Clinical Genetics
Congenital chromosomal aberrations

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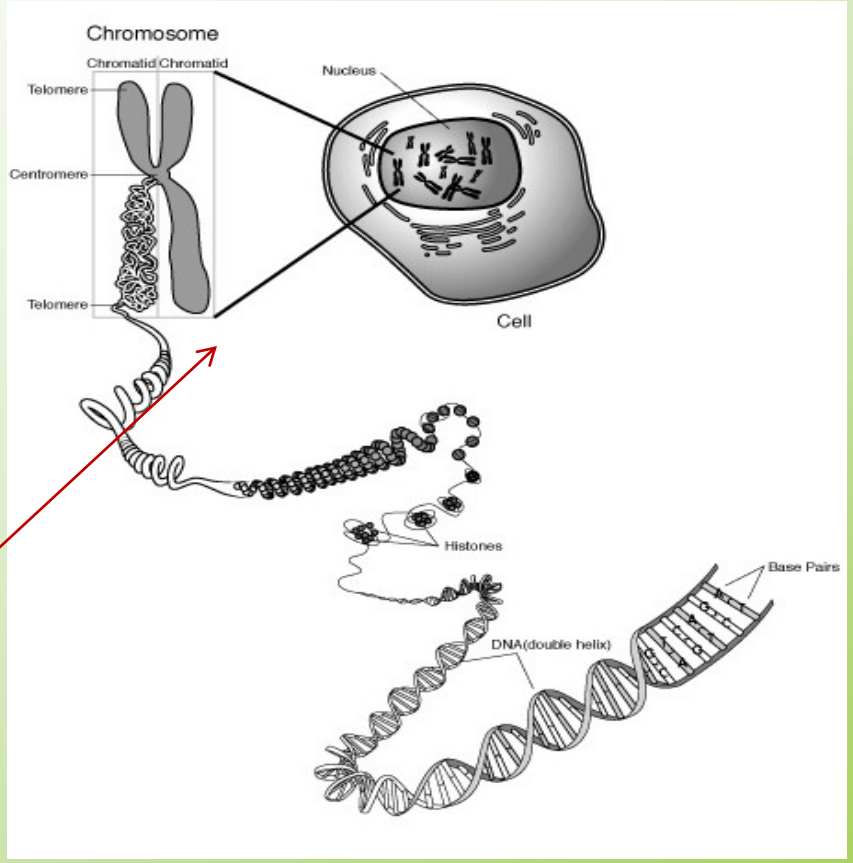
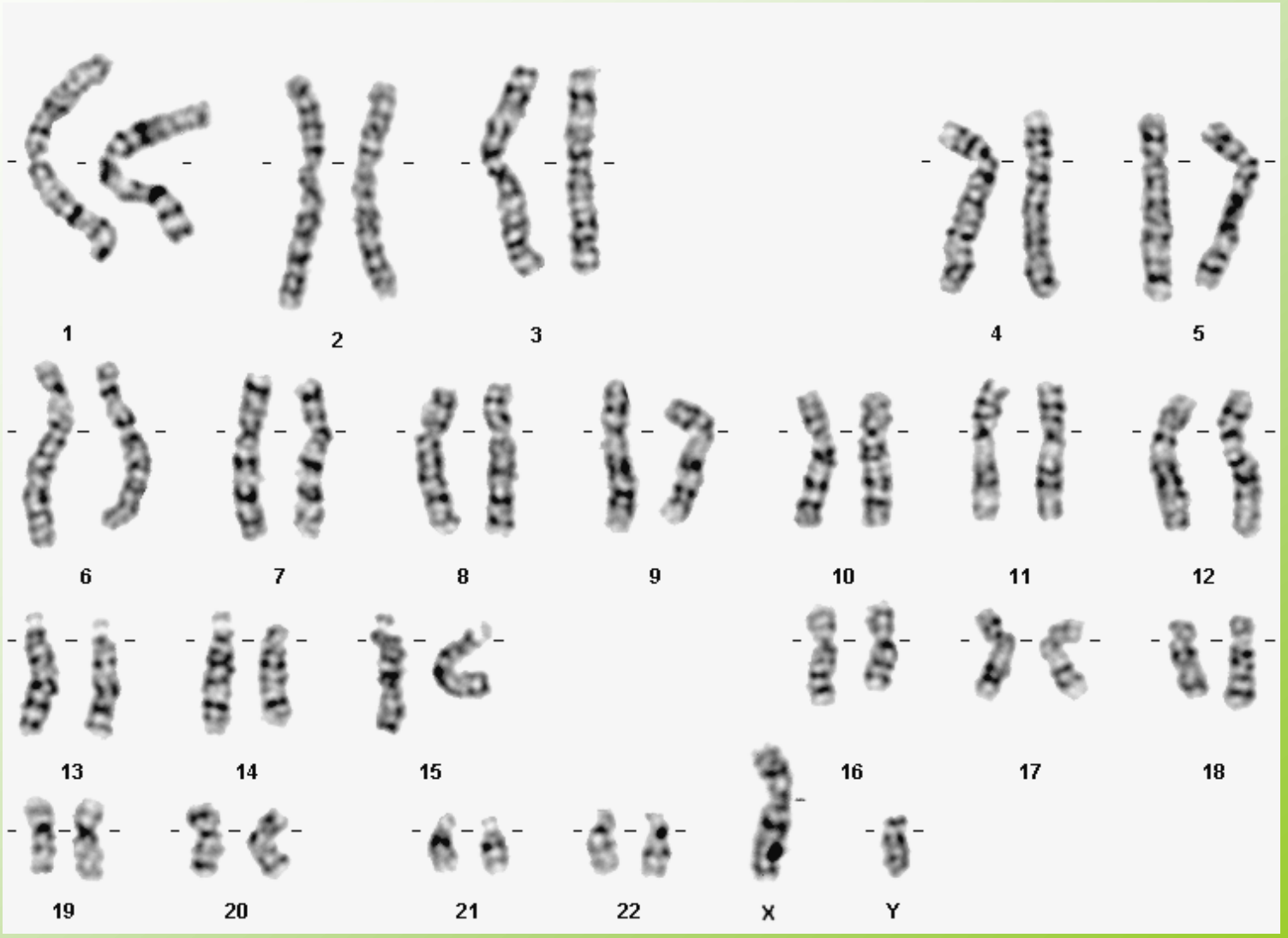
2014

Chromosomal aberrations

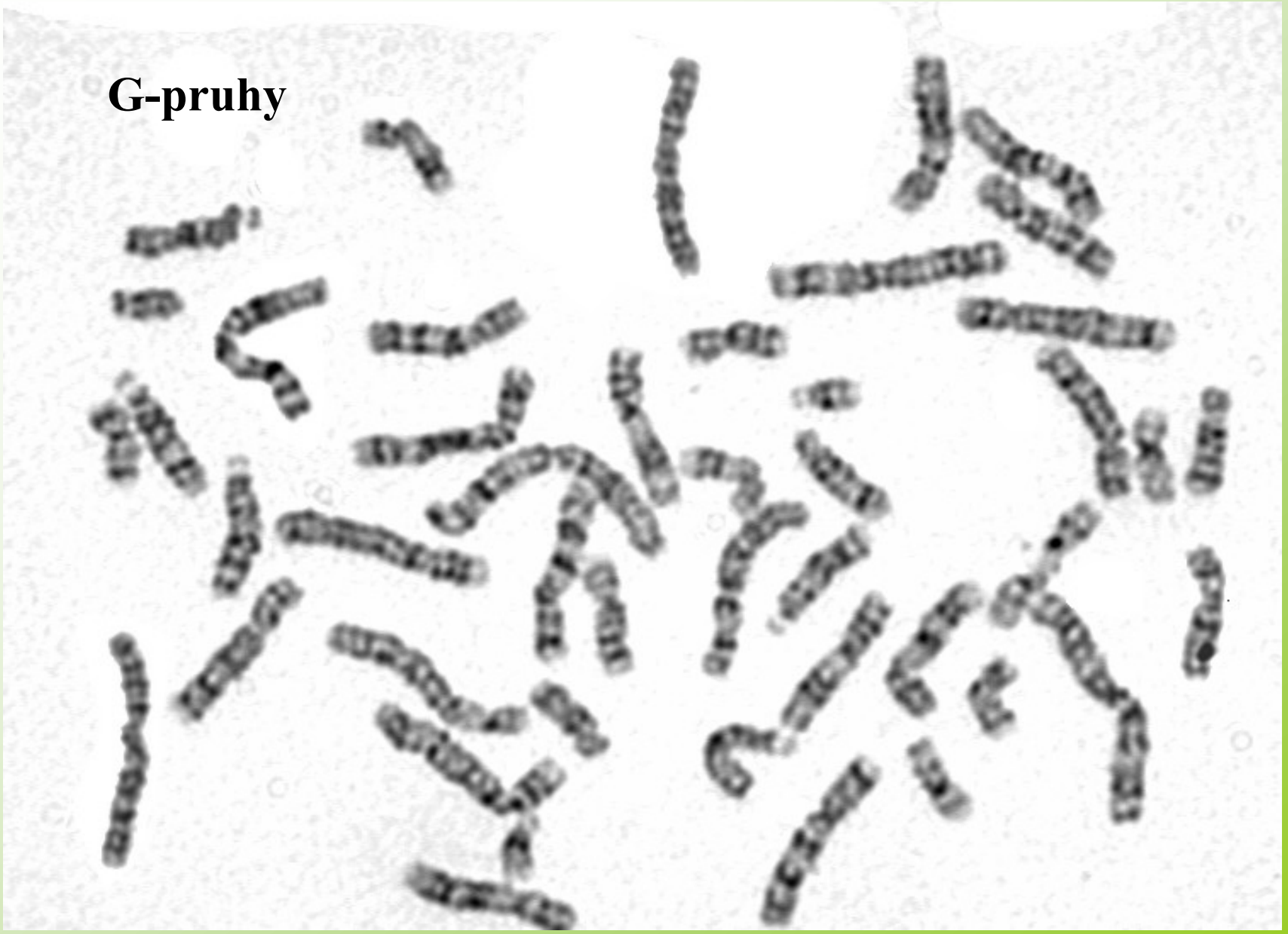


0,6-0,7% live born

Karyotyp 46,XY – normal in men



G-pruhy



Chromosomal aberrations

- **Inborn:**
- **20 – 50% all conceptions**
- **50 – 60% abortions (I. trimester)**
- **0, 56 - 0,7 % live born**

- **Acquired:**
- **Oncology – hematooncology**
- **Risks in enviroment (drugs, cigarettes,…)**

Congenital chromosomal aberrations

- Autosomes
- Gonosomes

- Numerous
- Structural

- Balanced
- Unbalanced

Frequency of congenital chromosomal aberations

- Live-born children 0,6%
- Balanced 0,2%
- Unbalanced 0,4%
- SA 50%
- Still born children 11,1%
- newborns with congenital malformations 15%
- Premature babies 2,5%

Chromosomal aberrations 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%

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

Cytogenetic analysis

- **Prenatal**
- **Postnatal**

Material for cytogenetic analysis

- **Cells from amnionic fluid**
- **Chorion villi**
- **Placenta**
- **Fetal blood**
- **Tissue – aborted fetuses**

- **Peripheral blood lymfocytes**
- **Tissue (skin biopsie, bucal smear,…)**

Indications for postnatal cytogenetic analysis

- The typical phenotype
- Newborn with multiple malformations
- Psychomotor / mental retardation
- Stigmatization
- Genital anomalies
- Disorders of sex development
- Infertile couples
- Gametes donors

Indications for amniocentesis

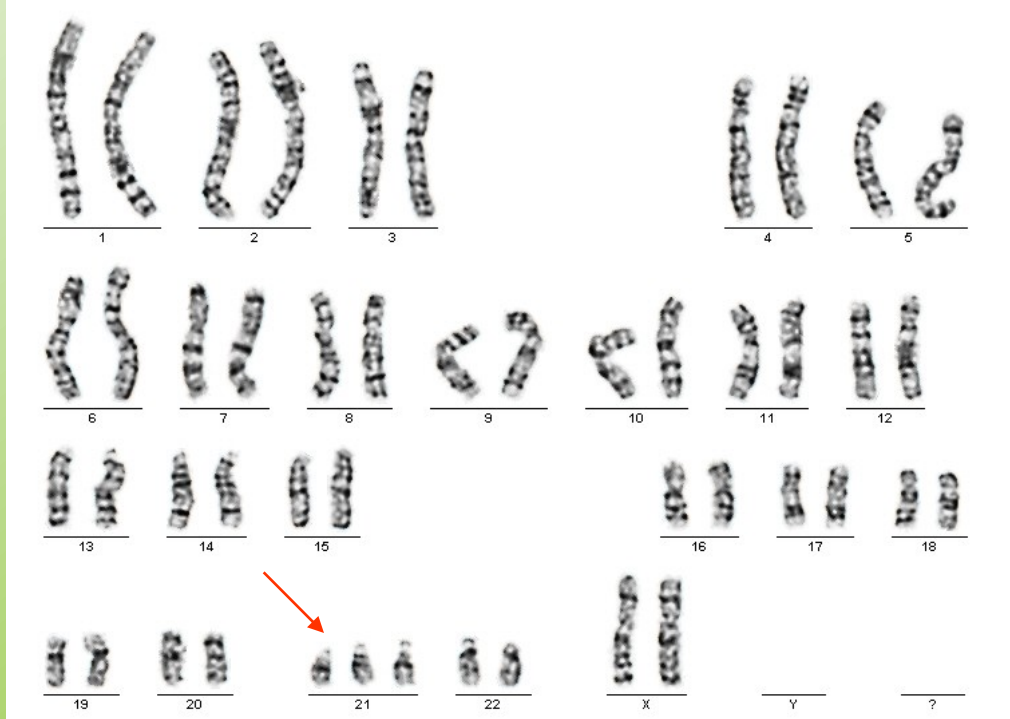
- Positive biochemical screening
- Pathological ultrasound findings in the fetus
- Balanced chromosomal aberrations in parents
- Chromosomal aberrations in the family
- Age of parents - ???

- Monogenic disease present in the family

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

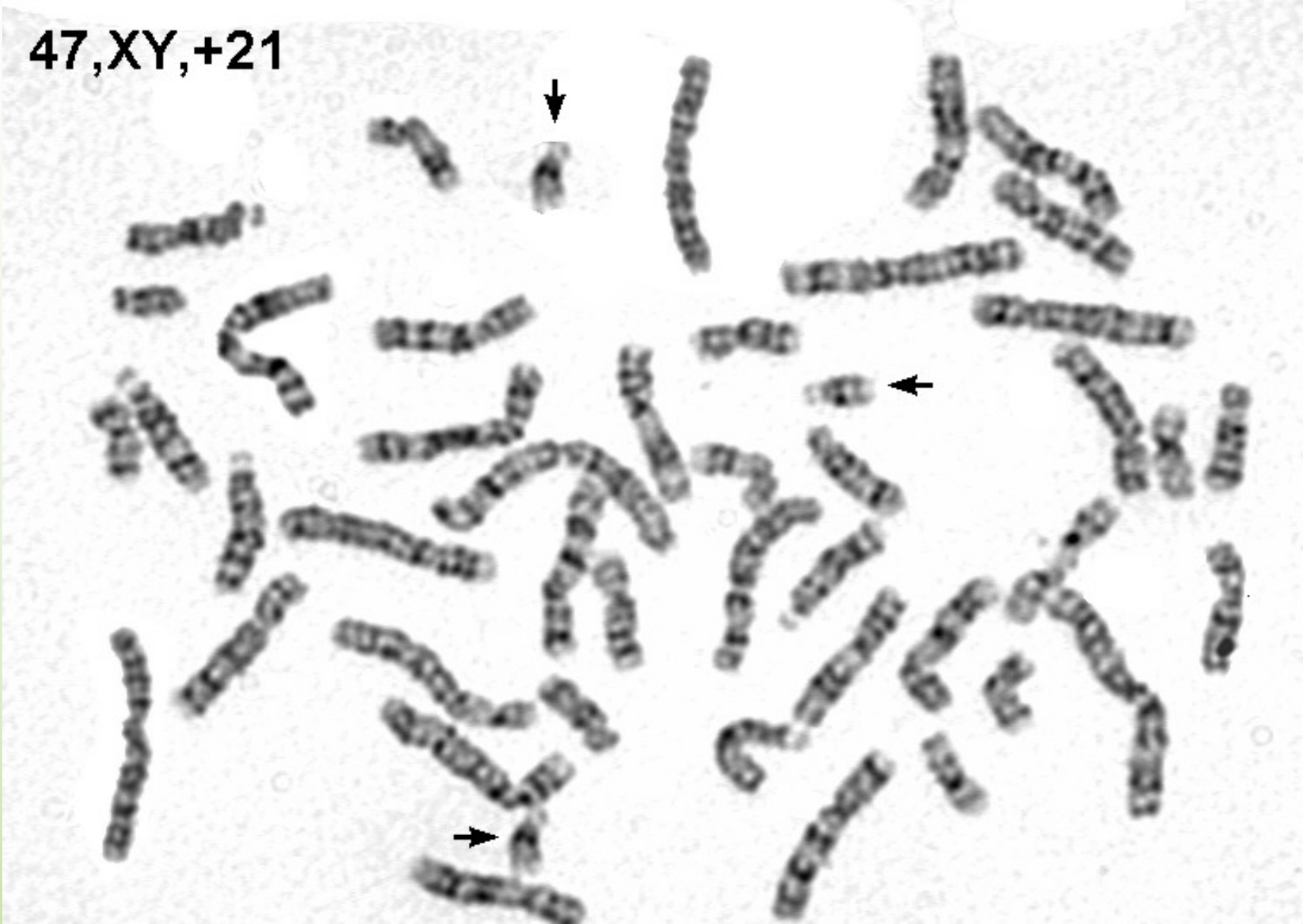


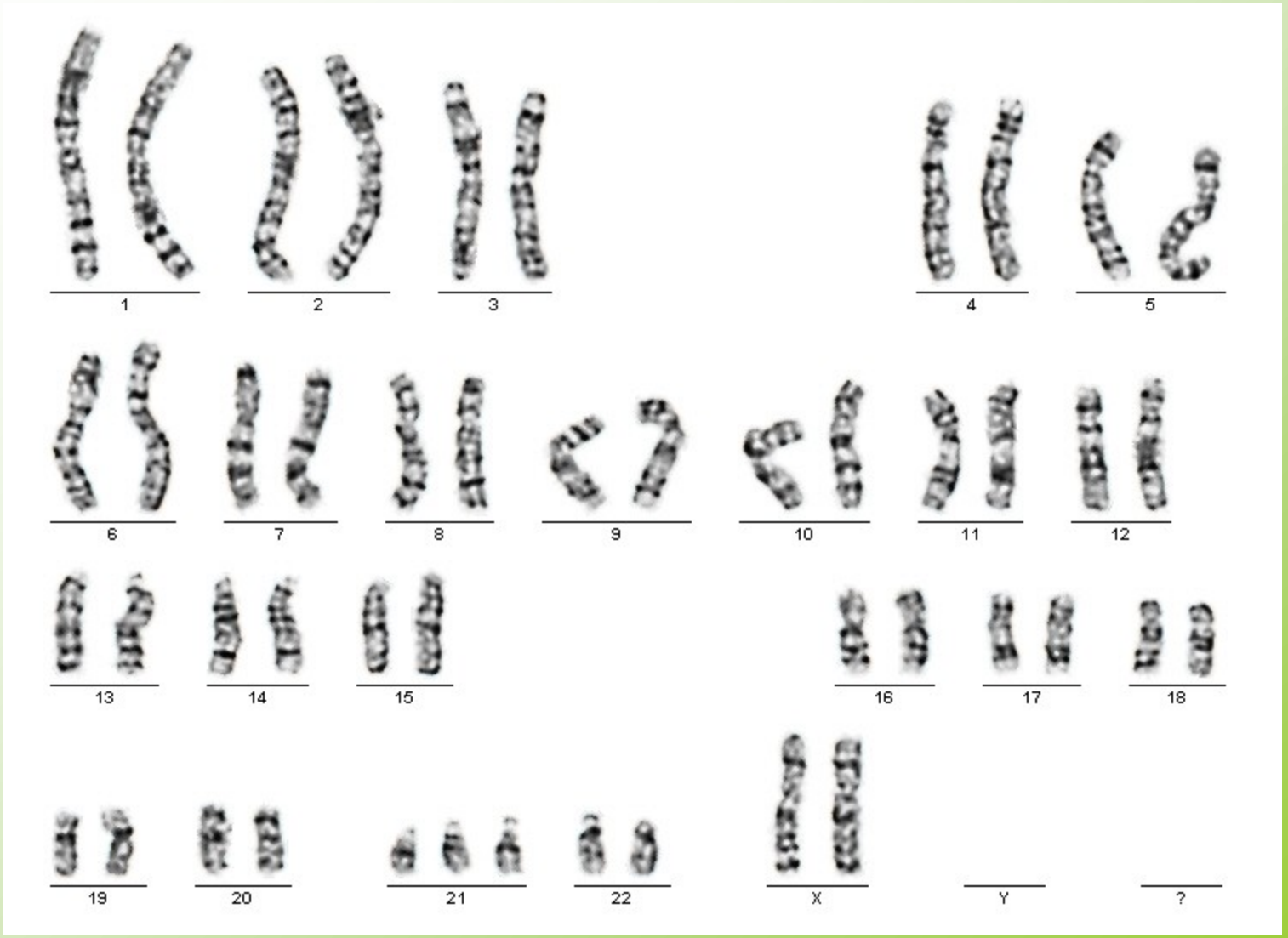
Down syndrome

- **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

Happy nature

Vision and hearing disorders

Hypothyroidism

Correlation between positive stimulation and height IQ

Male sterility

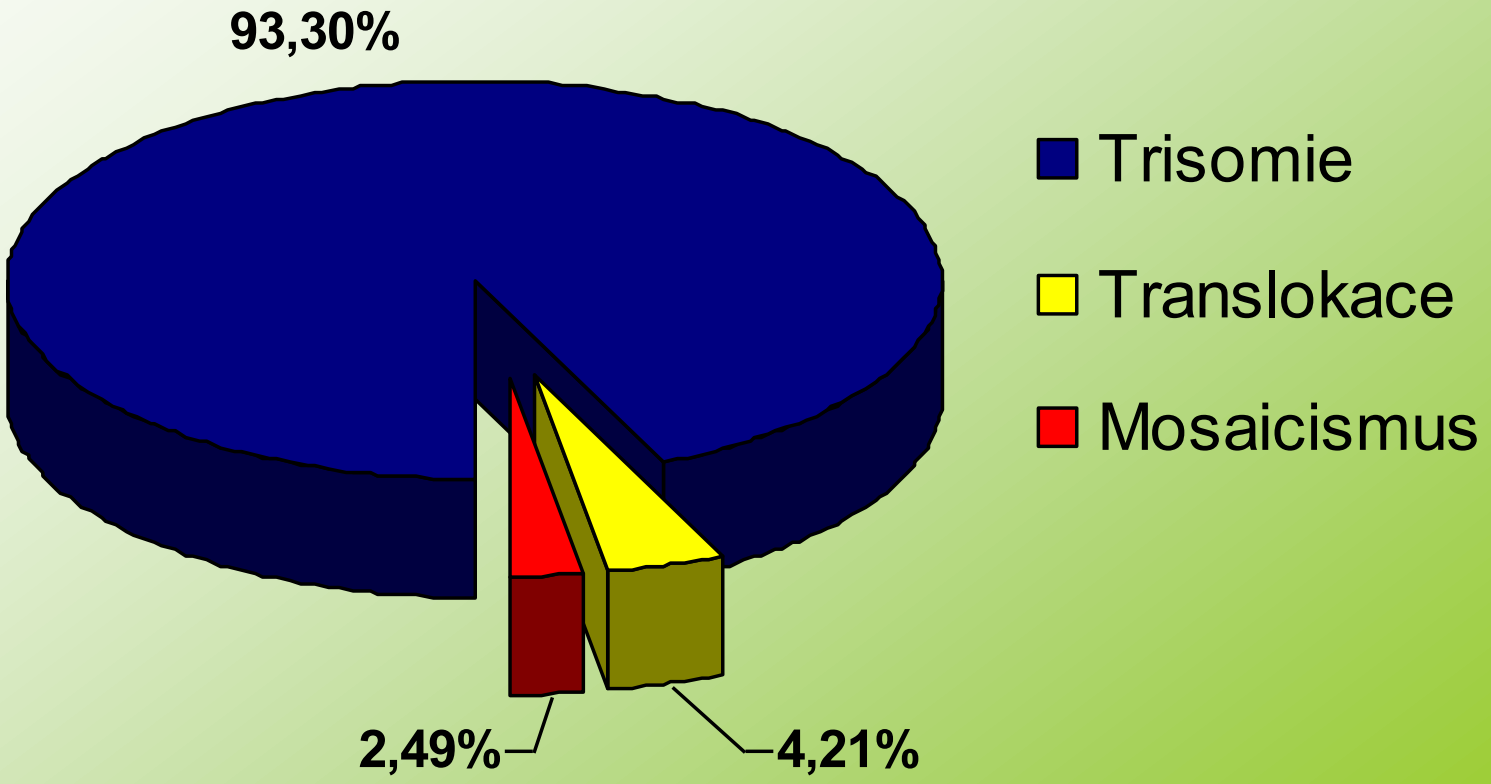
Alzheimer-like symptoms in 40

Risk of Down syndrome (live births)

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

Cytogenetic findings in DS in Czech republic

1994 - 2001



Down syndrome- prenatal screening

- 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 screening

- 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%

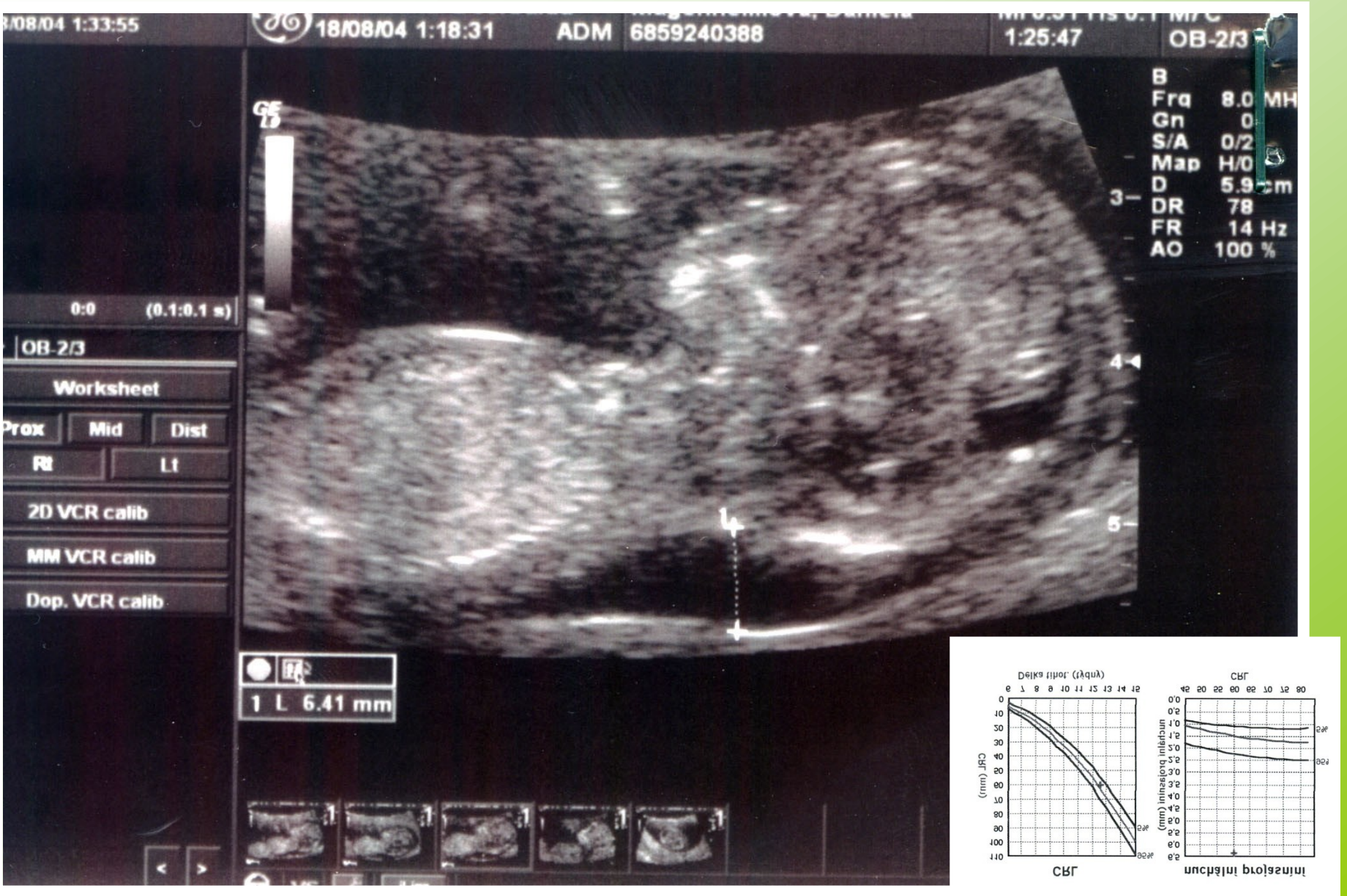
- Reveals about 70% of fetuses with Down syndrome

- 1/250 – positiv
- 1/250-1/350 – border
- 1/350 - negativ

Down syndrome- prenatal screening

- **Ultrasound**
- **10.-14. week**
- **NT**
- **NB**
- **Some congenital malformations**
- **20. week**
- **US**
- **Congenital malformations**
- **congenital heart disease**

Nuchal Translucency



I. Trimestr screening

- Age – 28,8
- Week of gestation 13+2 (US)
- FßhCG 26,66 - 1,09 MoM
- PAPP-A 2,93 – 0,82 MoM
- NT 2,0mm - 1,76 MoM

- Risk for Down syndrome in age 28,8 years – 1/1100

- Combine risk for DS 1/2700

- Negative I. trimestr screening

I. Trimestr screening

- Age – 33,6
- Week of gestation 12+5 (US)
- FßhCG 113,4 – 3,41 MoM
- PAPP-A 1,86 - 0,55 MoM
- NT 1,6 mm – 1,25 MoM

- Risk for DS in age 33,6 years – 1/550

- Combine risk for DS 1/80

- Positive I. trimestr screening

I. Trimestr screening

- Age – 33,6
- Week of gestation 12+5 (US)
- FßhCG 113,4 – 3,41 MoM
- PAPP-A 1,86 - 0,55 MoM
- NT 1,6 mm – 1,25 MoM
- Risk for DS in age 33,6 years – 1/550
- Combine risk for DS 1/80
- **Positive I. trimestr screening**

- **Recommendation**
- Genetic consultation
- Karyotyping of the fetus
- Detailed ultrasound examination of the fetus

II. Trimestr screening

- Age – 29,9
- Week of gestation
- 15+1
- AFP 48,0 - 1,66 MoM
- uE3 3,09 – 1,07 MoM
- Total hCG 40,2 – 0,99 MoM

- Risk for DS in age 29,9 years – 1/1000
- Combine risk for DS less then 1/50 000
- Negative II. trimester screening

- Recommendation
- Detailed ultrasound examination of the tetus in 20. week of gestation

II. Trimestr screening

- Age – 33,7
- Week of gestation
- 15+3
- AFP 21,1 – 0,71 MoM
- uE3 1,55 – 0,49 MoM
- Total hCG 35,1 – 0,95 MoM

- Risk for DS in age 33,7 years – 1/540
- Combine risk for DS 1/220
- Positive II. trimester screening

- Recommendation
- Genetic Consultation
- Karyotyping
- Detailed ultrasound examination of the fetus

II. Trimestr screening

- Age – 25,7
- Week of gestation
- 20+5
- AFP 27,6 - 0,50 MoM
- uE3 6,28 – 0,38 MoM
- Total hCG 4,2 – 0,21 MoM
- Risk for DS in age 25,7 years – 1/1300
- Combine risk for DS 1/6300
- Risk for Edwards syndrome 1/3
- Risk for Smith-Lemli-Opitz syndrome 1/65

- Recommendation
- Genetic Consultation
- Fetal karyotyping, DNA of the fetus (SLOS)
- Detailed ultrasound examination of the fetus
- DNA analysis SLOS – both parents

Integrated screening

- Age – 25,8
- Week of gestation
- 1. 12+6 (US)
- 2. 15+6
- AFP 29,8 – 0,97 MoM
- uE3 3,45 – 0,96 MoM
- Total hCG 48,5 – 1,48 MOM
- PAPP-A 4,1 – 1,16 MOM
- NT 1,3 mm – 1,01 MoM
- Risk for DS in age 25,8 years – 1/1300
- Combine risk for DS 1/15 000
- Negative integrated screening

- Recommendation
- Detailed ultrasound examination of the tetus in 20. week of gestation

Non-invative prenatal testing (NIPT)

- examination of free fetal DNA in maternal plasma
- performed outside the Czech Republic
- reliability over 98 %

Edwards syndrome

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

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

Edwards syndrome

- 1:5000
- 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

- 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 syndrome

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

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

Turner syndrome 45,X

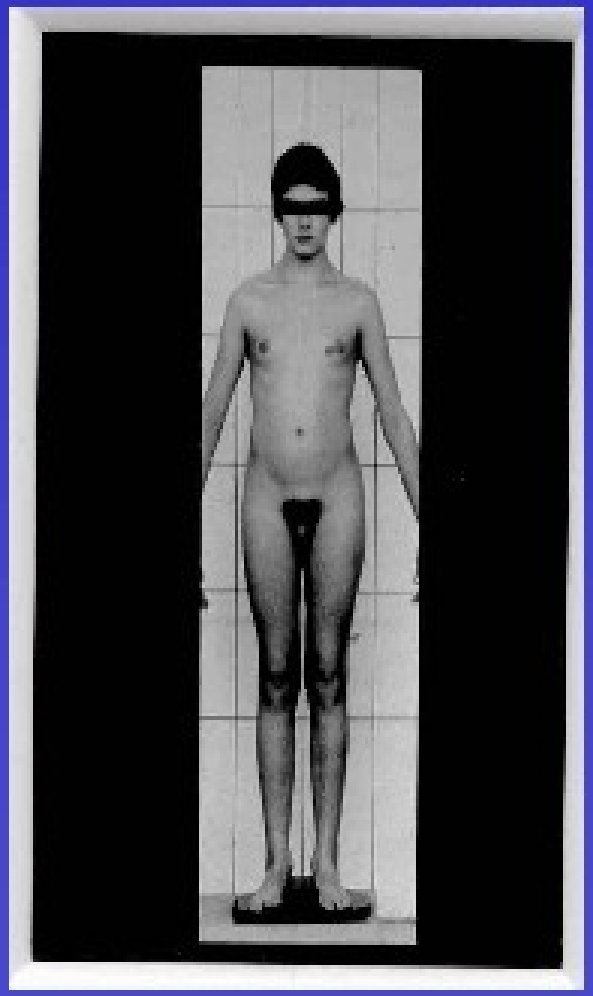
- 1:2000
- hygroma colli
- hydrops
- Low weight in newborns
- Lymfoedema
- Pterygia
- Cubiti valgi
- Aortal stenosis
- Small statue
- Sterility

Klinefelter syndrome

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

Klinefelter syndrome 47,XXY

Syndrome de Klinefelter



- Testicules de petit volume
- Atrophie tubulaire
- Gynécomastie
- Grande Taille
- Grande envergure
- Rapport SS/ SI diminué
- Difficultés Scolaires
- FSH ↗ et LH ↗, testo svt basse
- 47, XXY

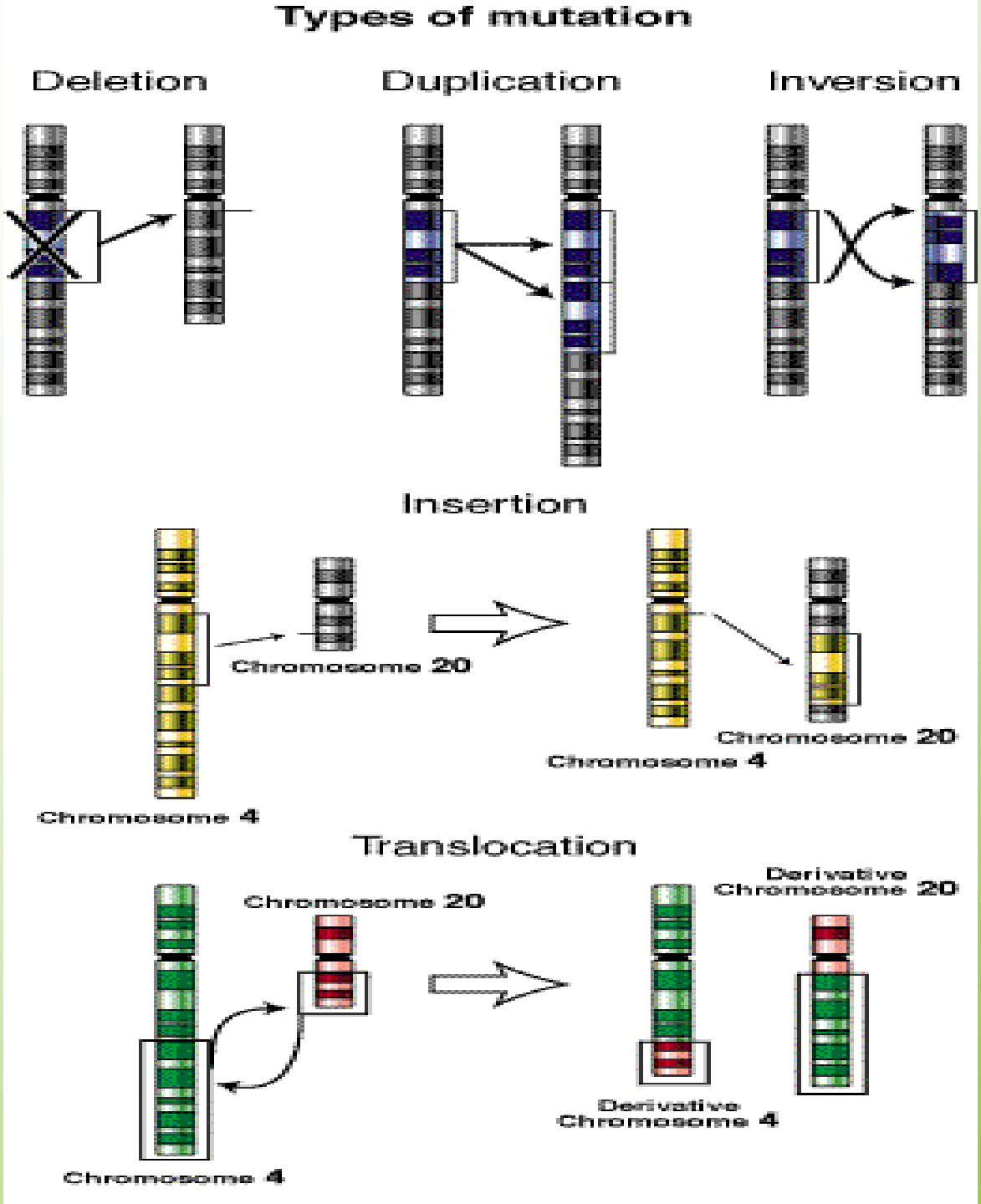
Others gonoseme abnormalities

- **47,XXX**
- **47,XYY**

- **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
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 ...

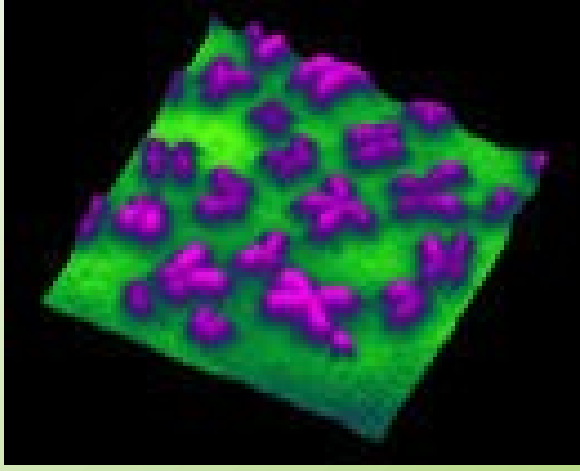
Cri du chat syndrome 46,XX(XY),5p-

- 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-

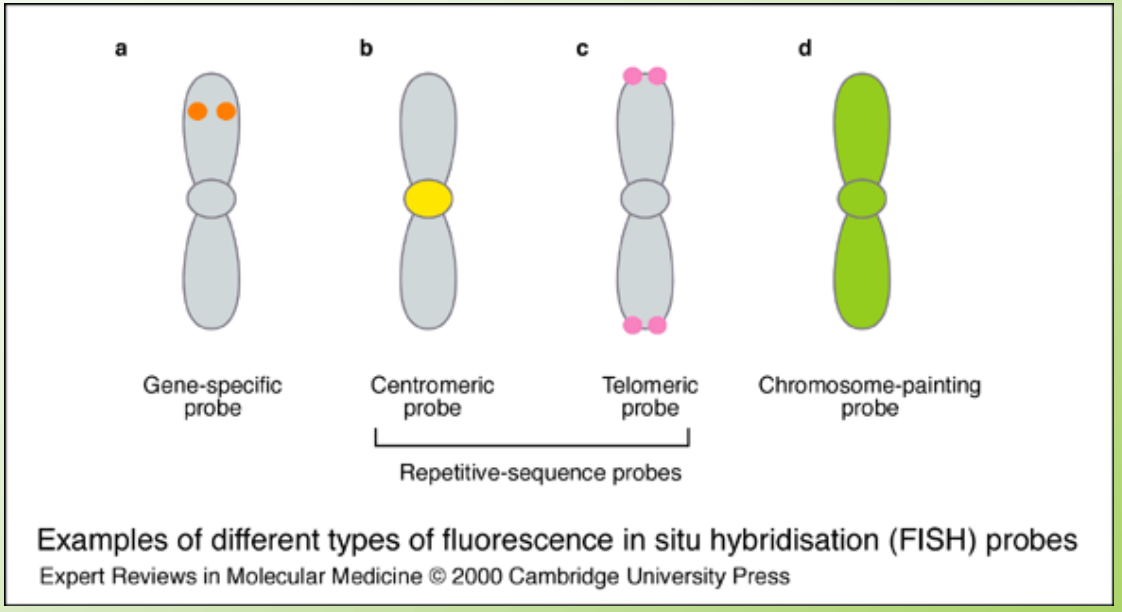
- 1:50 000
- Typicaly cri in newborns
- laryngomalacie
- antimongoloid
- epicanthi
- hypotonie
- hypotrofie

Mikrocytogenetic
Molekular cytogenetic

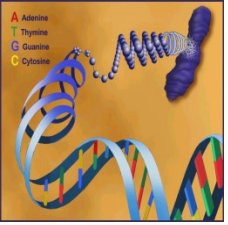


- FISH (fluorescenc in situ hybridisation), M-FISH, SKY (spektral karyoptyping), CGH (komparativ genom hybridisation), MLPA
- mikrodeletions or mikroduplications, marker chromosoms, complex rearegements, oncology – oncocytogenetics,fast prenatal diagnostics …)
- fast methods (possible for prenatal dg)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

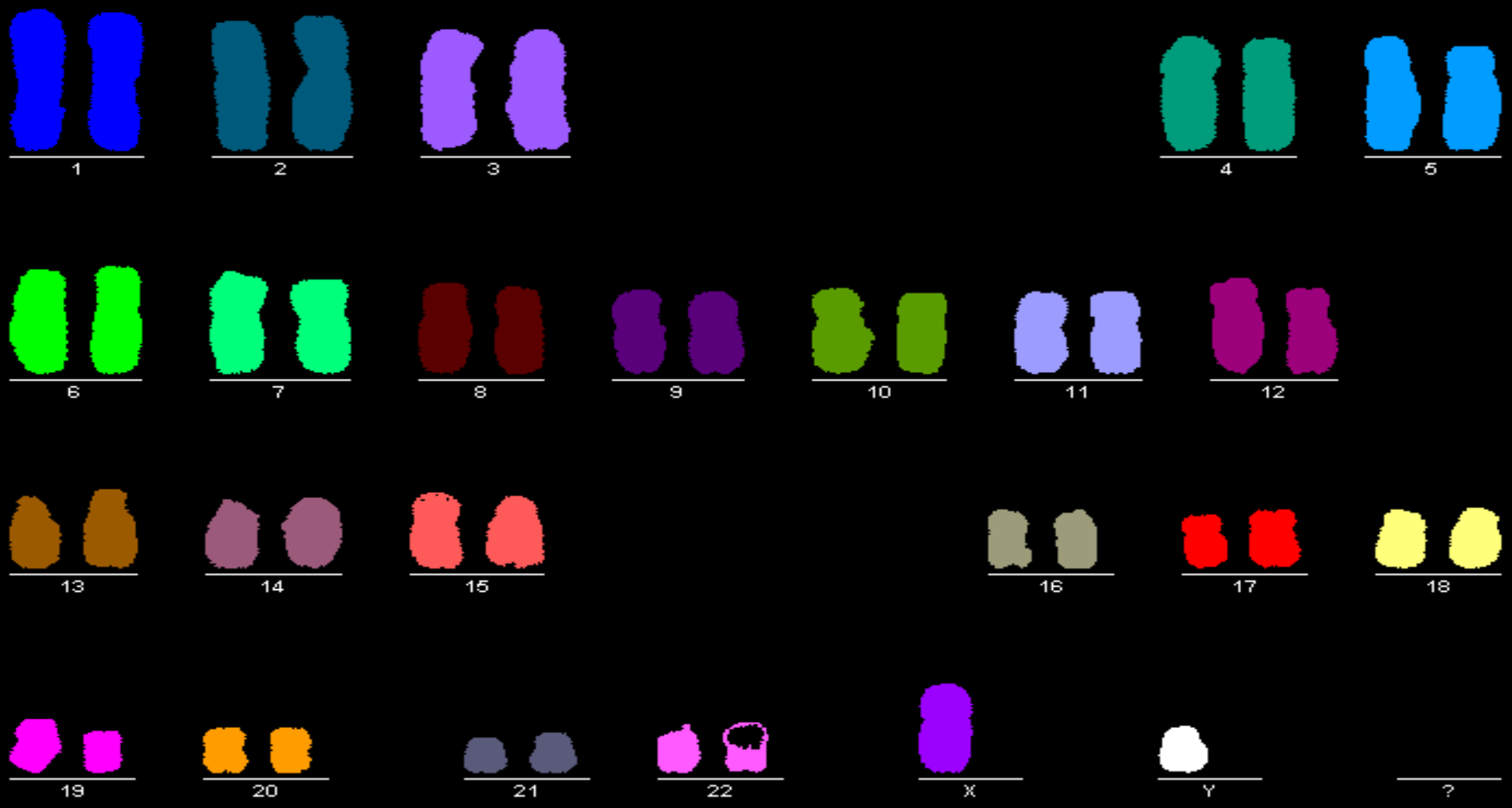
FISH



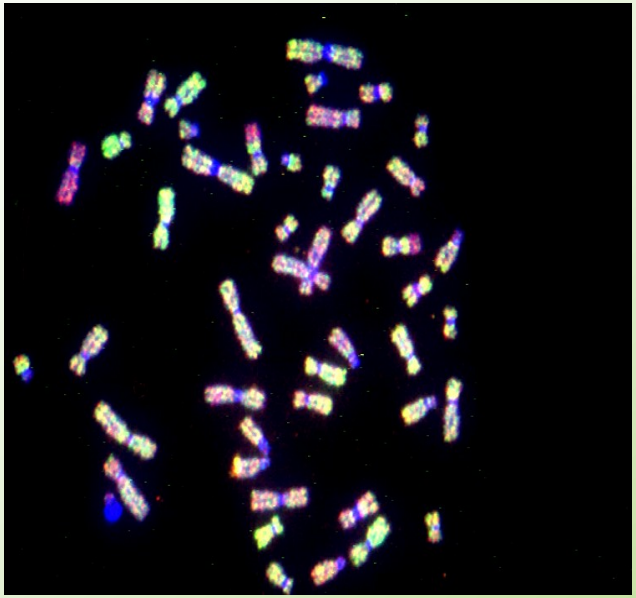
Examples of different types of fluorescence in situ hybridisation (FISH) probes

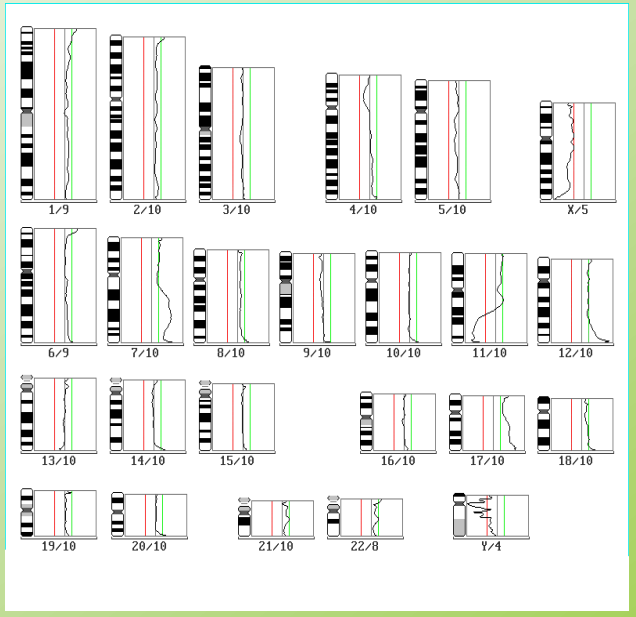


M-FISH (multicolor)
Spektral karyotyping (SKY)



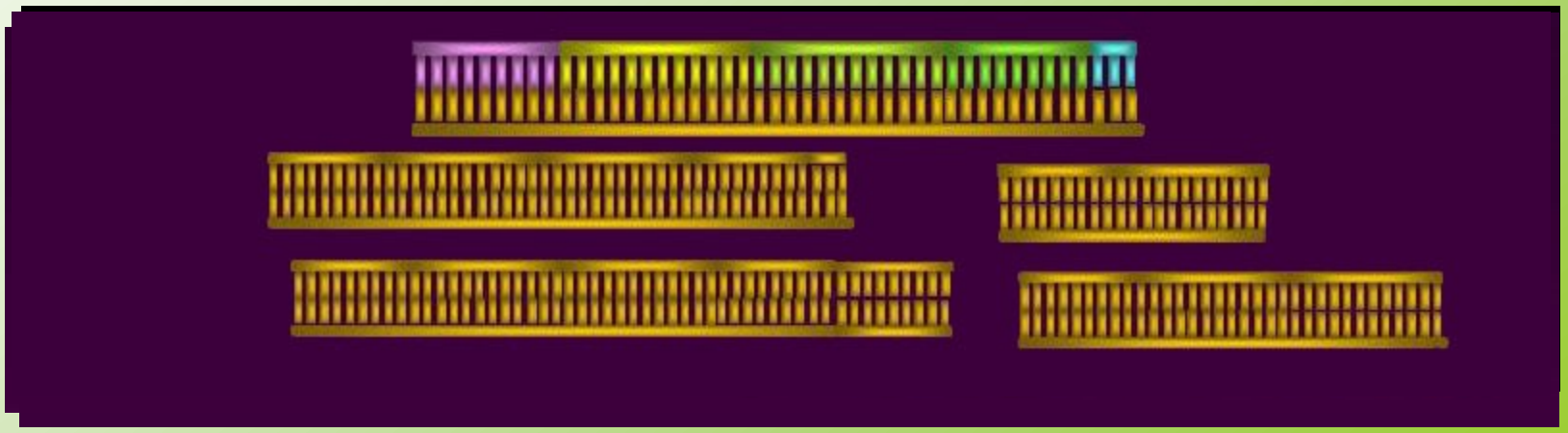
Comparativ genom hybridisation





MLPA

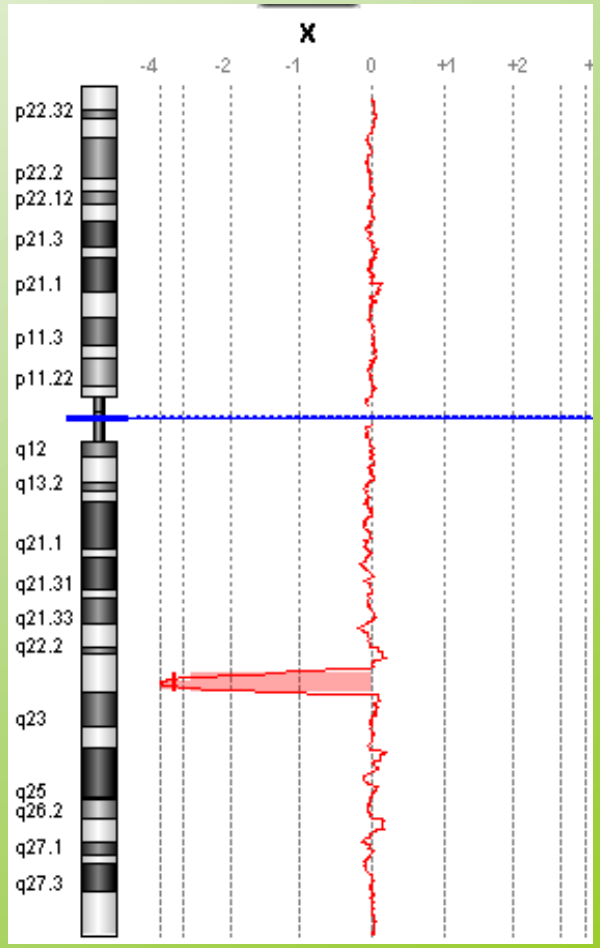
Multiplex Ligation-Dependent Probe Amplification



MRC-Holland
MLPA

Array CGH

- DNA mikroarray
- Chip technology

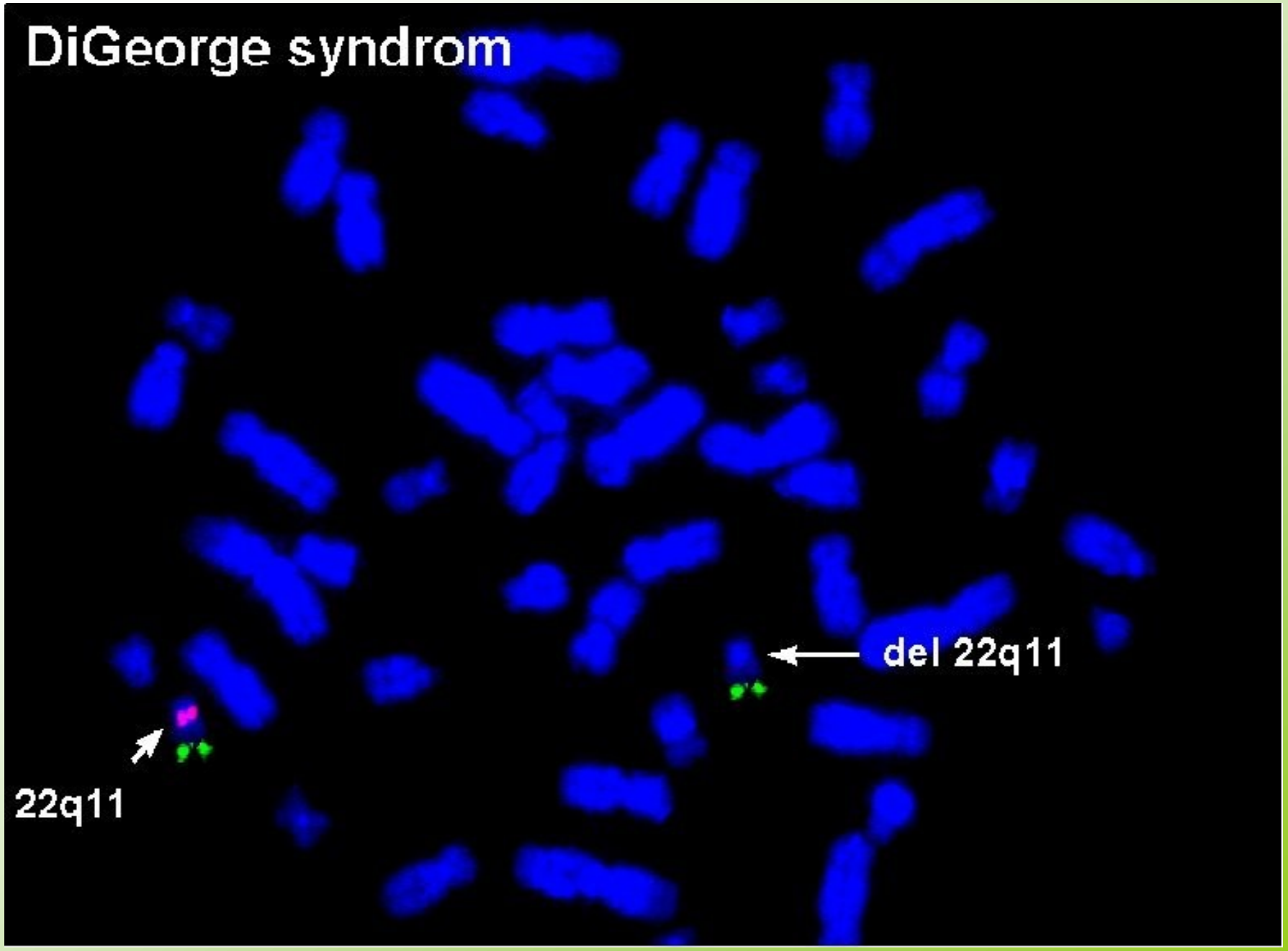


Microdeletions

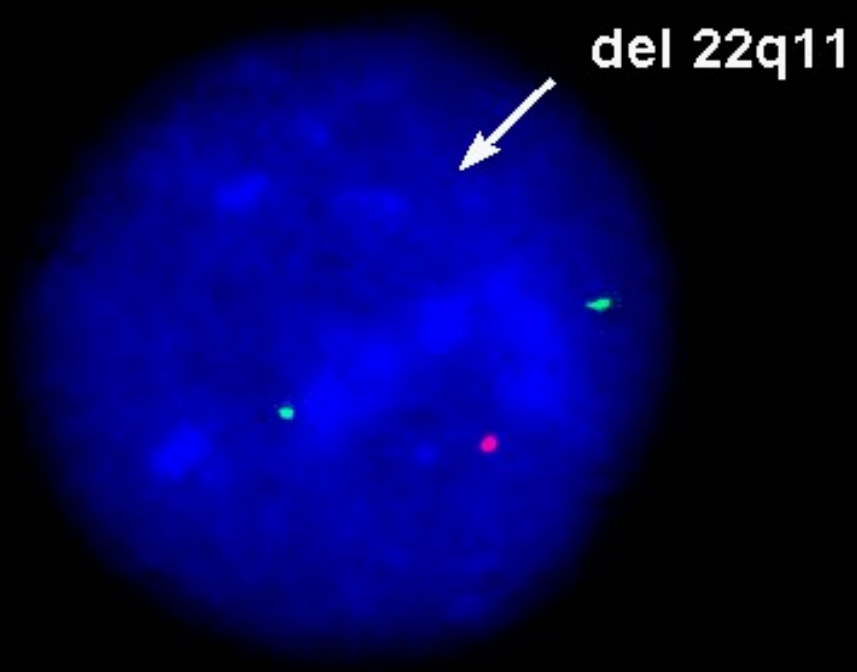
- **Di George syndrome (del 22q11)**
- **Prader-Willi / Angelman syndrome (del15q11-13)**
- **Williams Beuren syndrome (del7q11.23)**

Syndrom Di George

- Velo - Kardio- Facial syndrome
- CATCH 22
- Congenital heart desease - conotruncal, craniofacial dysmorfism, thymus aplasie, imunodefitient¨cy, hypoparathyreoidismus


DiGeorge syndrom
del 22q11
22q11

DiGeorge syndrom



Williams - Beuren syndrome

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

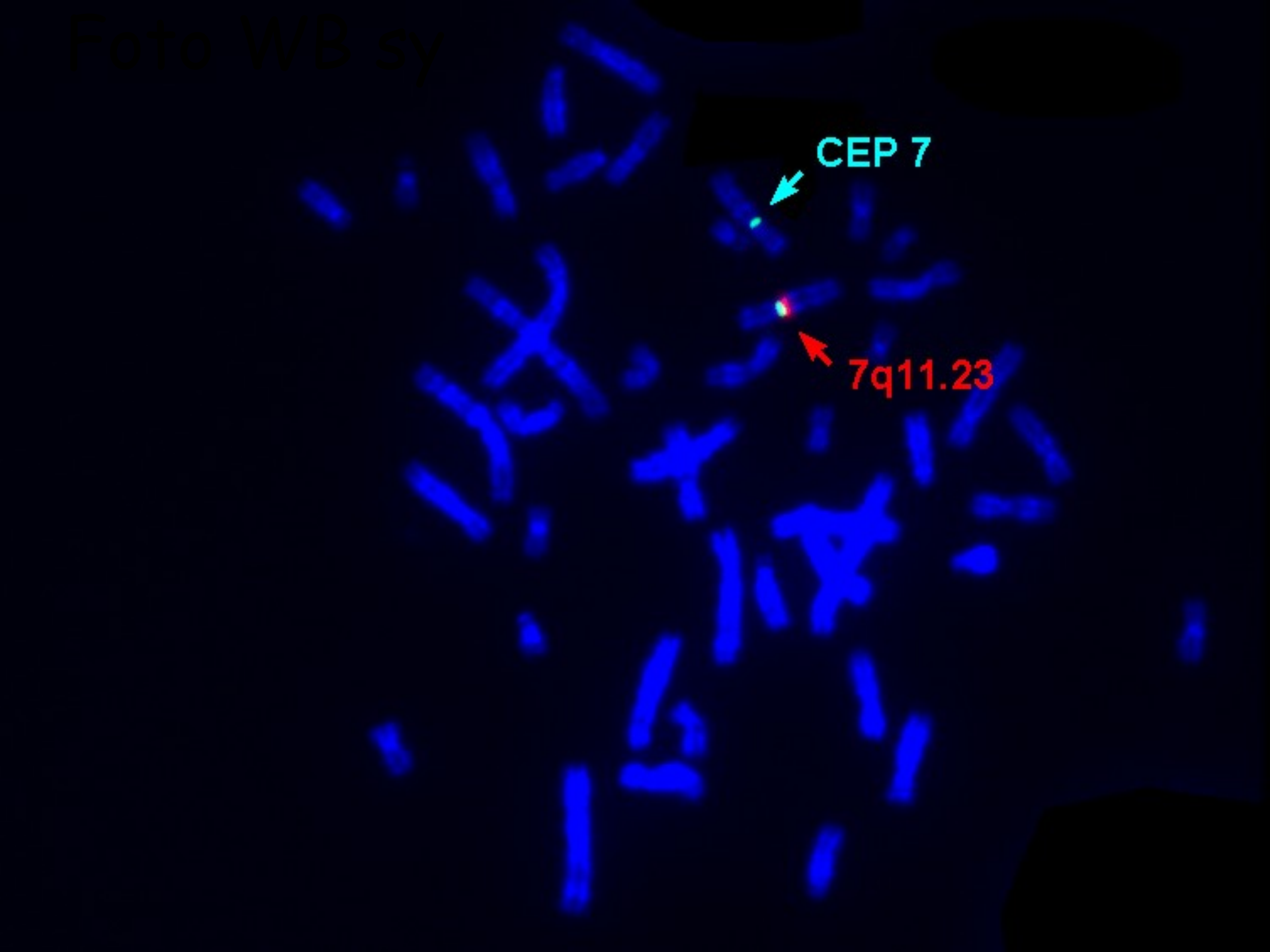


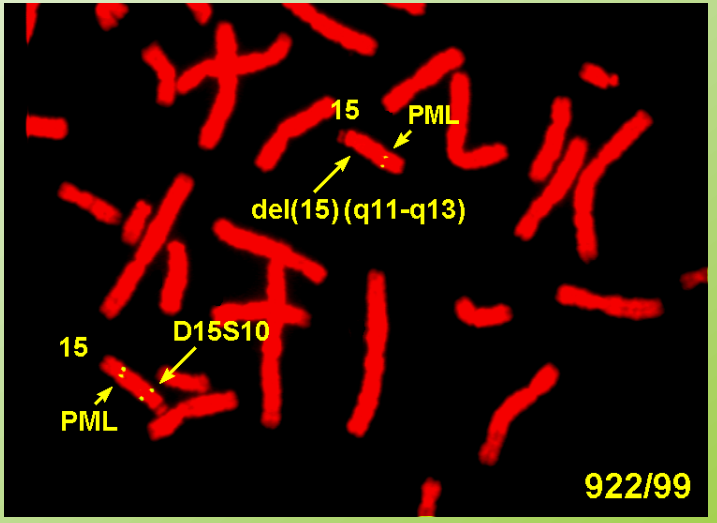
Foto WB sy
CEP 7
7q11.23

Prader-Willi syndrome

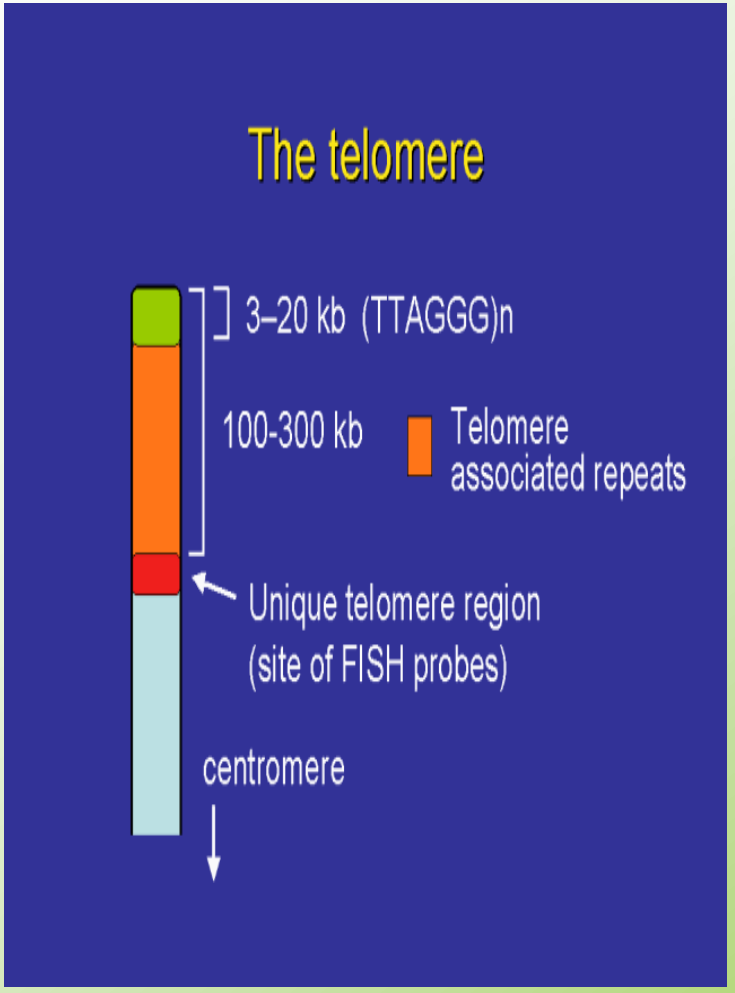
- **Hypotonie, hypotrofie in small children**
- **PMR, small statue, obesity, hyperfagie, akromikrie, hypogonadismus**
- **mikrodeletion15q11-12 paternal**

Angelman syndrome

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



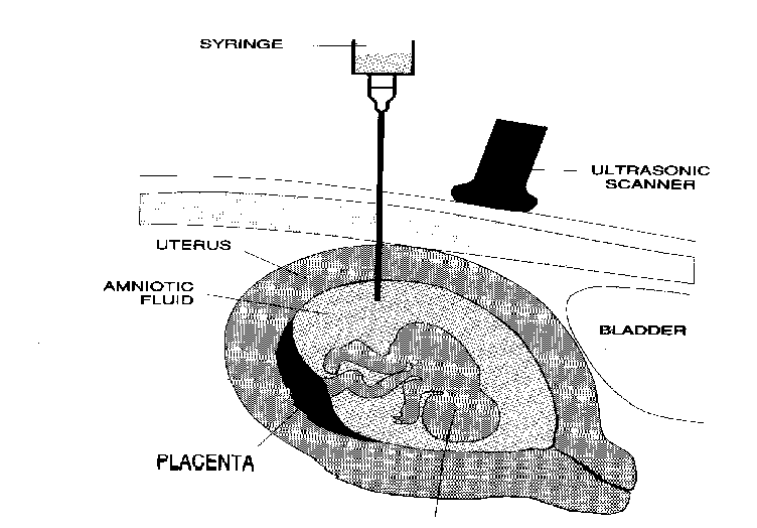
The telomeres



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

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
- Cordocentesis – after the 20. week of gestation

Indications for prenatal examination / genetic counselling

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

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

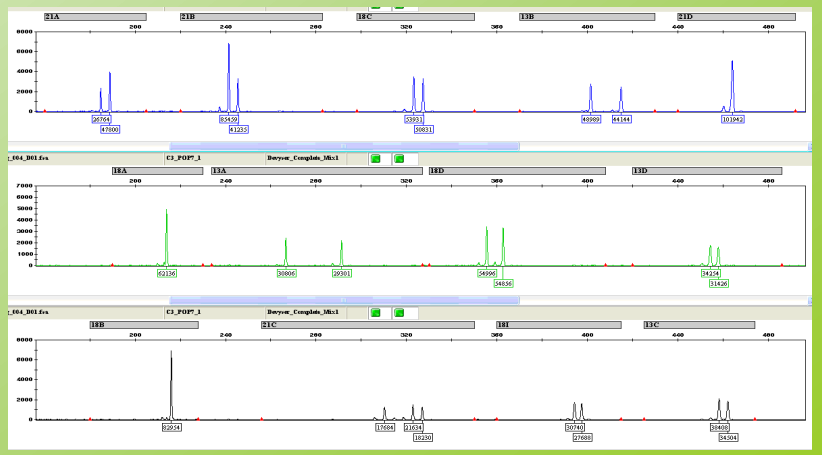
Prenatal diagnosis results

- 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 frewquent aneuploidias
QF PCR

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



Preimplatation Genetic Diagnostics

Preimplatation Genetic Diagnostics

- IVF – assisted reproduction

- Preimplantation genetic screening
- aneuploidias - 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

- **PG Diagnostic**
- **high genetic risk**
- **Structural chromosomal aberation in parents**
- **Monogen diseases**

- **PG Screening**
- **aneuploidies**

PGD – day 5, array-CGH