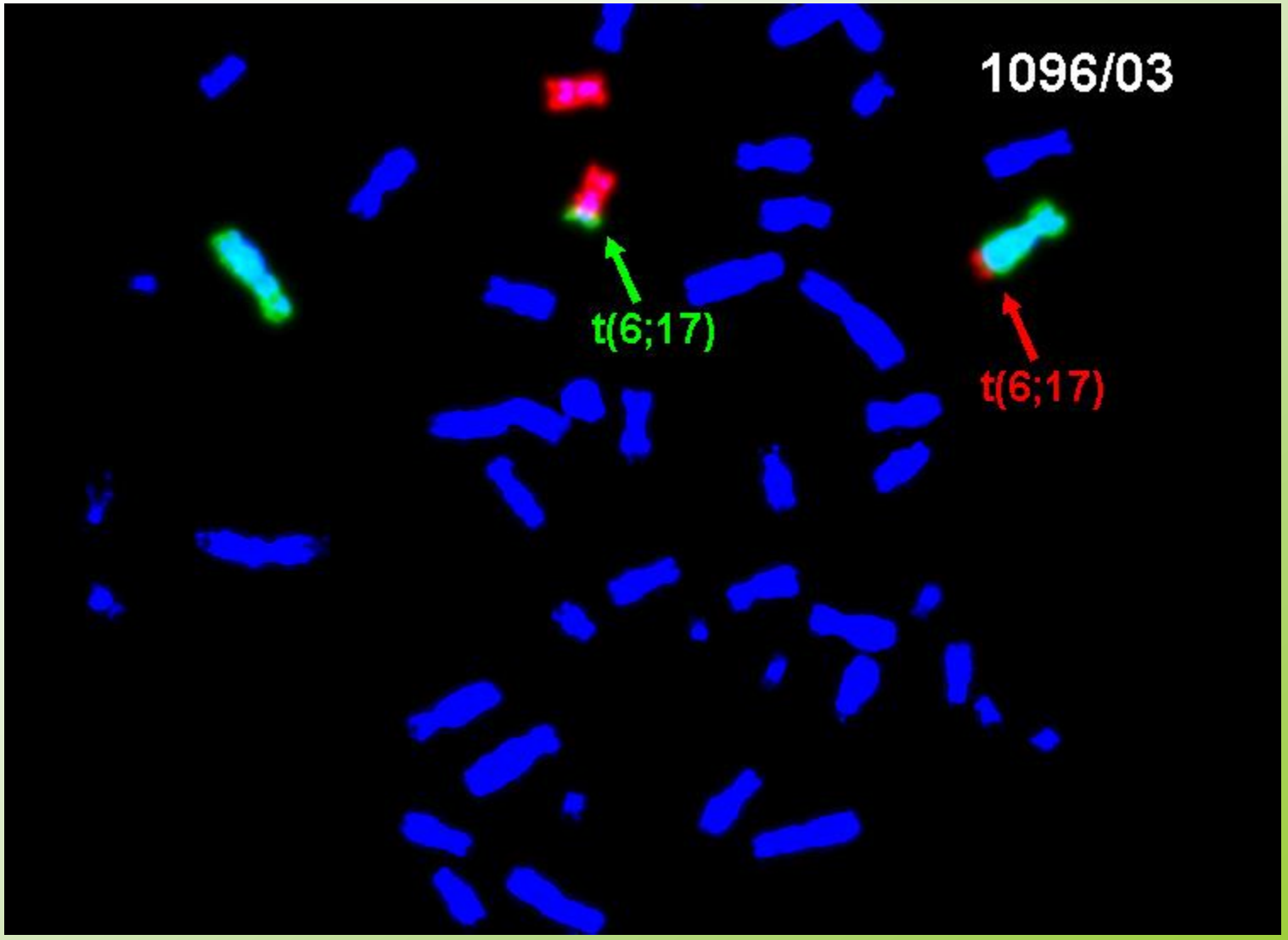
Cri du chat 46,XX(XY),5p-

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

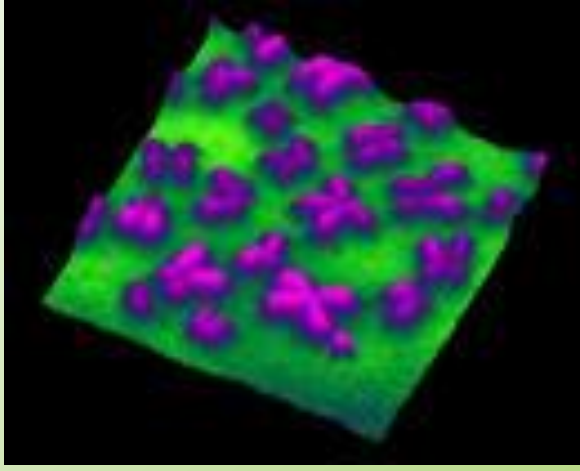
Other structural chromosomal aberrations

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



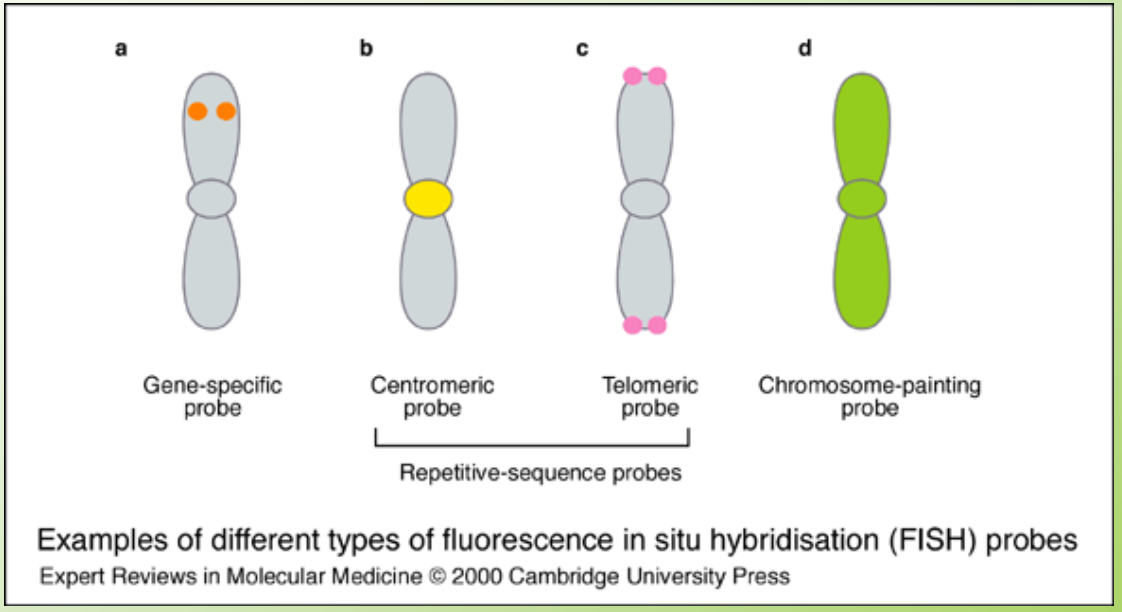

1096/03
t(6;17)
t(6;17)

Mikrocytogenetic
Molekular cytogenetic



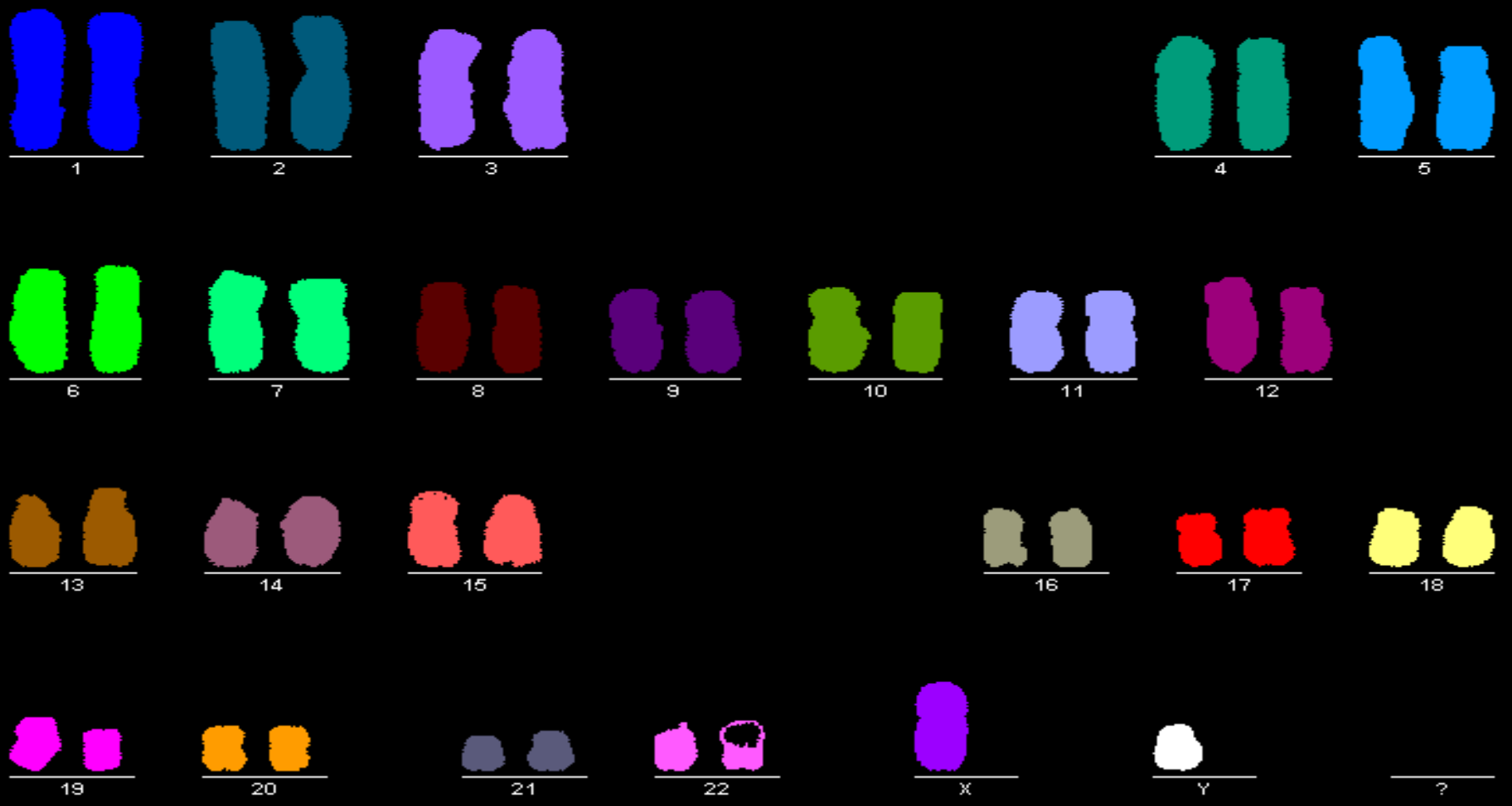
- FISH (fluorescenc in situ hybridisation), M-FISH, SKY (spektral karyoptyping), CGH (comparativ genom hybridisation), MLPA, array-CGH
- mikrodeletions or mikroduplications, marker chromosoms, complex rearegements, oncology – oncocytogenetics,fast prenatal diagnostics …)
- fast methods (possible for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

FISH



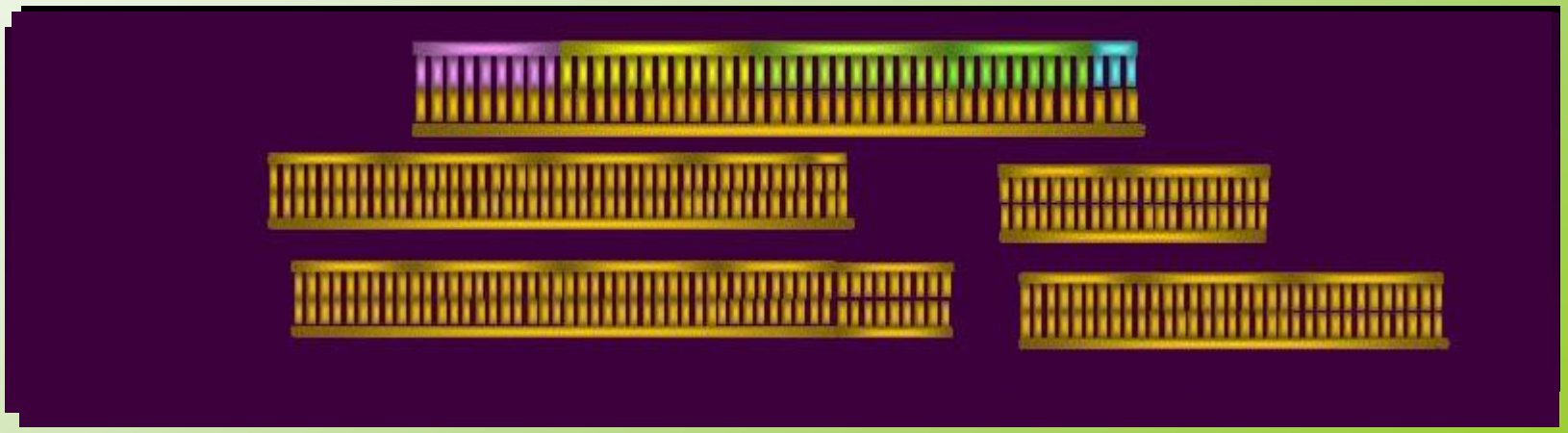
Examples of different types of fluorescence in situ hybridisation (FISH) probes

M-FISH (multicolor)
Spektral karyotyping (SKY)



MLPA

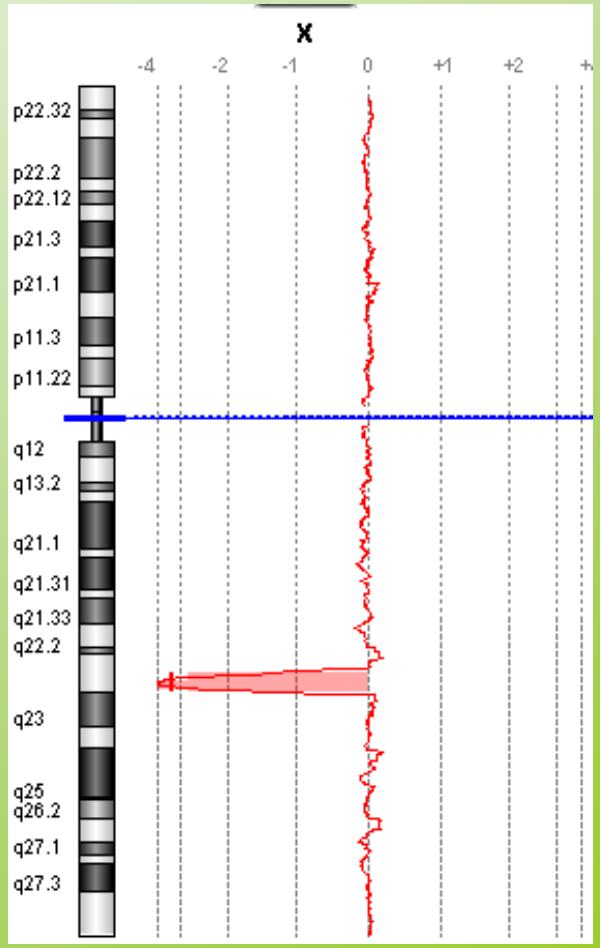
Multiplex Ligation-Dependent Probe Amplification



MRC-Holland
MLPA

array CGH

- DNA mikroarray
- Chip technology

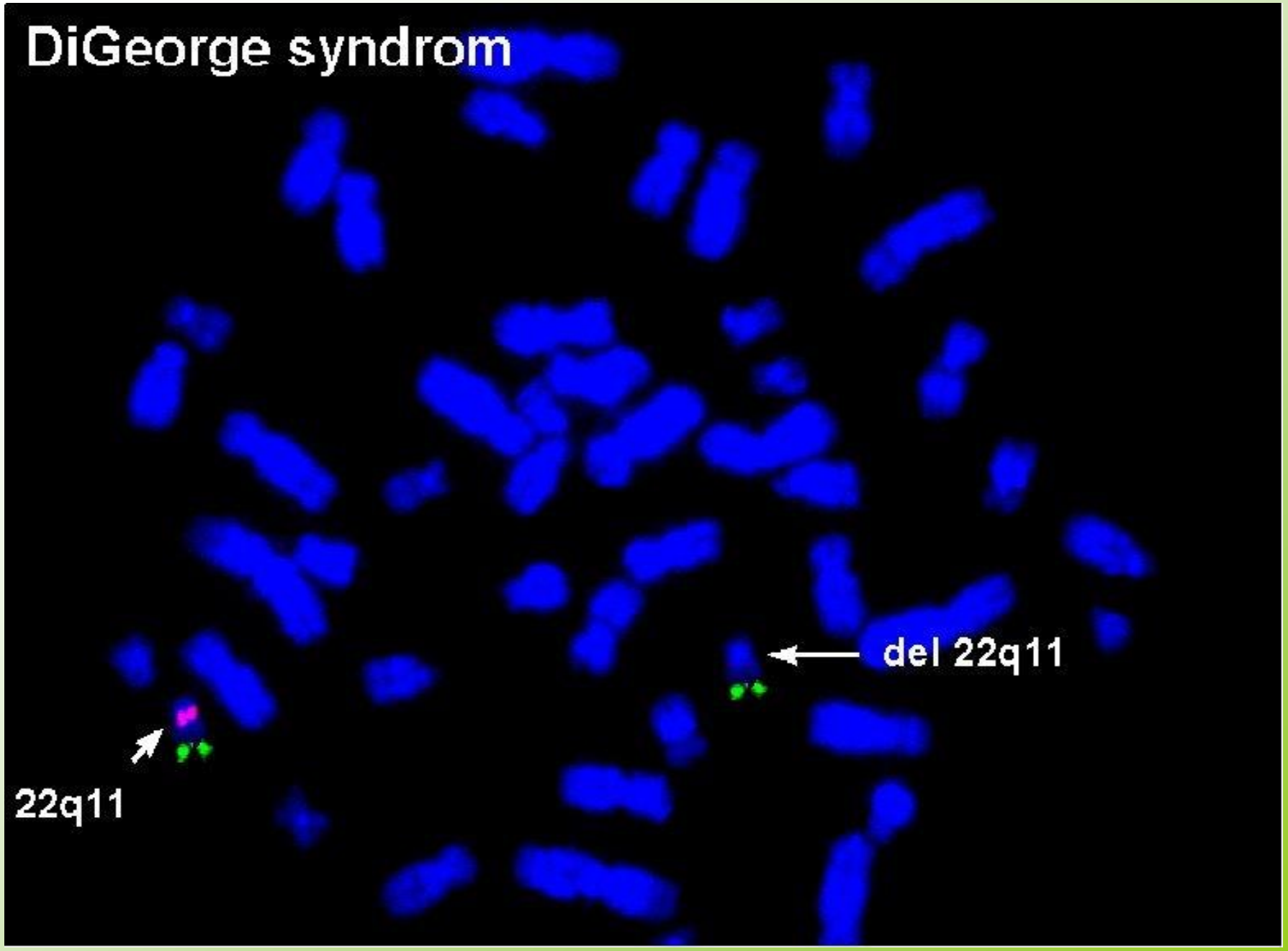


Microdeletions

- **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 dysmorfism, thymus hypoplasia/aplasia, hypoparathyreoidism, immunodeficiency**


DiGeorge syndrom
del 22q11
22q11

Williams - Beuren syndrom

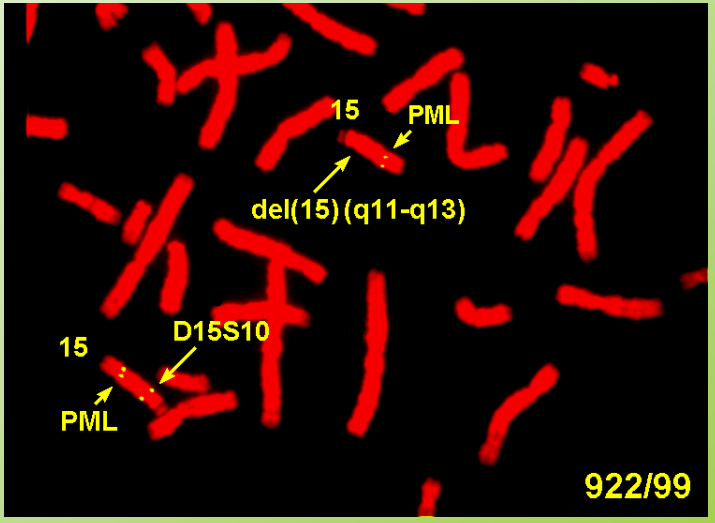
- **del 7q11.23**
- **Facial dysmorfie - Elfin face, congenital heart disease, aortal or pulmonal stenosis, hypokalcemie, small statue, MR, hernie,...**

Prader-Willi syndrome

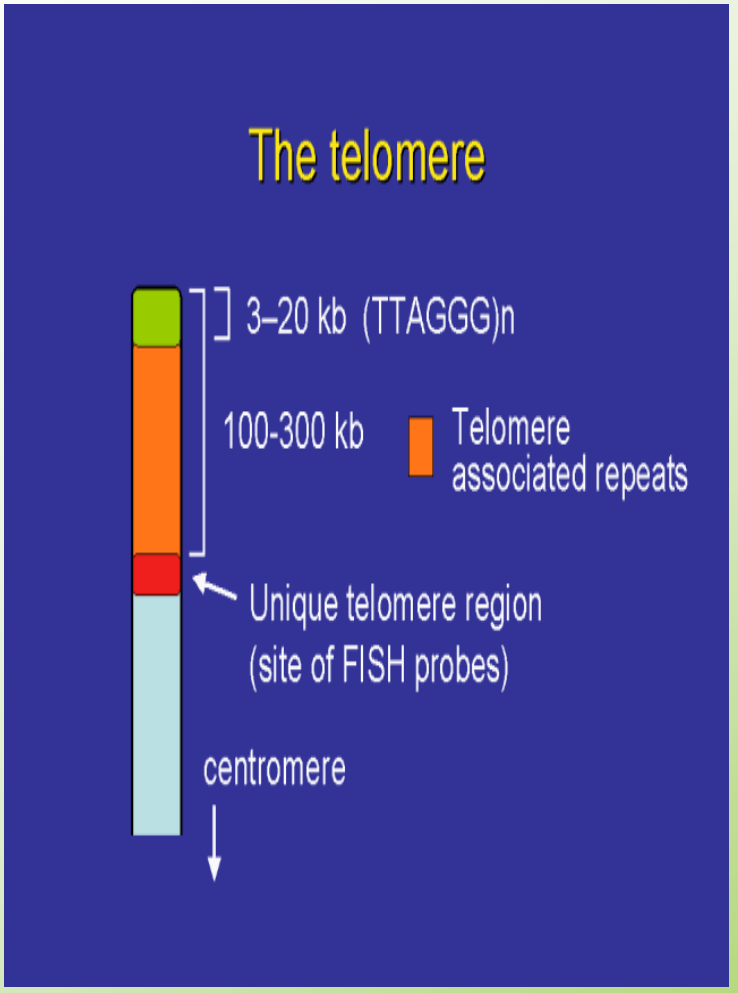
- **Hypotonie, hypotrofie in small children**
- **PMR, small statue, obesity, hyperfagie, akromikrie, hypogonadismus**
- **mikrodeletion15q11-12 paternal**

Angelman syndrome

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



The telomeres



Rearangement 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. - 2 0. - 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-invazive 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 (achondroplasie)**

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

Preimplatation 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 chromososmal aberations
- (parents are carries of balanced rearangement)
- Monogenic diseases (known in family history)

PG Diagnostic

X

PG Screening

- **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 if infertility give an increased risk of malformations in the offspring?**

- **Genetic testing before use of metods of asisted reproduction.**

Infertility

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

- 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 managment of prenagncies with malformation or genetic disease in the fetus

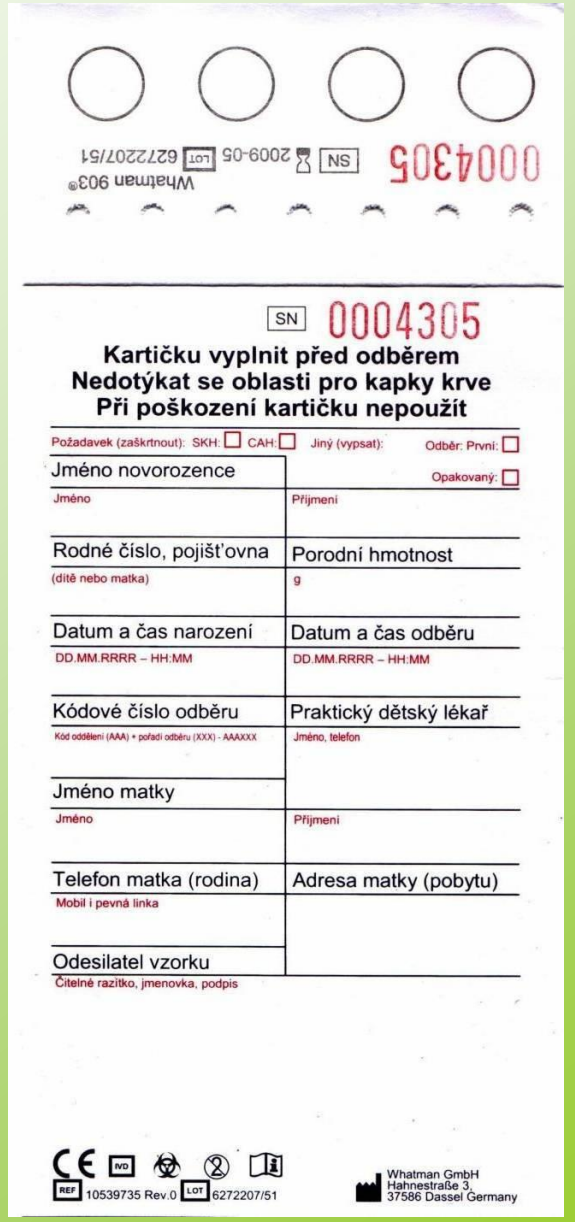
- **Consultation with experts, who will continue to take care of the pregnant woman - ultrasound specialist, gynecologist, obstetrician, psychological support ..**

  Consultions 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



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)**
- **Leucinosis**
- **MCAD**
- **LCHAD**
- **VLCAD**
- **Def.karnitinpalmitoyltransferasis I a II**
- **Def.karnitinacylkarnitintranslocasis**
- **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 karnitinpalmitoyltransferasis I deficiencyl (CPT I)
8. karnitinpalmitoyltransferasisII 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 (methylentetrahydrofoltred. def.)(MTHFR)
14. izovaleric aciduria (IVA)
15. leucinosis (MSUD)

Screened diseases

- **Cystic fibrosis**

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