Genetic counselling

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Clinical genetics

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

Dept. of Medical genetics

- Genetic ambulance – genetic counselling

- Laboratory part
- Cytogenetic lab. (pre- and postnatal)
- Oncocytogenetic lab.
- Molecular – cytogenetic lab.
- Lab. for DNA and RNA analysis (clinical genetics and oncogenetics)

Characteristic of Medical Genetics

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

Primary prevention of genetic

- Before pregnancy
- Folic acid (cca 1mg/day, 3+3 months)
- Vaccination (rubella)
- Genetic counselling
- Contraception, adoption
- Donor (oocytes, sperm)
- Pregnancy planning
- Environmental hazards (drugs, radiation, chemicals…)

Secondary prevention of genetic

- Prenatal diagnosis

- Prenatal screening, treatmwent if possible
- Genetic counselling
- Postnatal screening, treatment, dispensary
- Termination of pregnancy (the law in Czech Republic- end of 24. week of gestation)

Genetics diseases

- Chromosome abnormalities – about 0,6 -0,7%

- Monogen diseases – about 0,36% (in 1 000 000 newborns)

  most then 90% in childhood

- Multifactorial disorders – about 80%

Patients on genetic departements

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

Patients on genetic departements

- 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

Genetic counselling

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

Mother

- Name, surname, date of birth, maiden name
- Place of birth
- Place of birth parents
- Relationship
- Jobs - employment risks
- Addictive substances

  alcohol, cigarettes,

  drugs ..

Mother

- Health problems from birth yet
- Long-term medication
- Long-term monitoring of a doctor
- Gynecological anamnesa
- The number of births, children, pregnancy, birth weight children, the health status of children
- The number of abortions, failed pregnancy
- Unsuccessful attempt to become pregnant

Mother

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

Father

- Name, surname, date of birth
- Place of birth
- Place of birth parents
- Relationship
- Jobs - employment risks
- Addictive substances

alcohol, cigarettes,

drugs ..

Father

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

Father

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

Child - Patient

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

Child

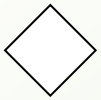
- Birth - in time, early, after the deadline?
- Complications, neonatal icterus, birth weight and length, nutrition, home state of release
- The mental and motor development
- Diseases
- Monitoring of specialists
- Drugs
- Test results

Child

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

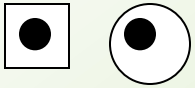
man

woman

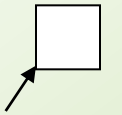


Unknown gender

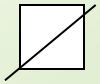
diseased



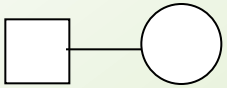
carrier



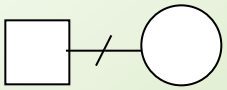
proband



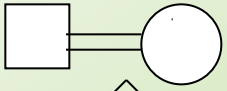
dead person



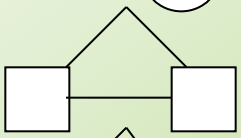
marriage



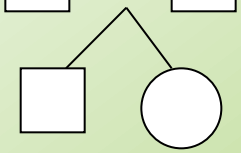
divorce



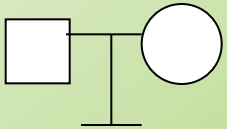
konsanguinity



monozyg. twins



dizygot. twins



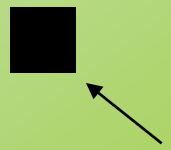
childless

miscarriage

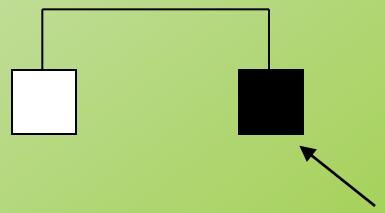
Three-generation pedigree

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

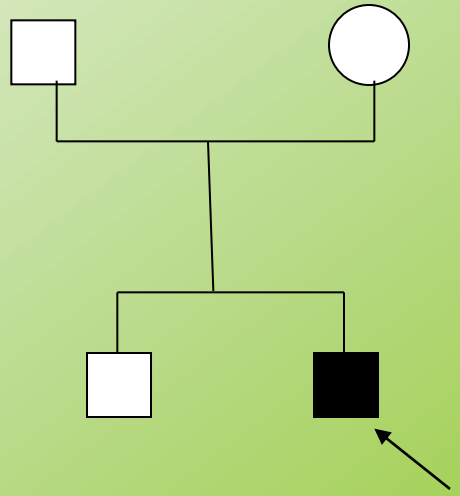
Pedigree



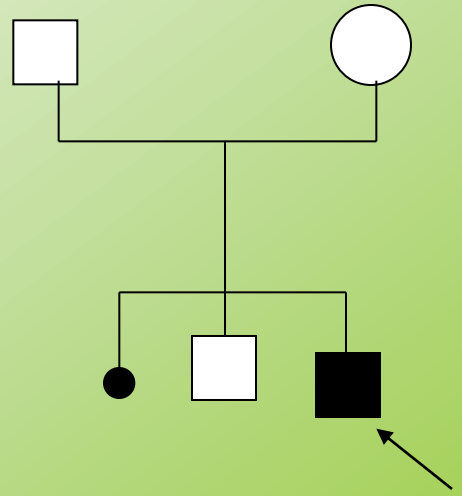
Pedigree



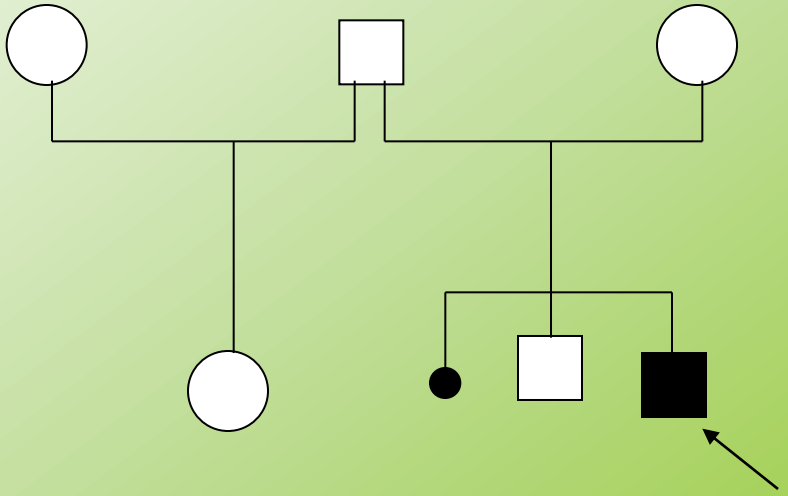
Pedigree



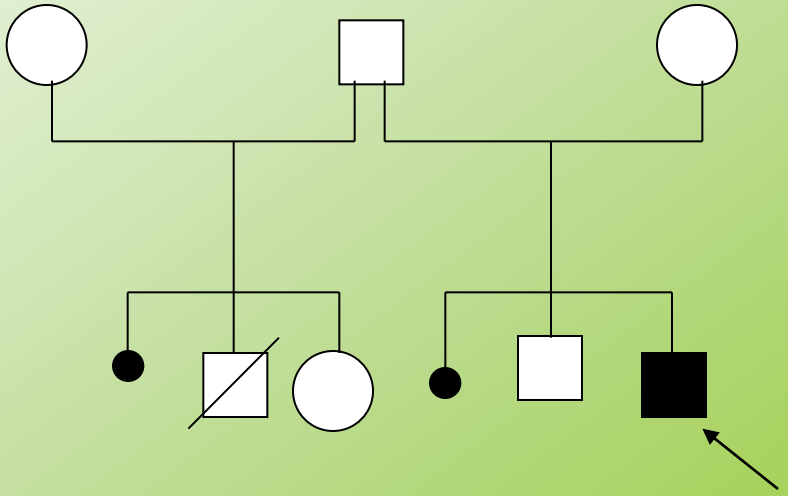
Pedigree



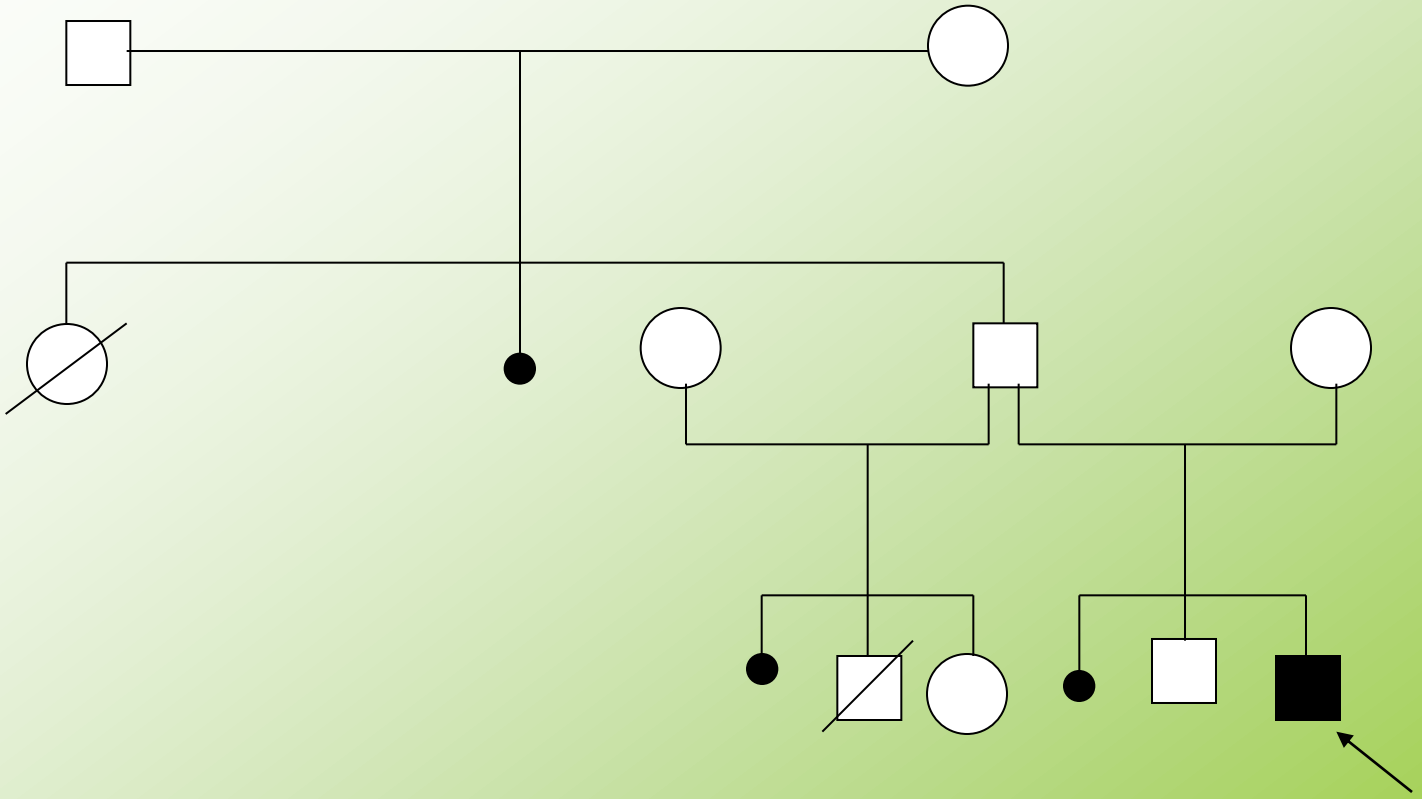
Pedigree



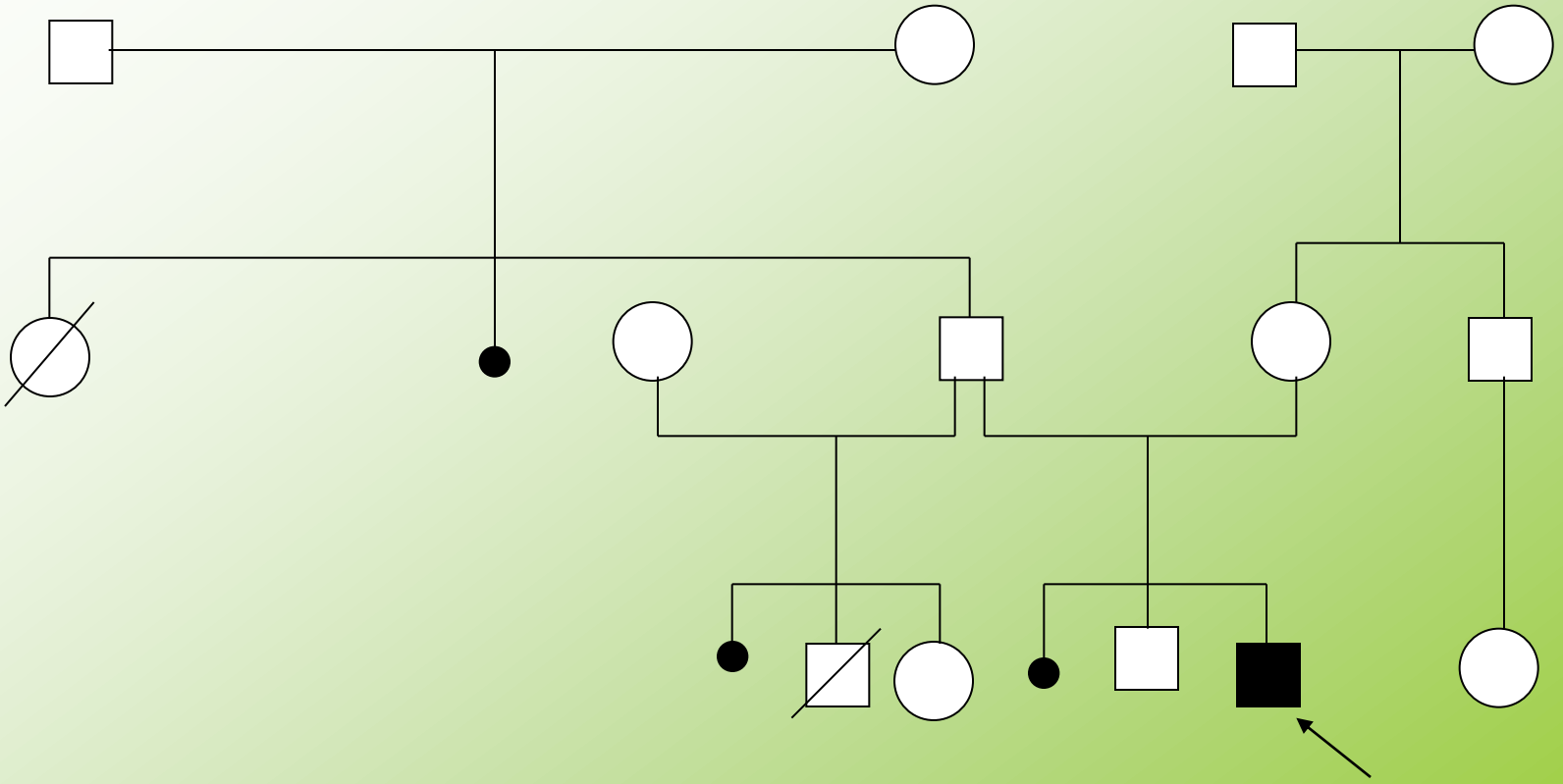
Pedigree



Pedigree



Pedigree



Next steps

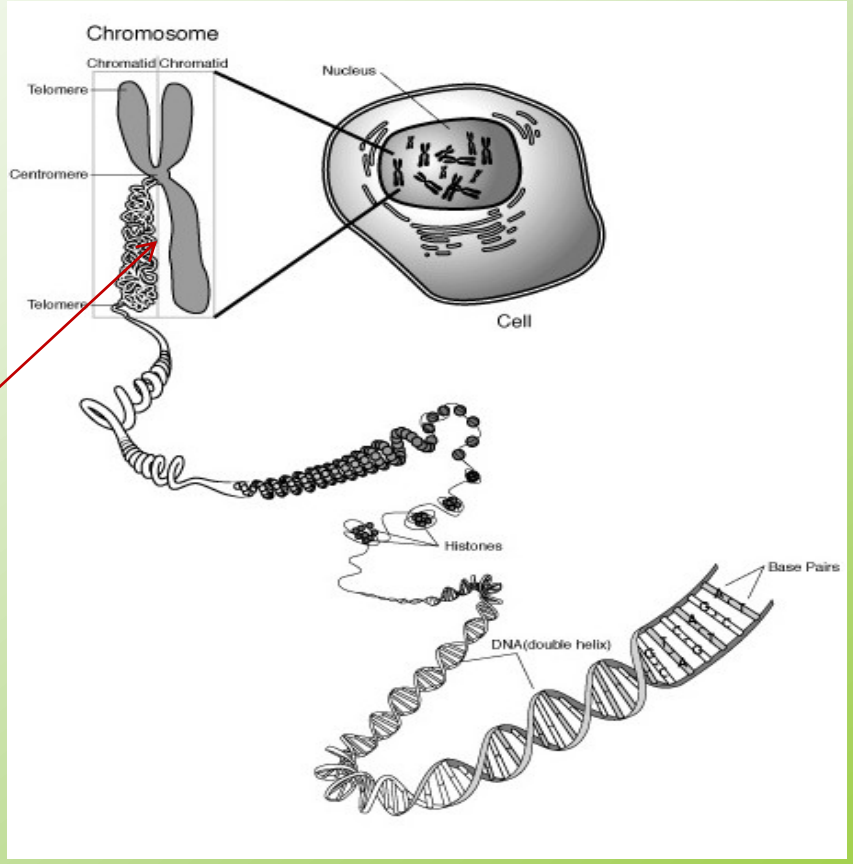
- Recommend the laboratory genetic testing
- Recommend other specialists if needed
- Require medical documentation in the absence
- Make photodocumentation

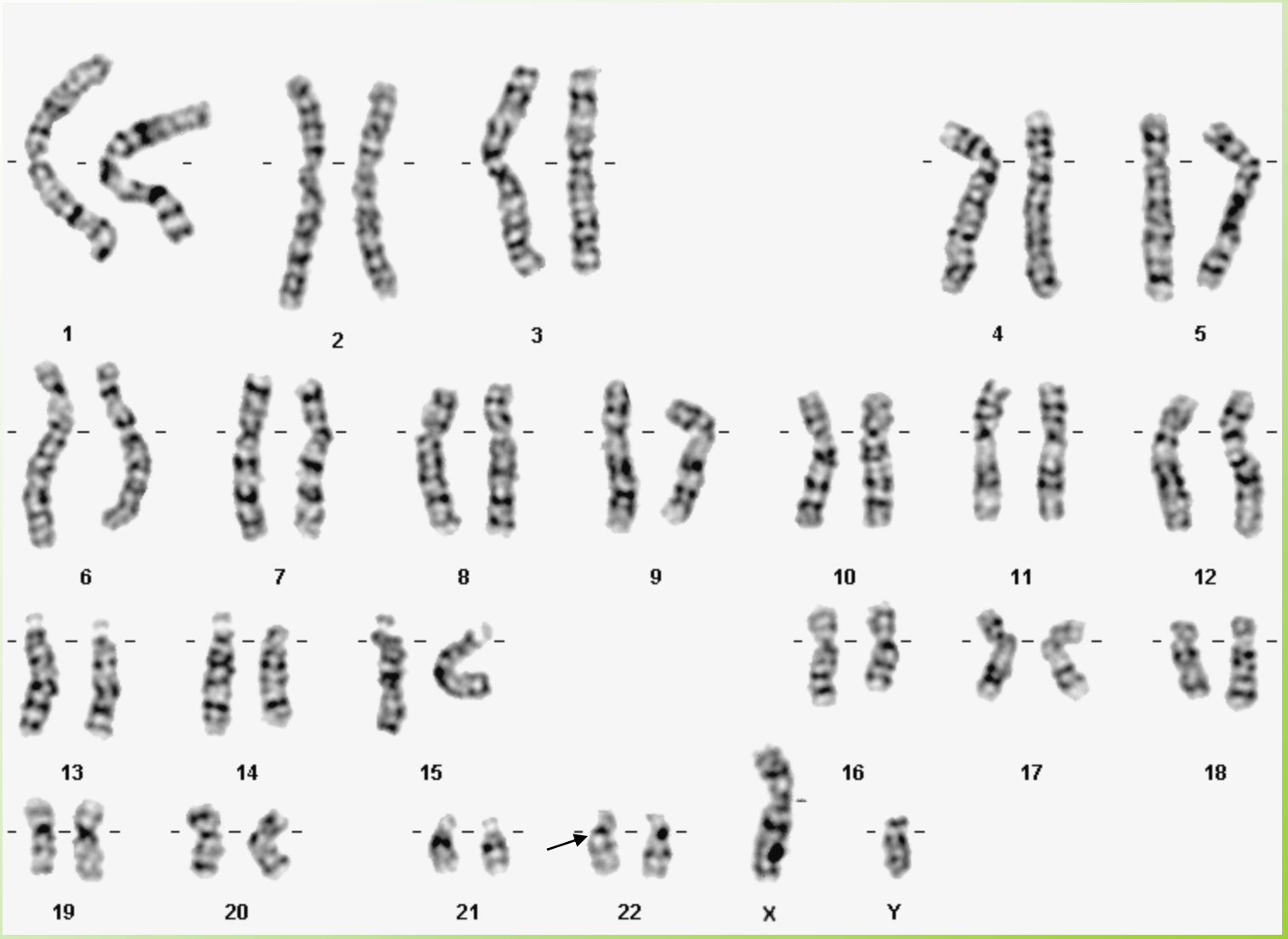
Genetic counselling

- **Exact diagnosis** (if possible)

- **Genetic prognosis**
- Is the disease hereditary?
- Type of inheritance
- Genetic risks for other family members
- Posibilities of treatment, prenatal analysis

Chromosome abnormalities

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X
Y

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%
Upto 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

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

Happy nature

Vision and hearing disorders

Hypothyroidism

Correlation between positive stimulation and height IQ

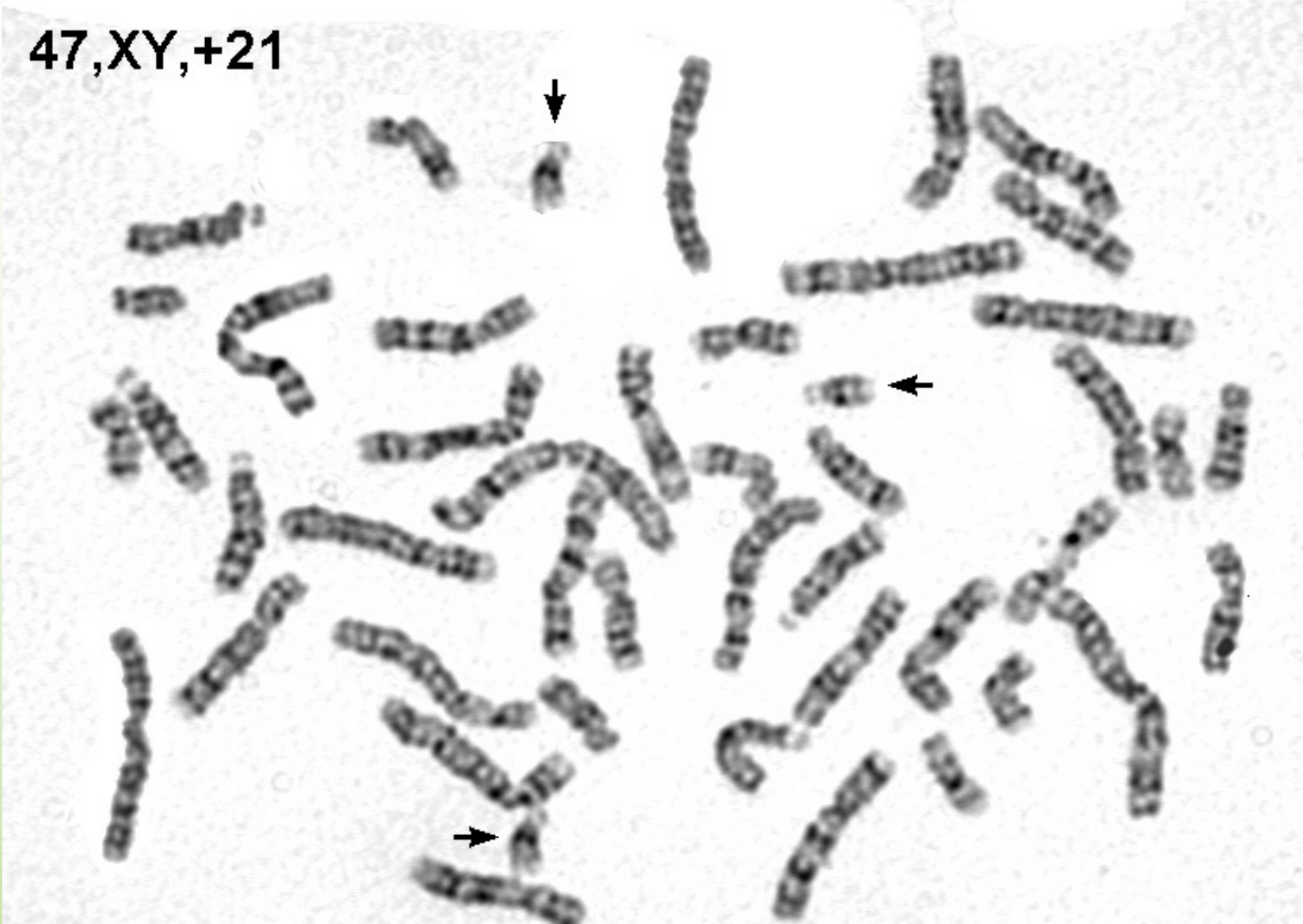
Male sterility

Alzheimer-like symptoms in 40

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, specling of the irides (Brushfield´s spots), small, down set ears, small nose, protruding tongue, simian crease in the hands (about 45%), short statue, mental retardation, congenital heart disease (50%), A-V communis

Down syndrome (G-banding)



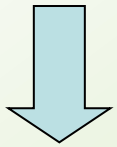
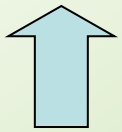
Down syndrom- prenatal diagnosis

- I. trimester screening
- Ultrasound - 10.-12. week of. gest.
- Nuchal translucency more than 2,5-3 mm, absence of nose bone
- PAPP-A, free-beta hCG

- II. trimester screening
- 16. week – AFP, total hCG, uE3

- 20. week – US, congenital heart disease

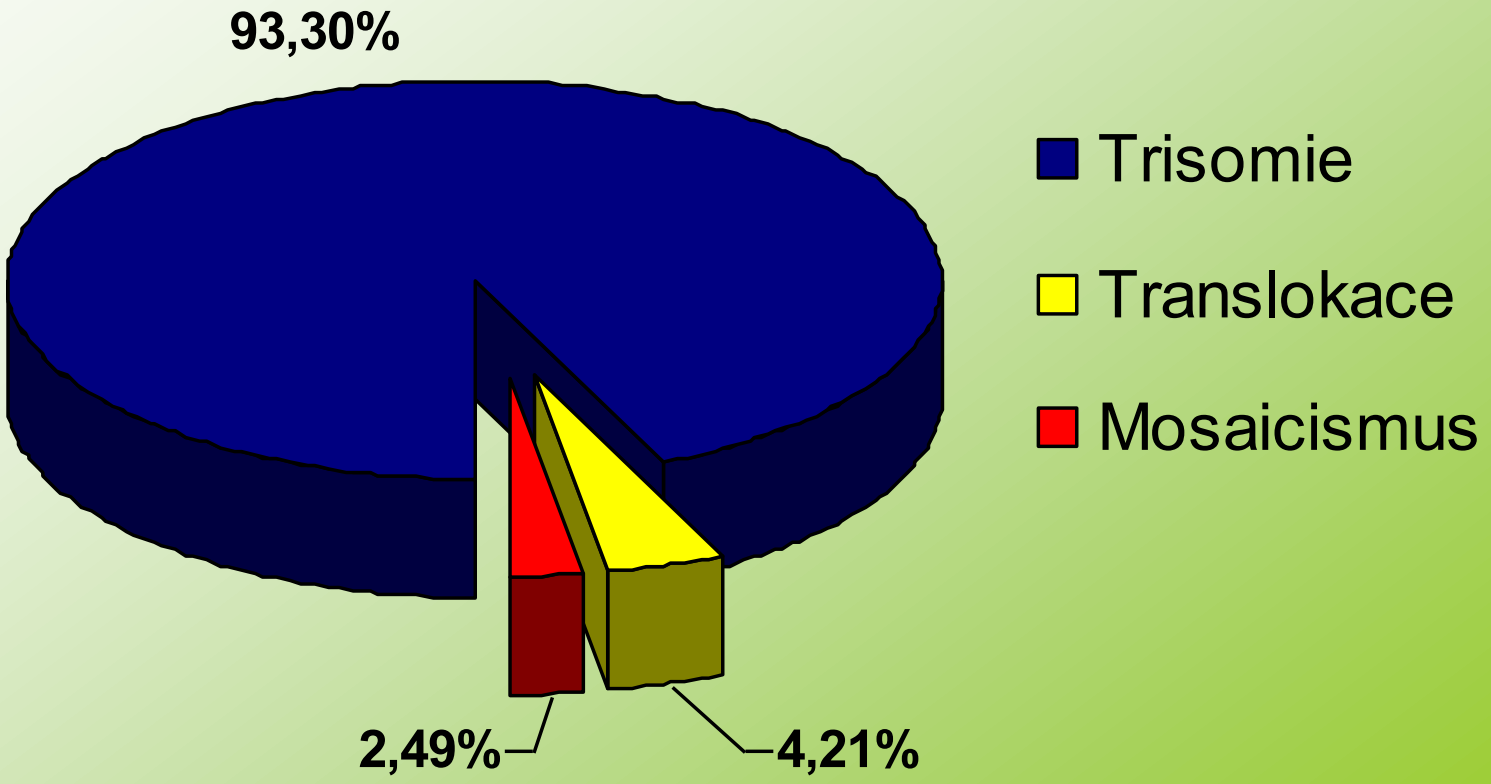
II. Trimester screening

- AFP 
- hCG 
- uE3 

- Risk 1 in 250 – borderline
- Maternal age, week of gestation by US

Cytogenetic findings in DS in Czech republic

1994 - 2001



Edwards syndrome

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

- hypotrophy, atypical hands and 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

Prenatal dg. +18 – II. trimester

- AFP, HCG, uE3 ⇩

- Risk 1/250 - borderline
- Ultrasonography

Patau syndrome

- 47,XX(XY), +13
- 1/5000-10 000 in newborns, 1/90 SA
- 95% SA
- death before 1 year mostly

- cleft lip and palate bilateral, congenital defects (CNS, eyes, postaxial hexadaktily…)

Patauův syndrom + 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 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 syndrom 45,X

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

Klinefelter syndrome

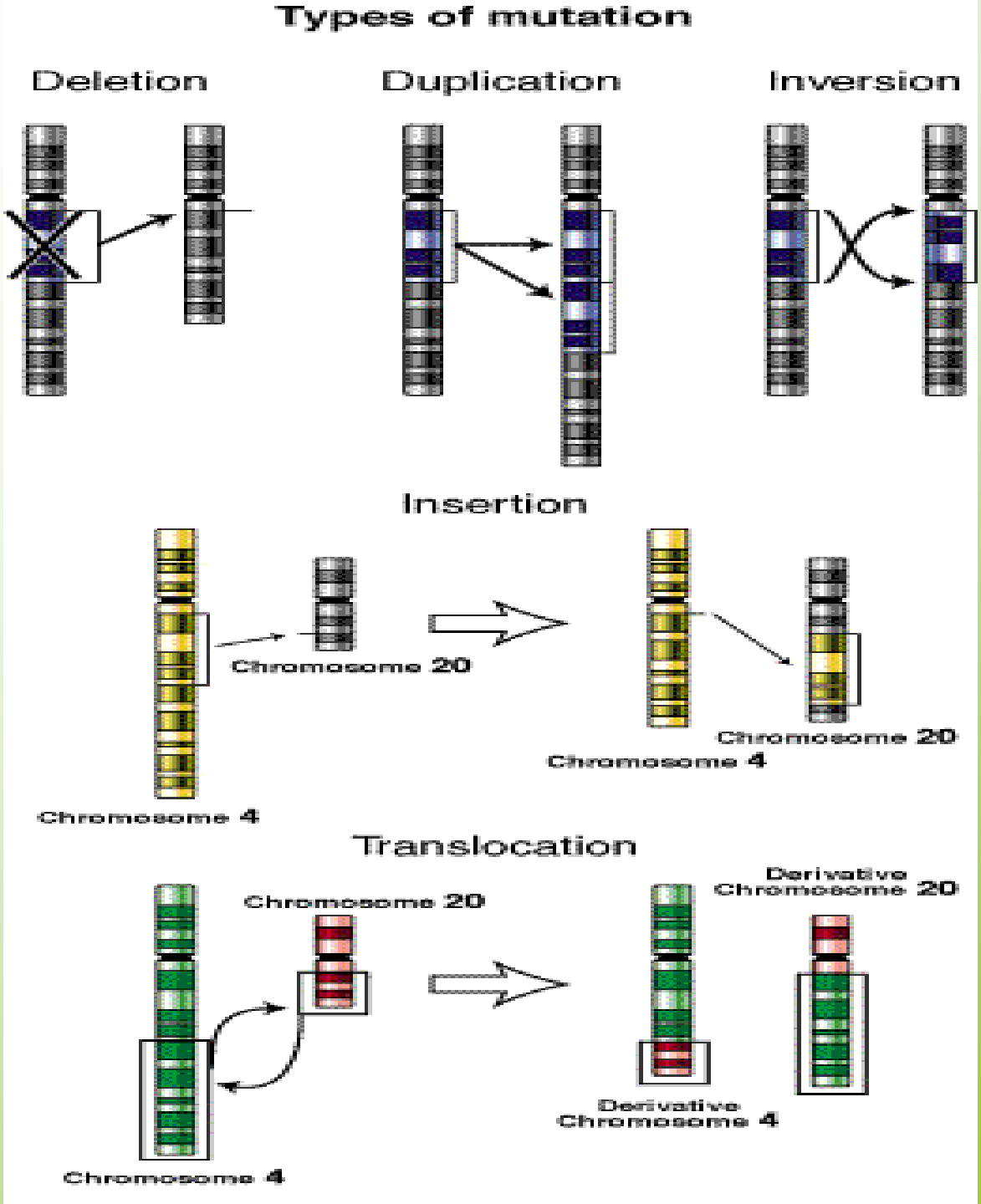
- 47,XXY
- relatively frequent 1/600-1000 liveborn males
- tall stature
- hypogonadism, gynekomastia
- sterility, infertility

Others gonoseme abnormalities

- 47,XXX
- 47,XYY
- 48,XXXX
- 48,XXYY….

Structural chromosomam 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

Syndrom Wolf-Hirshorn 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 ...

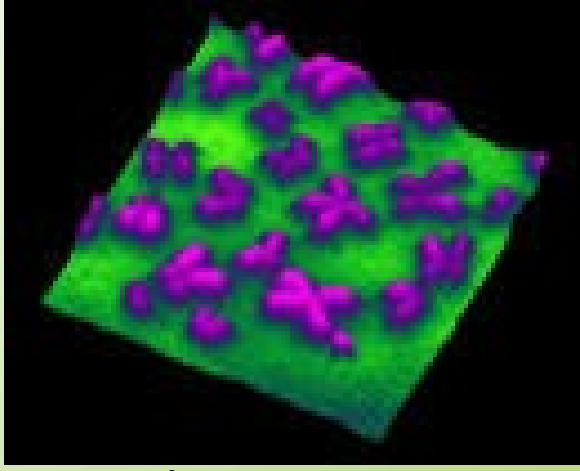
Syndrom Cri du chat 46,XX(XY),5p-

- 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-

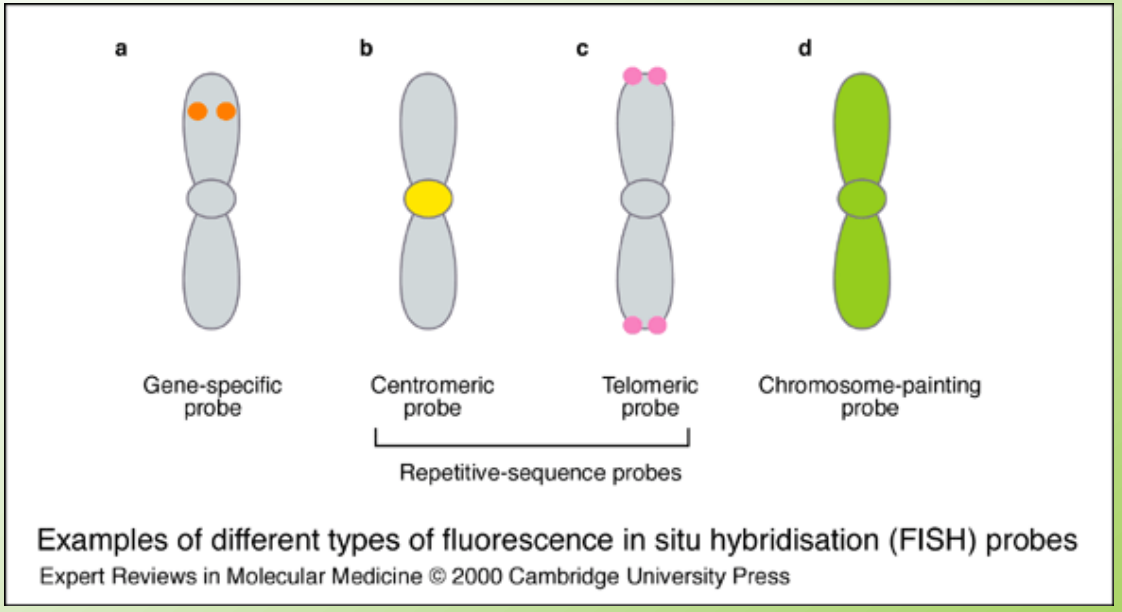
- 1:50 000
- Typicaly cri in newborns
- laryngomalacie
- antimongoloid
- epicanthi
- hypotonie
- hypotrofie

Mikrocytogenetic Molekular cytogenetic



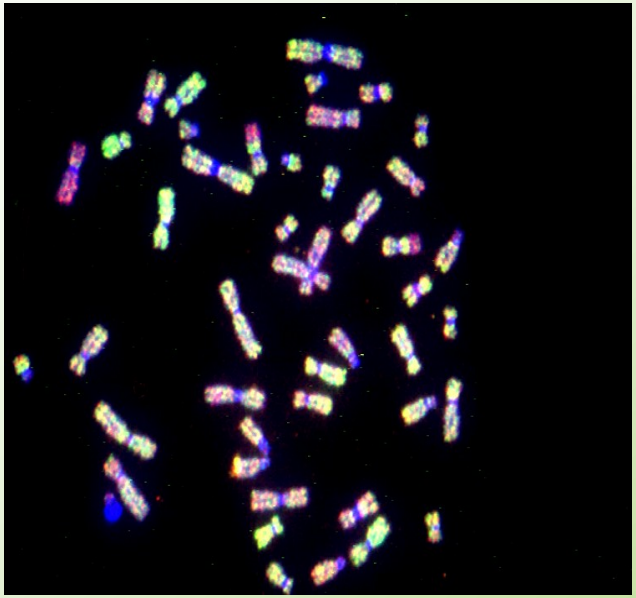
- FISH (fluorescenc in situ hybridisation), M-FISH, SKY (spektral karyoptyping), CGH (komparativ genom hynridization), MLPA
- mikrodeletions or mikroduplications, marker chromosoms, complex reareGemnts, oncology – oncocytogenetics,fast …)
- fast methods (possible forprenatal dg)
- metafase and intesfase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

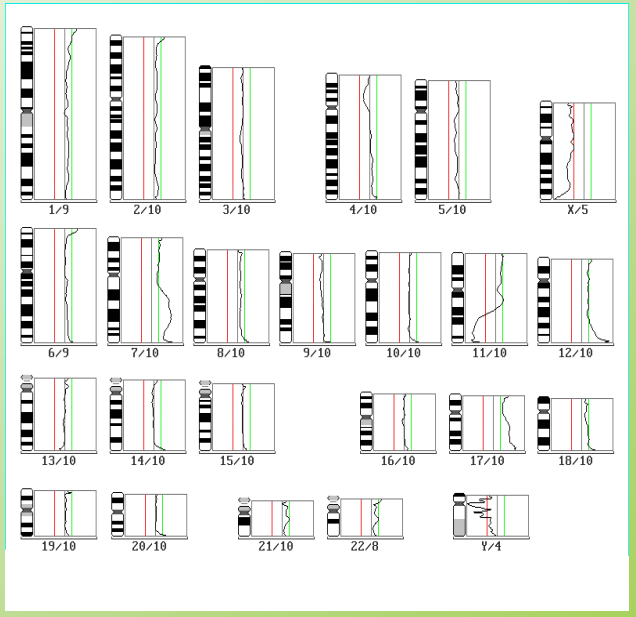
FISH



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

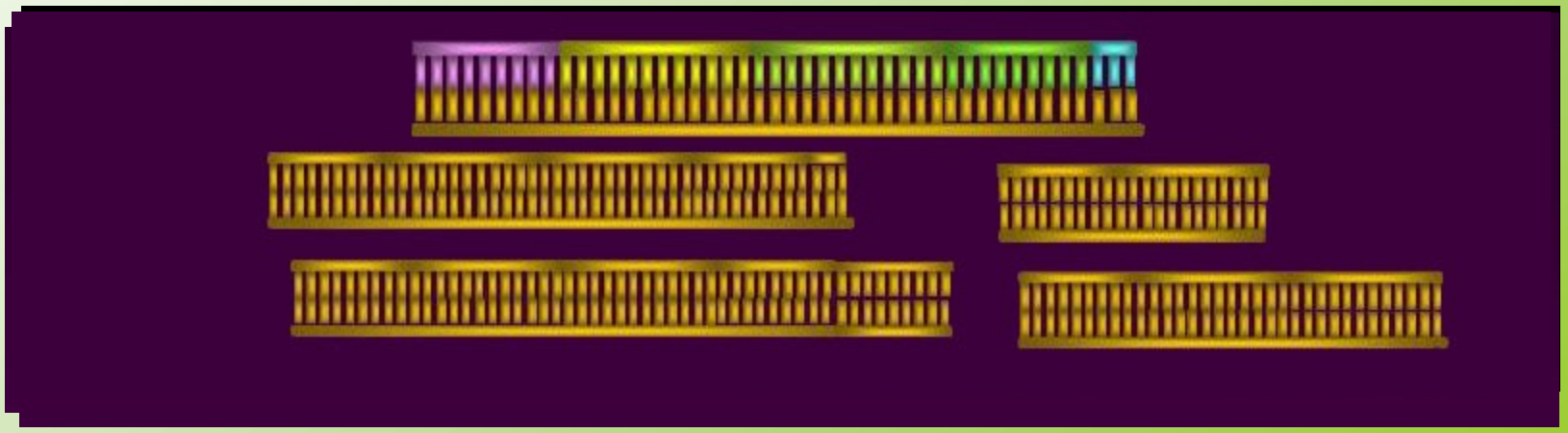
Komparativ genom hybridisation





MLPA

Multiplex Ligation-Dependent Probe Amplification



MRC-Holland
MLPA

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

Williams - Beuren syndrom

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

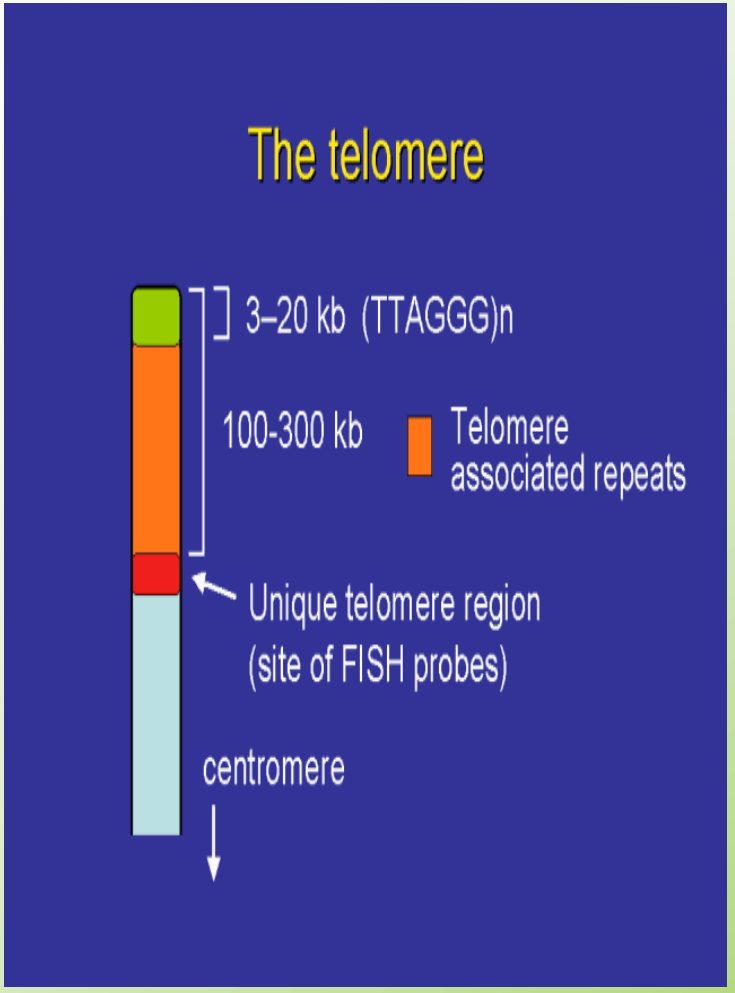
Prader-Willi syndrom

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

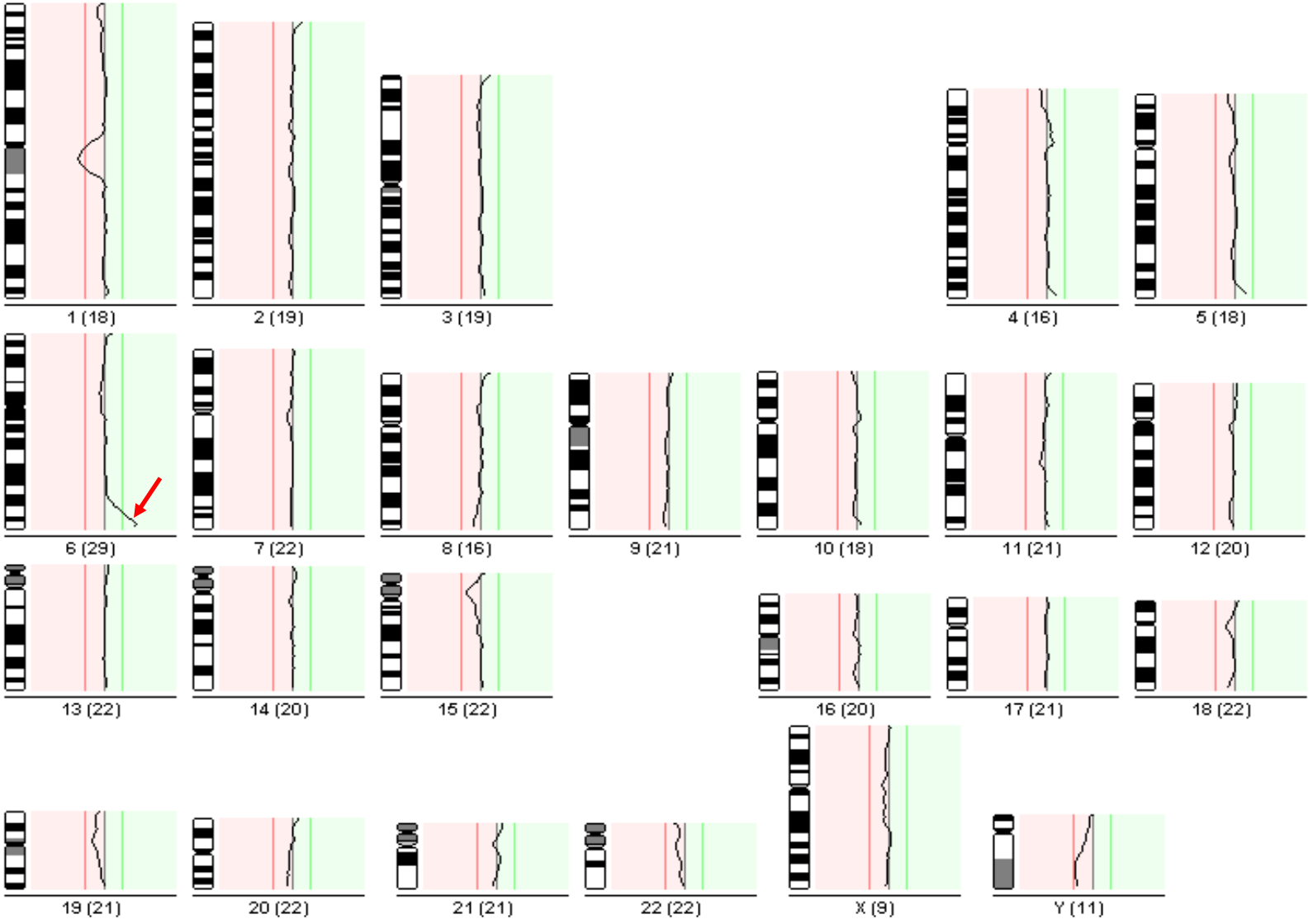
Angelman syndrom

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

The telomere



Rearangement in about 6-8% children with mental retardation with or without congenital defect (FISH, HR-CGH, MLPA)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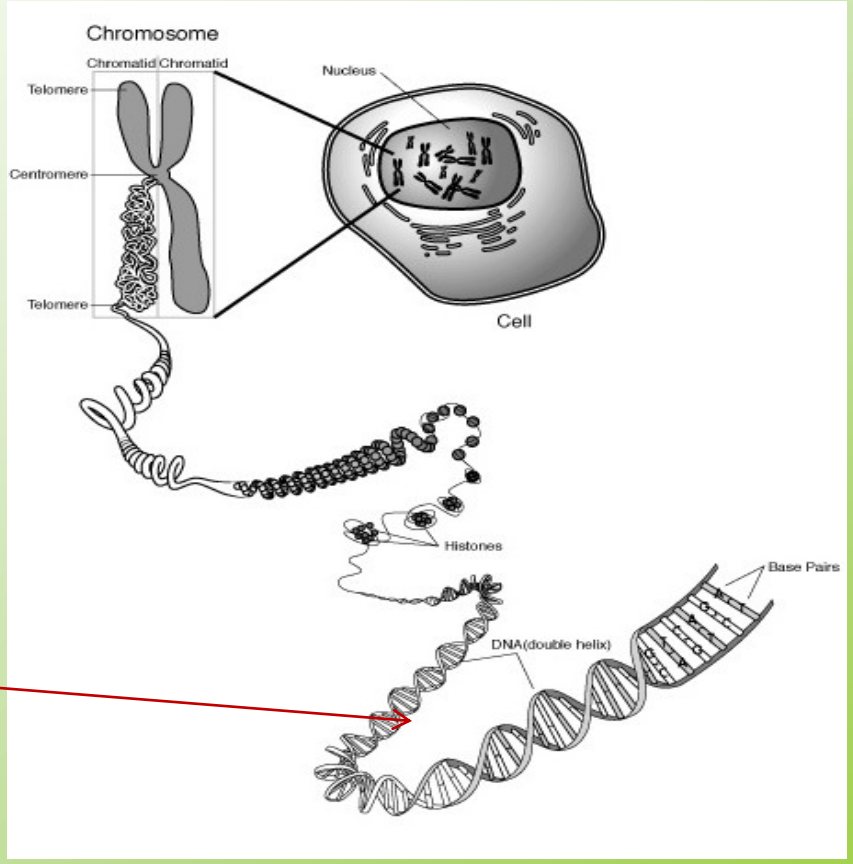
22 (22)
X (9)
Y (11)

Mendelian inheritance

Monogenetic diseases

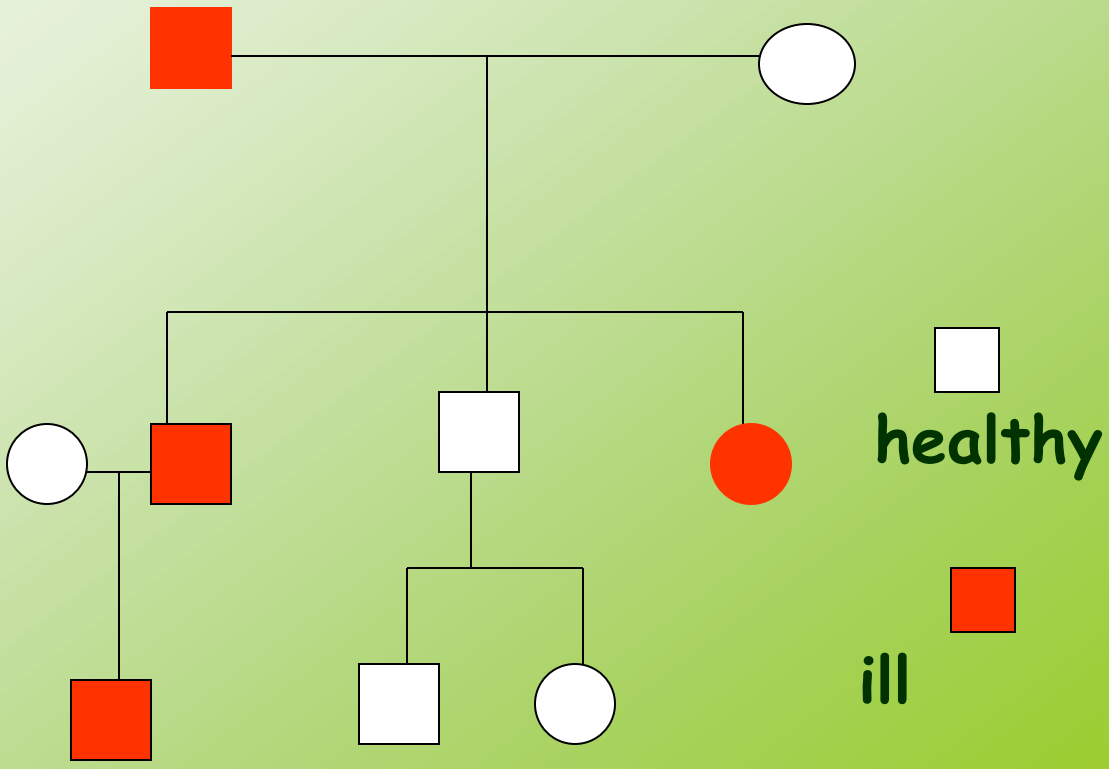


Autosomal Dominant

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

Pedigree AD inheritance

- the risk 50%



AD - diseases

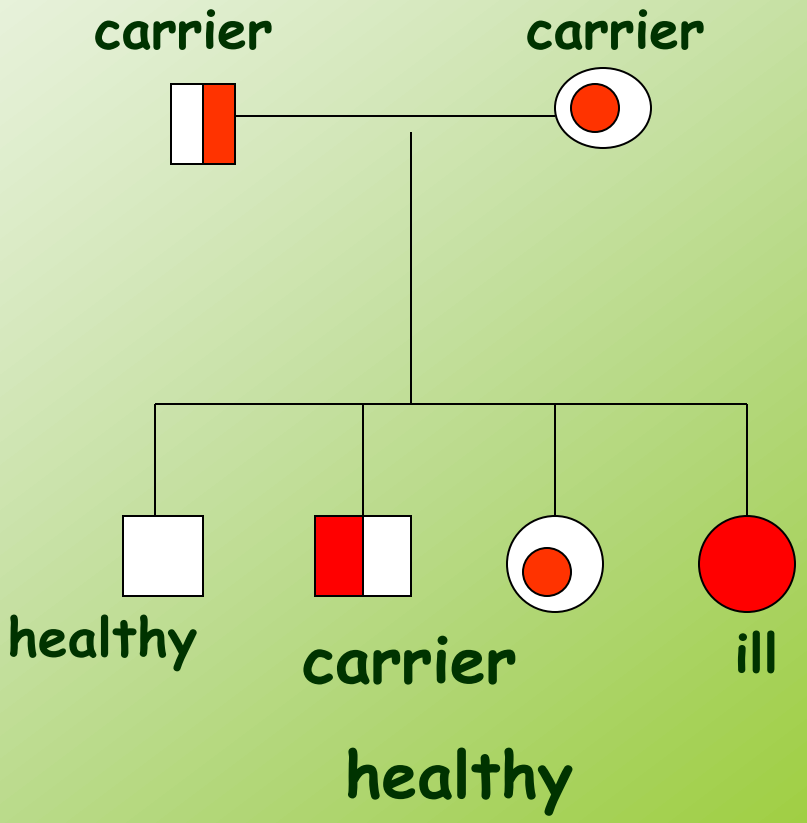
- Neurofibromatosis 1 and 2
- Achondoplasia
- Huntington disease
- Marfan syndrome
- Myotonic dystrophy

Autosomal Recesive

- Heterozygotes are generally unaffected clinicaly
- The sexes are involved equaly
- An individual manifesting a recesive disorder usually has heterozygous parents
- Once a homozygote is identified, the recurence risk for other child of some parents is 25%

Pedegree - AR inheritance

- The risk for next child 25%



AR - diseases

- Cystic fibrosis

(frequency of heterozygotes CR- 1/26)

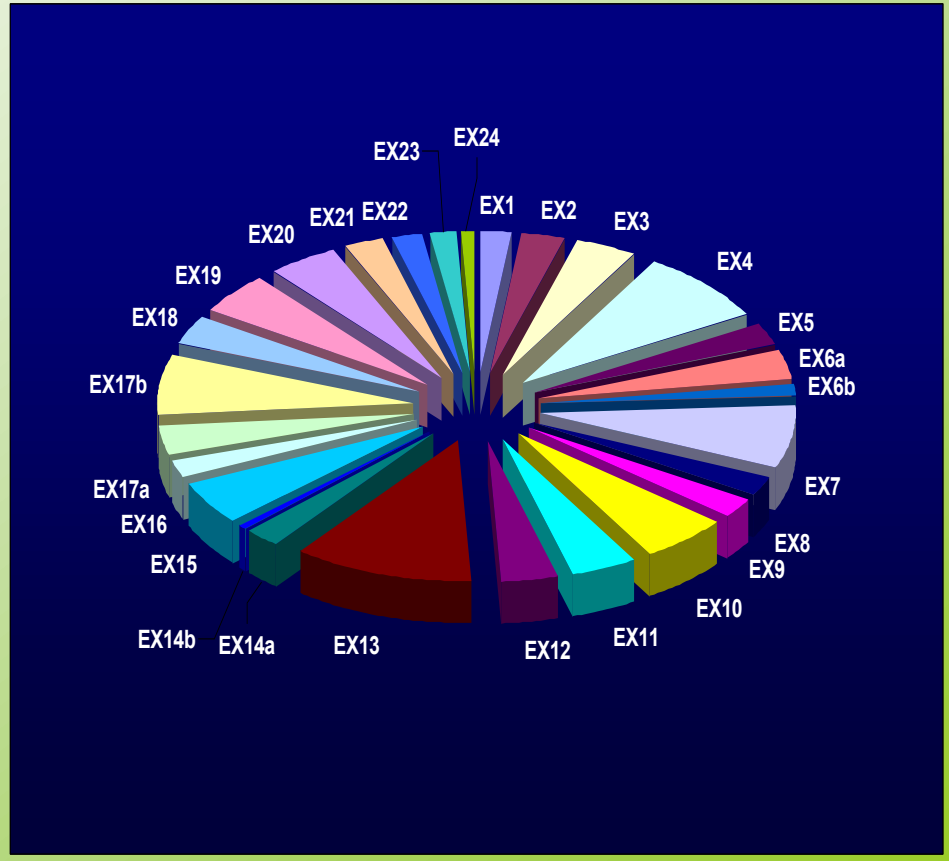
- Phenylketounria (1/40)
- Congenital adrenal hyperplasia (1/40)
- Spinal muscular atrophy (1/60-80)

Cystic fibrosis

- Localized on chromosome 7q
- Frequency of Cystic Fibrosis in the Czech Republic: about 1/2000 – 1/3000
- Frequency of heterozygots in the Czech Republic about 1/25-1/29
- About 1600 mutations in CFTR gene were identified

The reason for CFTR gene analysis

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



CFTR gene - distrubitions od mutations

Most frequent CFTR mutations in Czech population

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

X-linked Recesive

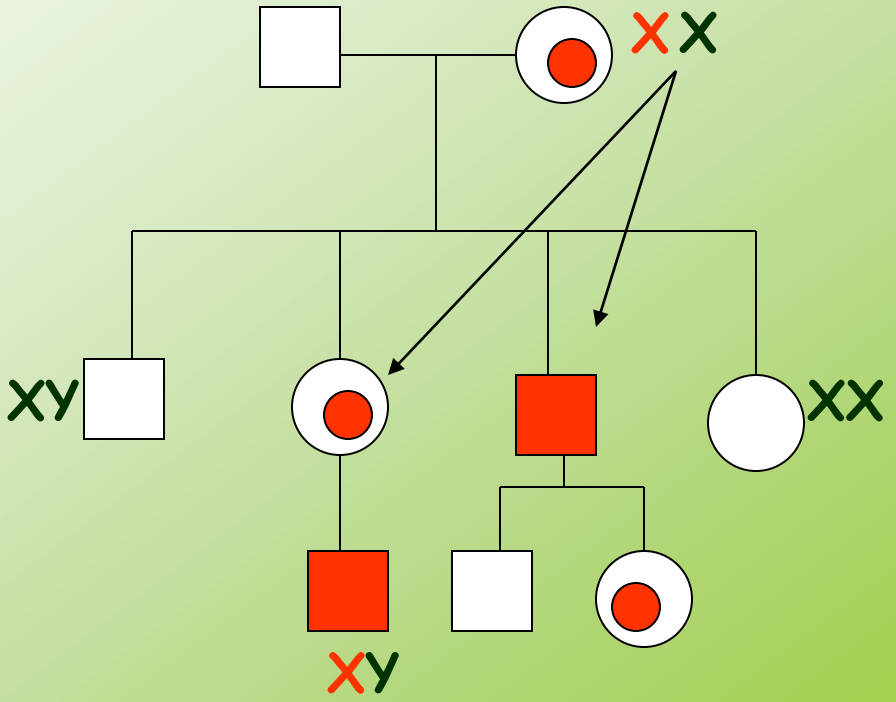
- Females are not affected as severaly as males or are not affected
- An affected male cannot transmit the train to his sons, becose the trait is on X-chromosome, and the father must necessarily transmit his Y-chromosome to a son
- All of the daughters of an affected male must be carriers, because the only X-chromosome that the father can give to a daughter contains the mutation

X-linked Recesive

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

- Risk for sons of carrier - mother
- 50% for diseas

X- recesive inheritance



XR - diseases

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

Multifaktorial –polygenic inheritance
Dieseases with complex heritability

Teratogens

Charakterization

- disease with multifactorial inheritance include not mendelian types of inheritance

- diseases exhibit familial aggregation, because the relatives of affected individuals more likely than unrelated people to carry diseases predisposing predisposition

Charakterization

- in the pathogenesis of the disease play a basic role non-genetic factors

- disease is more common among close relatives and in distant relatives is becoming less frequent

Examples

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

Common congenital defects

Congenital heart diseases

- 0,5 - 1% in liveborn infantsn - population incidence
- etiology not known mostly
- about 3% + chromosomal syndromes (+21,+13,+18, 45,X, 18q-, 4p-, del 22q11 Di George sy)
- some mendelian syndromes associated with congenital heart disease (Holt-Oram, Williams, Noonan, Ivemark...

Congenital heart diseases prenatal diagnosis

- For most serious congenital heart diseases
- Ultrasonography in 21. week of gestation - by specialists for prenatal kardiology

Congenital heart disease - genetic risks

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

Congenital heart disease genetic risks

	Risk in %
More than two affected first-degree relatives	50
Sib of isolated case	2-3
Second-degree relatives	1–2
Offspring-affected father	2-3
Offspring—affected mother	5
Two affected sibs	10

Cleft lip and palate

- Population incidence CL 1/500-1/1000
- Multifactorial mostly
- With chromosomal trisomies (+13,+18)
- Syndromes associated with CL/CP/CLP
- (van der Woude sy, EEC sy, Pierre Robin sequence…)
- Prenatal diagnosis by ultrasonography not sure

Cleft lip and palate- genetic risks

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

Neural tube defects

- Multifactorial inheritance (risk for I. degree relatives about 2 - 4%)
- Maternal serum AFP screening
- Prenatal diagnosis by ultrasonography
- Raised AFP levels in amniotic fluid
- Primary prevention in pregnancies by folic acid
- Risk populations - probably related to nutritional status

Teratogens

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

  action may be direct or through the maternal organism

Human Teratogens

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

The effect of teratogens depends on :

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

Critical period

- 14.-18. days after conception – the rule „all od nothing "

- 18.-90. day – organogenesis
- The most sensitive period for the emergence of developmental defects

Drugs

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

A

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

  product appears to be safe

B

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

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

C

- Animal studies confirm the teratogenic embryotoxic or other adverse effects on the fetus,
- non-controlled studies in women

- lack of studies in animals and humans

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

D

- risk to the human fetus is known

- medicine may be administered in a situation where its use for a woman needed (lifesaving)
- no other safer drug is available

X

- studies in animals and in humans clearly demonstrate a teratogenic effect

- drugs absolutely contraindicated in pregnancy

Drugs with teratogenic effect

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

Drugs with teratogenic effect

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

Thalaidomid

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

Hydantoin

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

Aminopterin a Methotrexat

- **folic acid antagonist**
  facial dysmorfism, cleft lip and/or palate, small mandible, malá dolní čelist, ears anomalies, hydrocephalus, growth and mental retardation, miscarriage

Warfarin

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

Retinoids

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

Infection

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

- TORCH

Toxoplasmosis

- chorioretinitis
- hydrocephalus or mikrocephaly
- intracranial calcification, mental retardation
- icterus, hepatosplenomegalia, carditis
- prematurity

- positiv IgM in the mother – treatment with Rovamycin
- Prenatal dg.: serology, DNA-PCR)

Rubella

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

- prevention- vaccination

Cytomegalovirus

- Intrauterin growth retardation
- mikrocephaly, cacification in the brain, mental retardation,
- hepatosplenomegaly

- Repeated maternal infection is possible
- Prenatal dg.: serology,DNA-PCR

Varicella zoster

- Skin lesions and defects
- Brain domage, mental retardation
- Eye defects

- Prenatal dg. - serology, DNA-PCR

Metabolic dysbalance

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

Fetal alcohol syndrom

- Hypotrophy, growth retardation, mental retardation
- facial dysmorphism
- Congenital heart defects
- Limb defekts

- Abuse of 60g pure alcohol / day (longterm)
- Combine with malnutrition, folic acid deficit...

Maternal Phenylketonuria

- Low birth weith
- nízká porodní váha, hypertonus
- mikrocefalie, PMR
- VCC
- hyperaktivita

- novorozenecký screening
- (frekvence 1/10 000 novorozenců, dědičnost AR)
- Léčbu je třeba zahájit do 3 týdnů, jinak PMR

Hypothyreosa matky

- hrubé rysy obličeje, makroglosie, vpáčený nos
- brachycefalie
- suchá kůže, spavost, zácpa
- opožděné kostní zrání

- neléčená - malý vzrůst, oligofrenie, postižení sluchu, narušení kyčlí (kachní chůze)
- novorozenecký screening
- hyperthyreosa – spíše riziko SA

Prenatal diagnosis

- **Non invasive - screening**
- **Invasive - CVS, AMC, kordocentesis**

Prenatal screening (ČR)

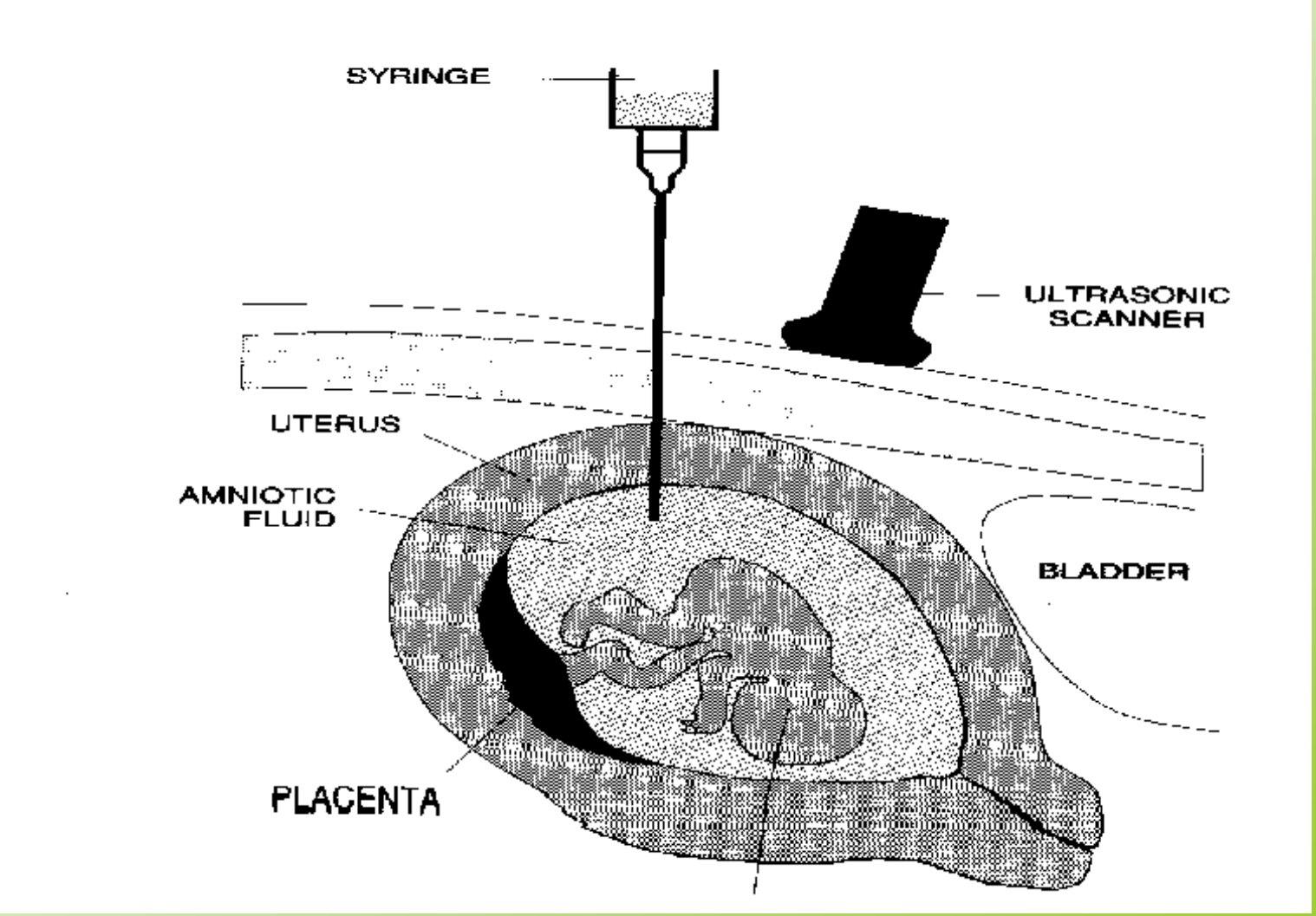
- Ultrasound (12. - 2 0. - 33. week)
- Ultrasound 20.week – cong. defect
- Ultrasound 20-22. week – cong. heart defect

- Free beta hCG and PAPP-A -10-14. week
- AFP, hCG, uE3 - 16.week

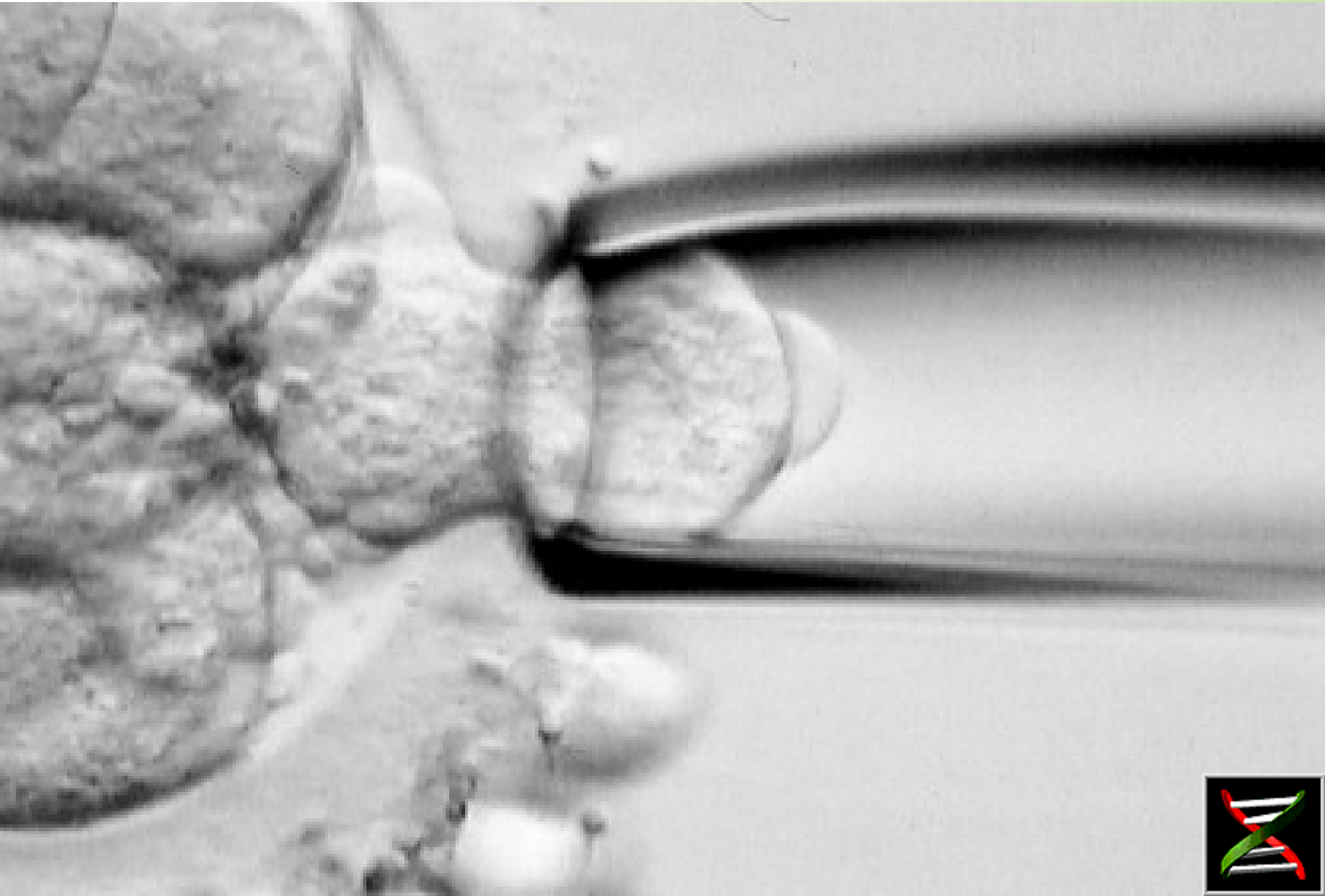
Indications for prenatal diagnosis / counselling

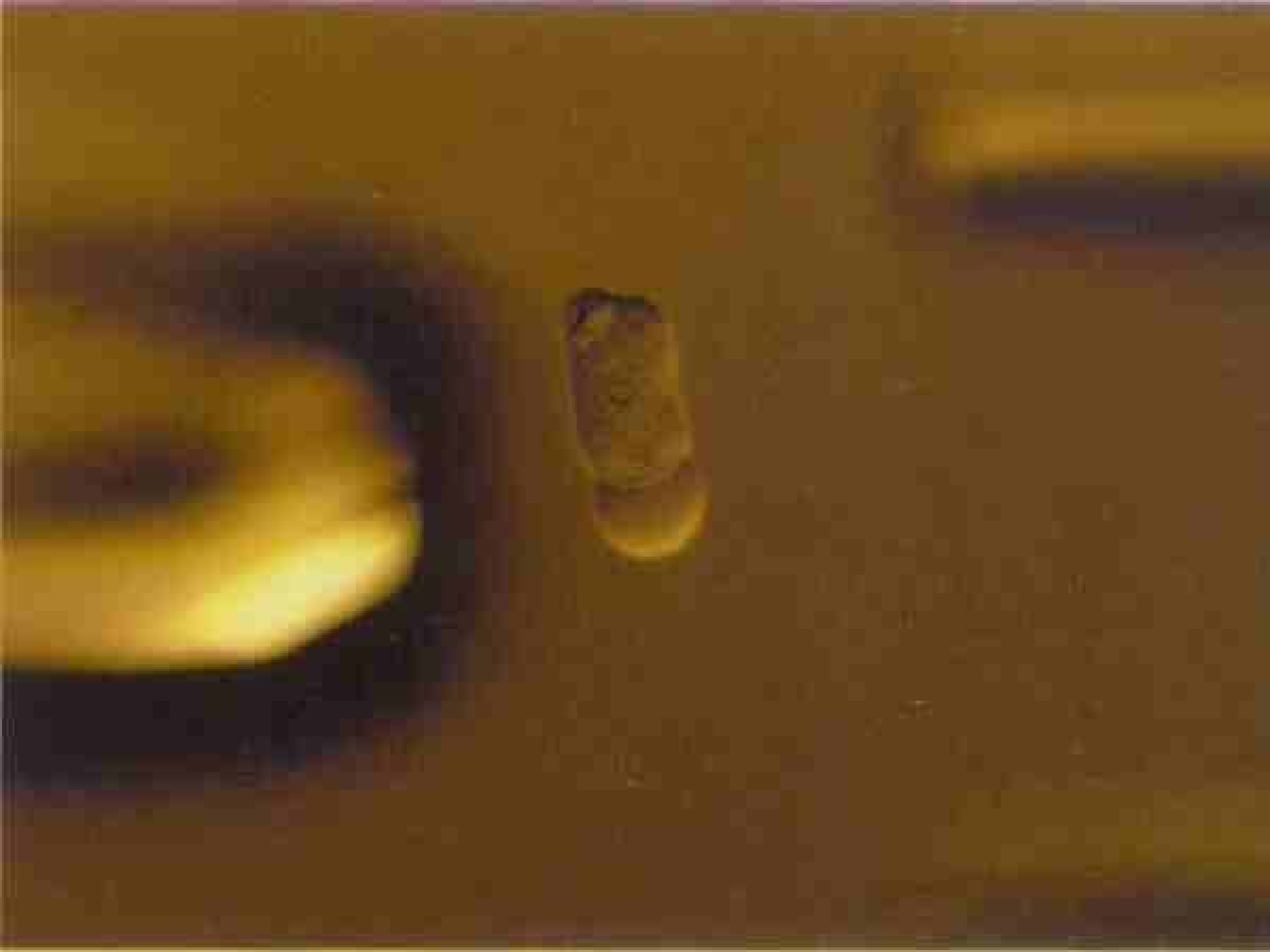
- Advanced maternal age (35)
- Risk factors for neural tube defects (US)
- Family history of known conditions for which diagnosis is possible (DNA)
- Known chromosomal abnormality (de novo finding in previous child, structural change in parents)
- Positive prenatal screening for chromosomal abnormalities

Amniocentesis



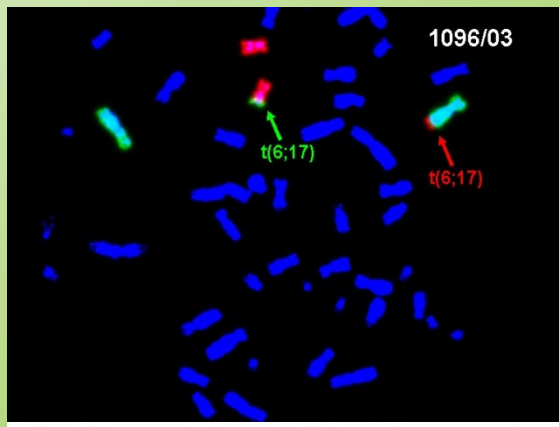
PGD



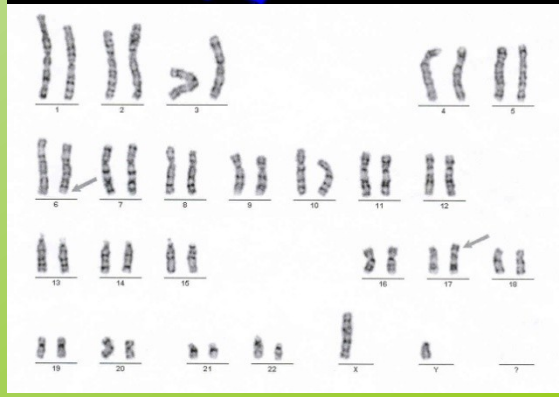


PG Diagnostic
X
PG Screening

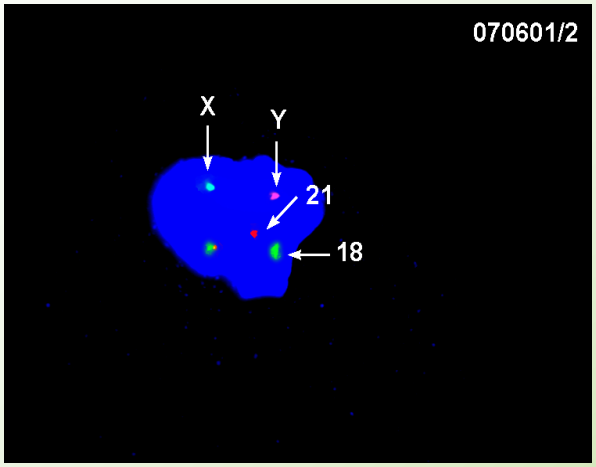
- PGD high genetic risk

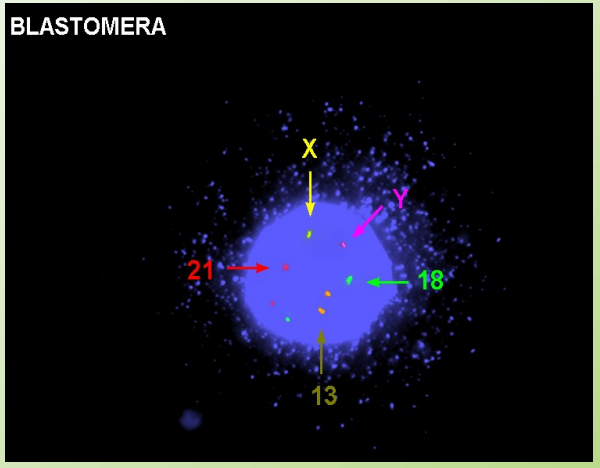


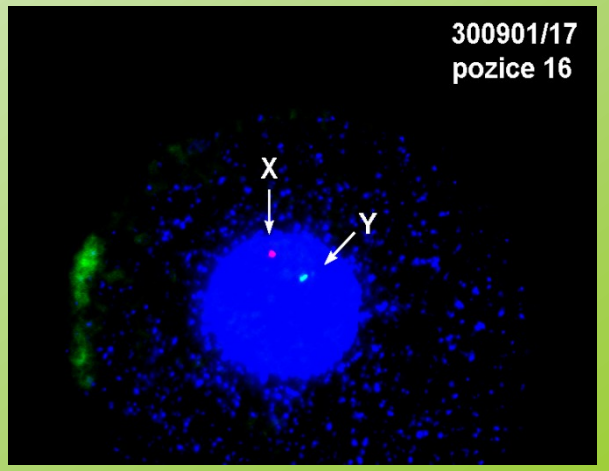
- PGS frequent aneuploidie

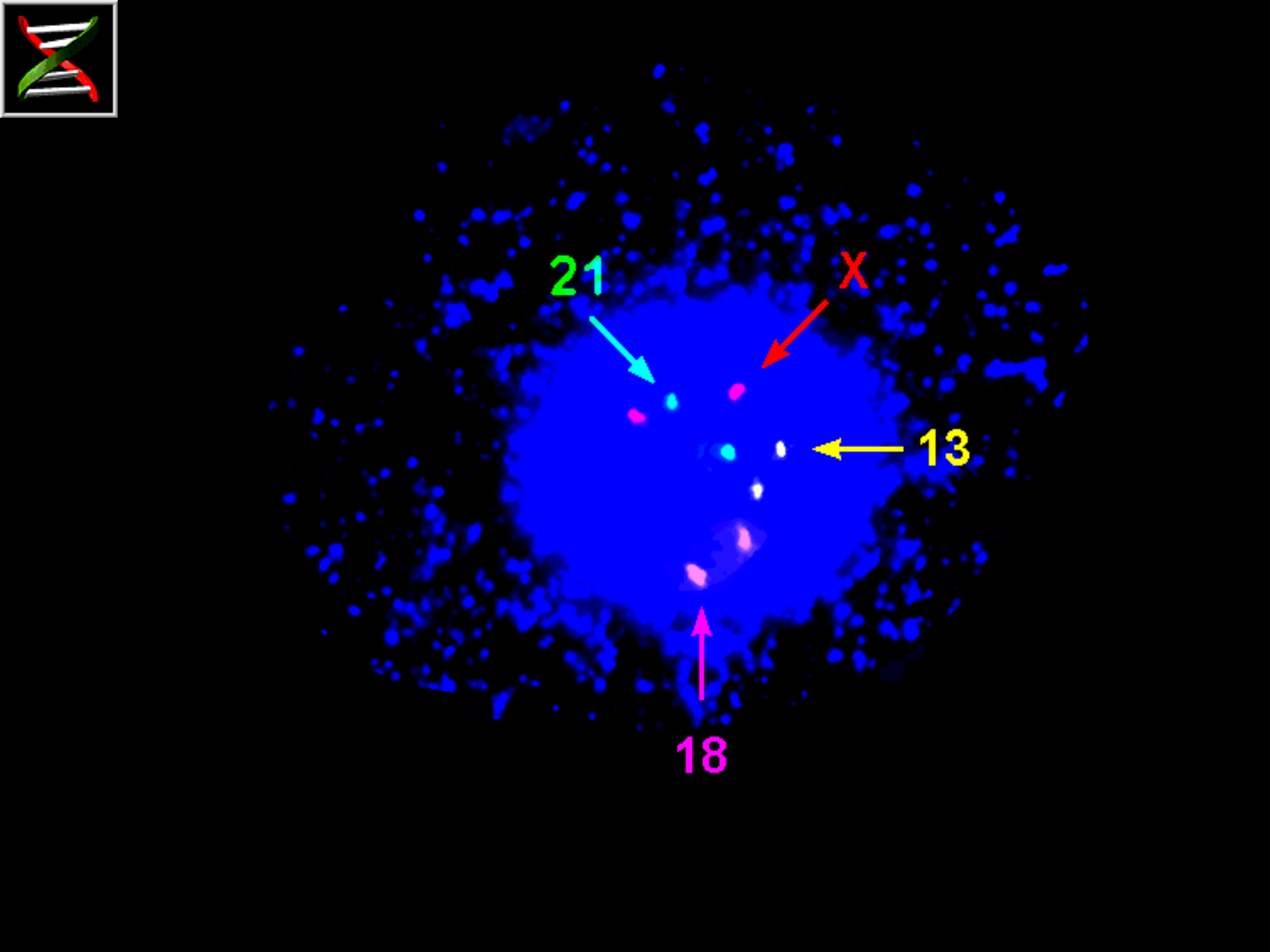


PGD aneuploidy- FISH








21
X
13
18

Genetic counselling in infertility

Infertility

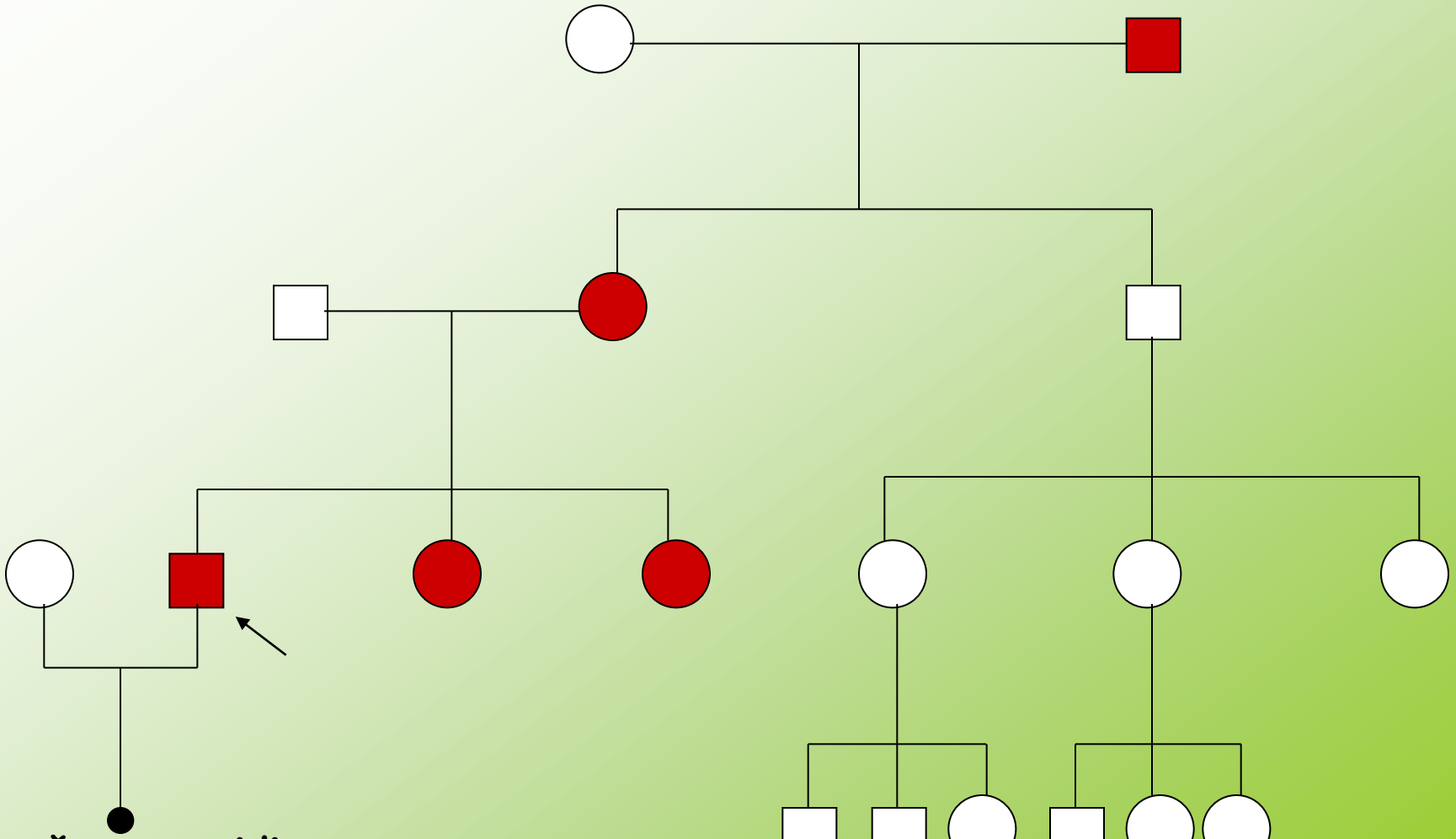
- **Is the infertility one aspect of a genetic disorder that might be transmitted?**

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

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 ti affect the genetic risks.

Potvrzena balancovaná translokace 46,XY,t(2;7)

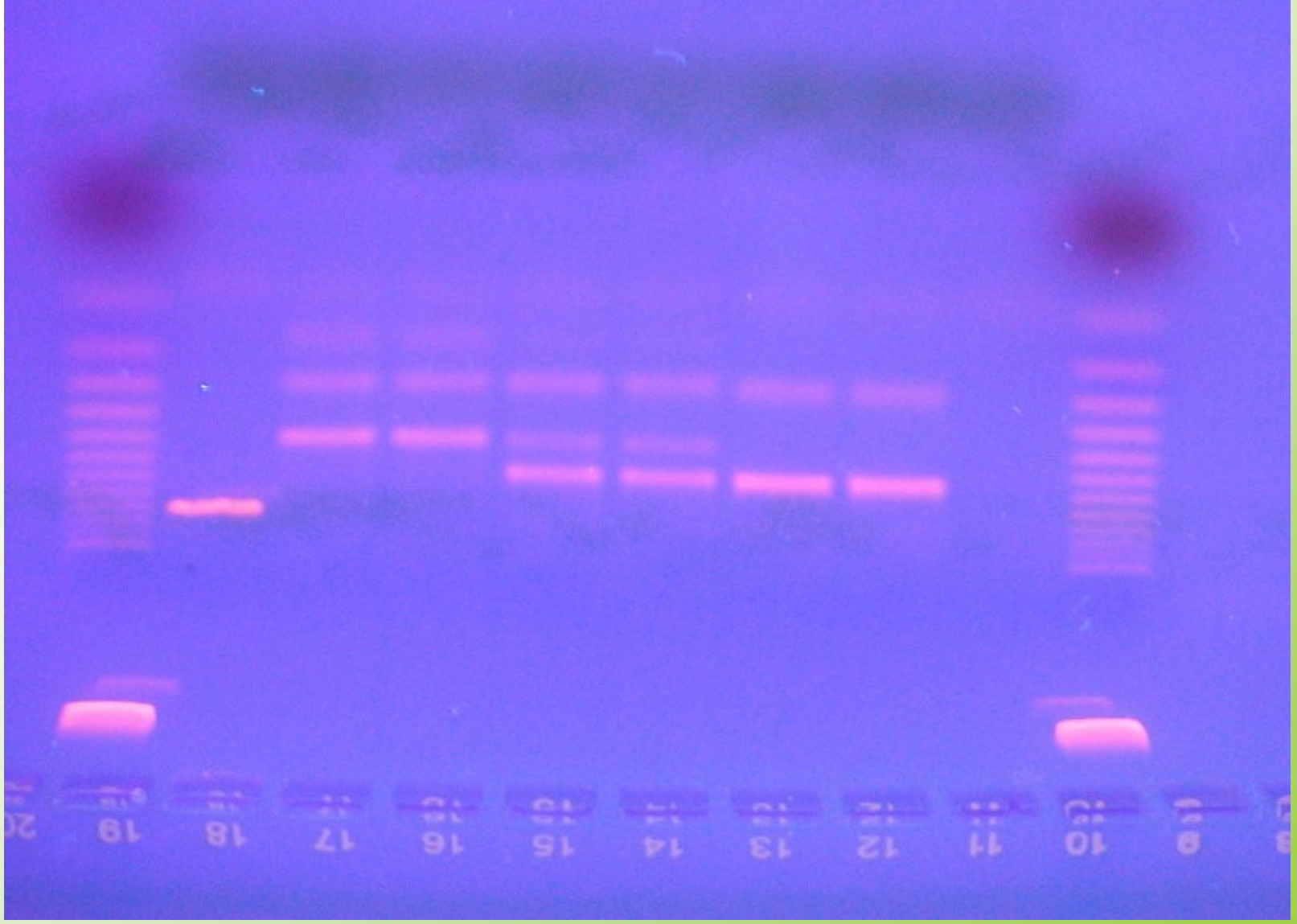


Ukončena gravidita,

VVV a VCA u plodu

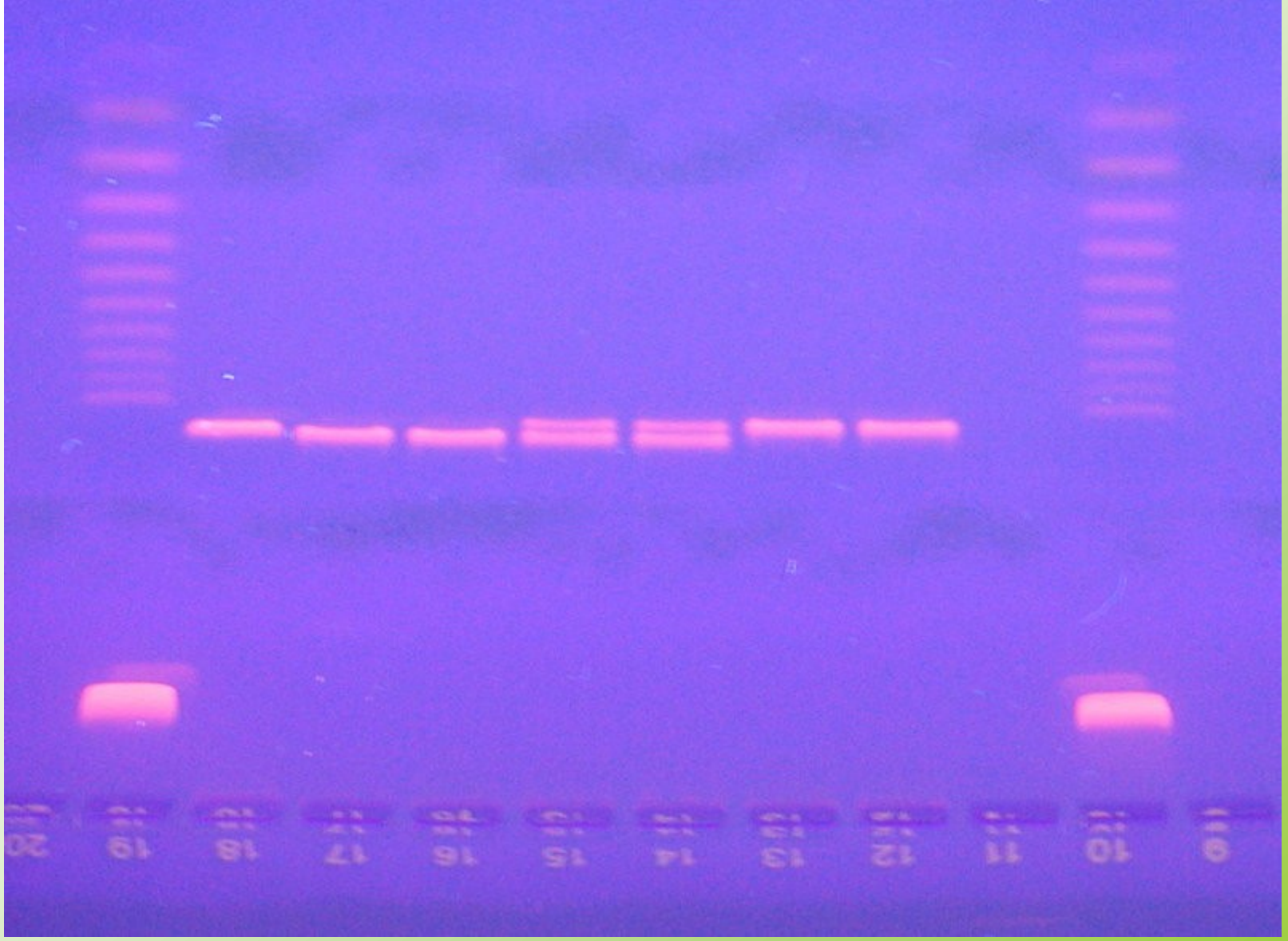
Infertility

- 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)



Detekce Leidenské mutace G1691A v genu pro faktor II:

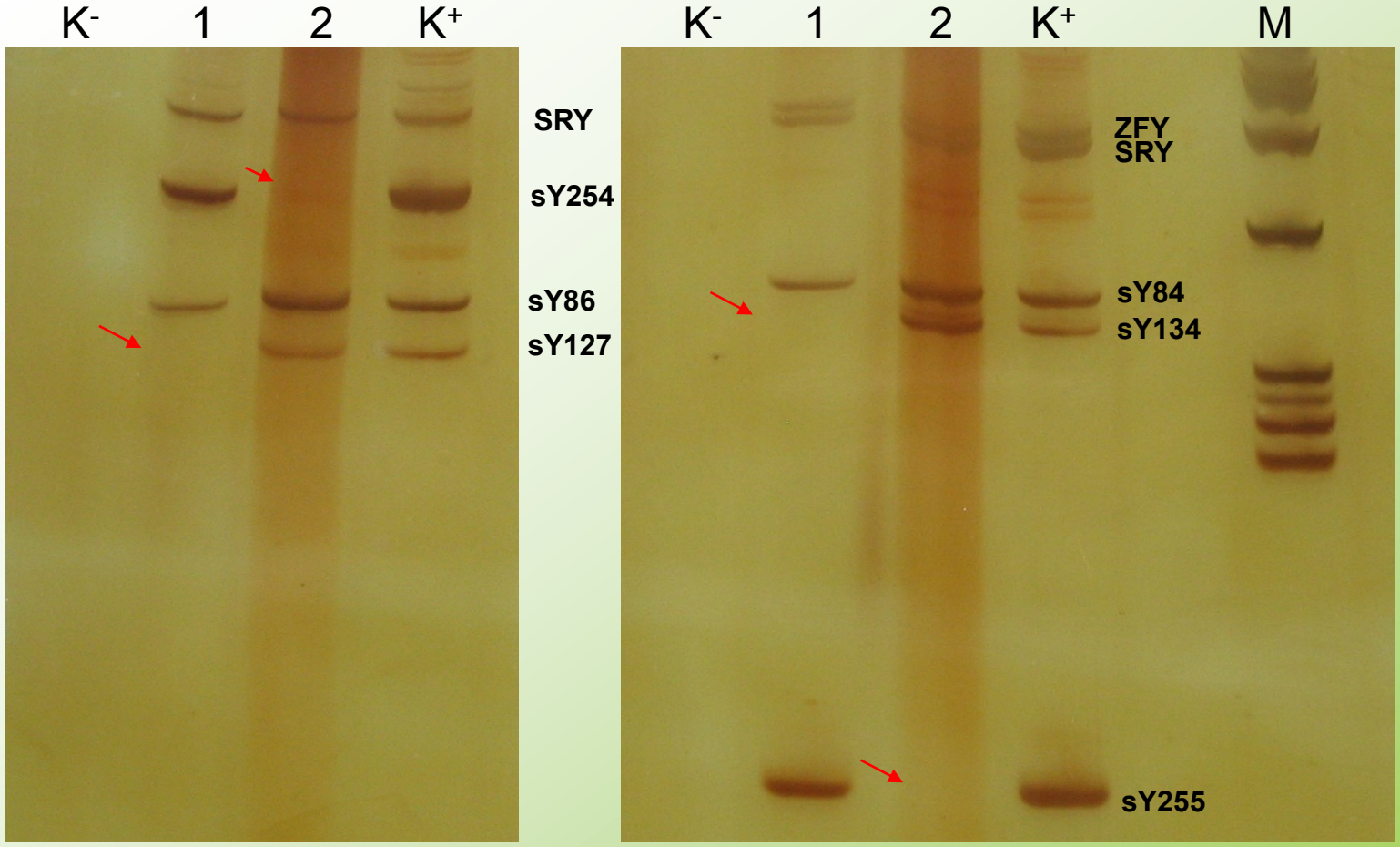
Fotografie zleva: marker, neštěpený produkt, 2x negativní, 2x heterozygot, 2x pozitivní - homozygot, neg. kontrola, marker



Detekce mutace G20210A v genu pro faktor II (Prothrombin): Zleva: marker, neštěpený produkt, 2x zdravý homozygot (wild), 2x heterozygot, 2x positivní - homozygot, neg. kontrola.

Sterility in male

- **AZF deletions (DAZ gene) Yq**
- **CFTR mutations and polymorphisms**



1, 2 - pacienti

K^+, K^- - pozitivní a negativní kontrola

M - marker

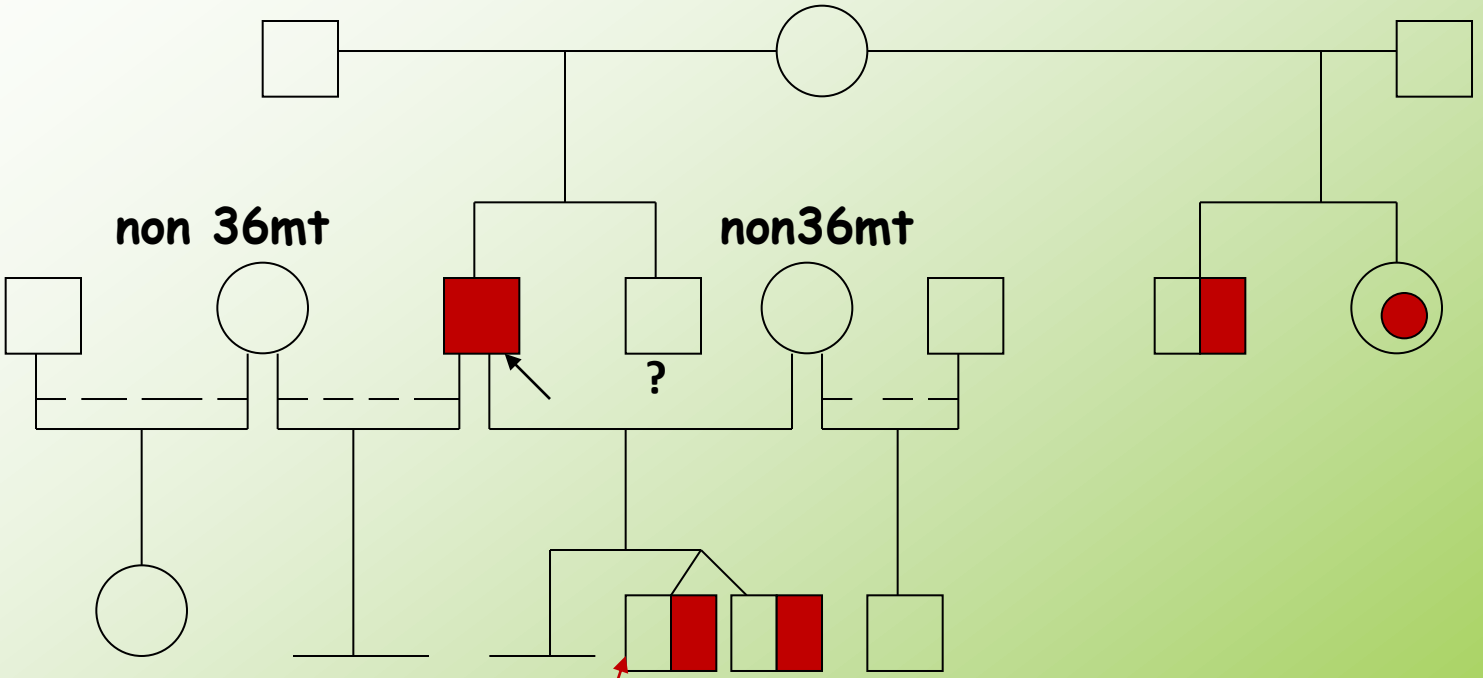
AZFa: sY84, sY86,

AZFb: sY127, sY134

AZFc: sY254, sY255

pacient	1	2
delece	AZFb	AZFc

Susp. CF, azoospermie



Gravidita po IVF/ICSI/MESA, prenatálně

(AMC) 46,XY,46,XY,

CFTR gen - F508del/non

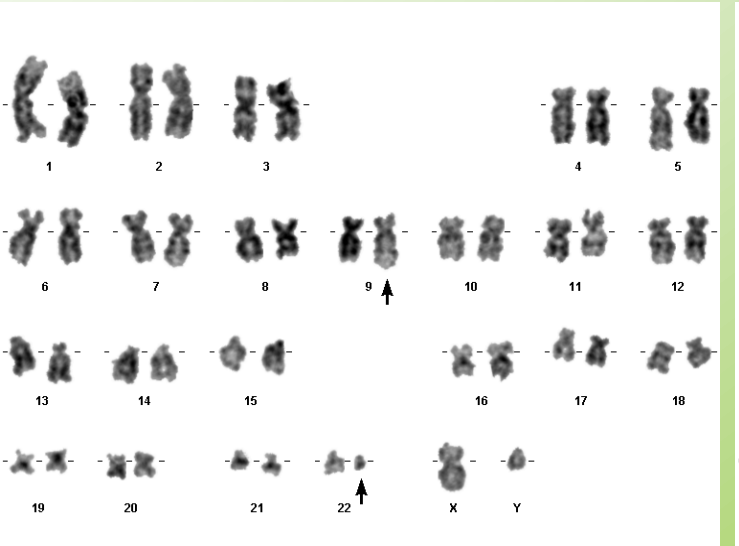
F508del/F508del

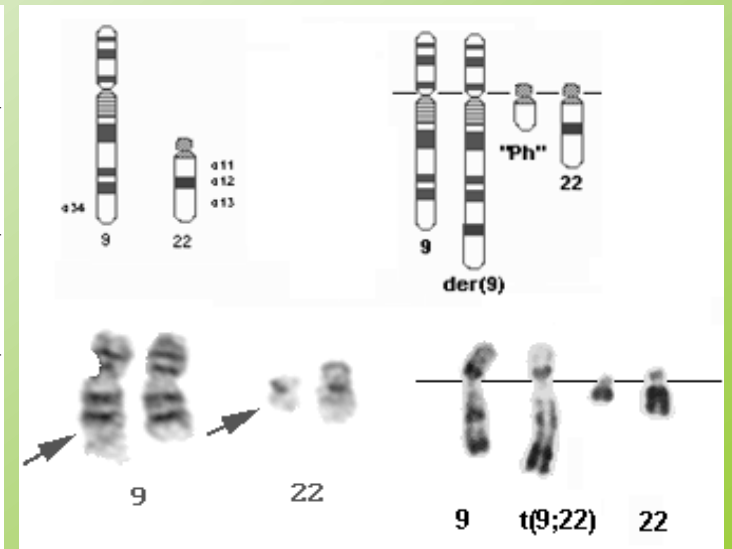
F508del/non

Genetic risk in cancer

Genetic testing in the tumours

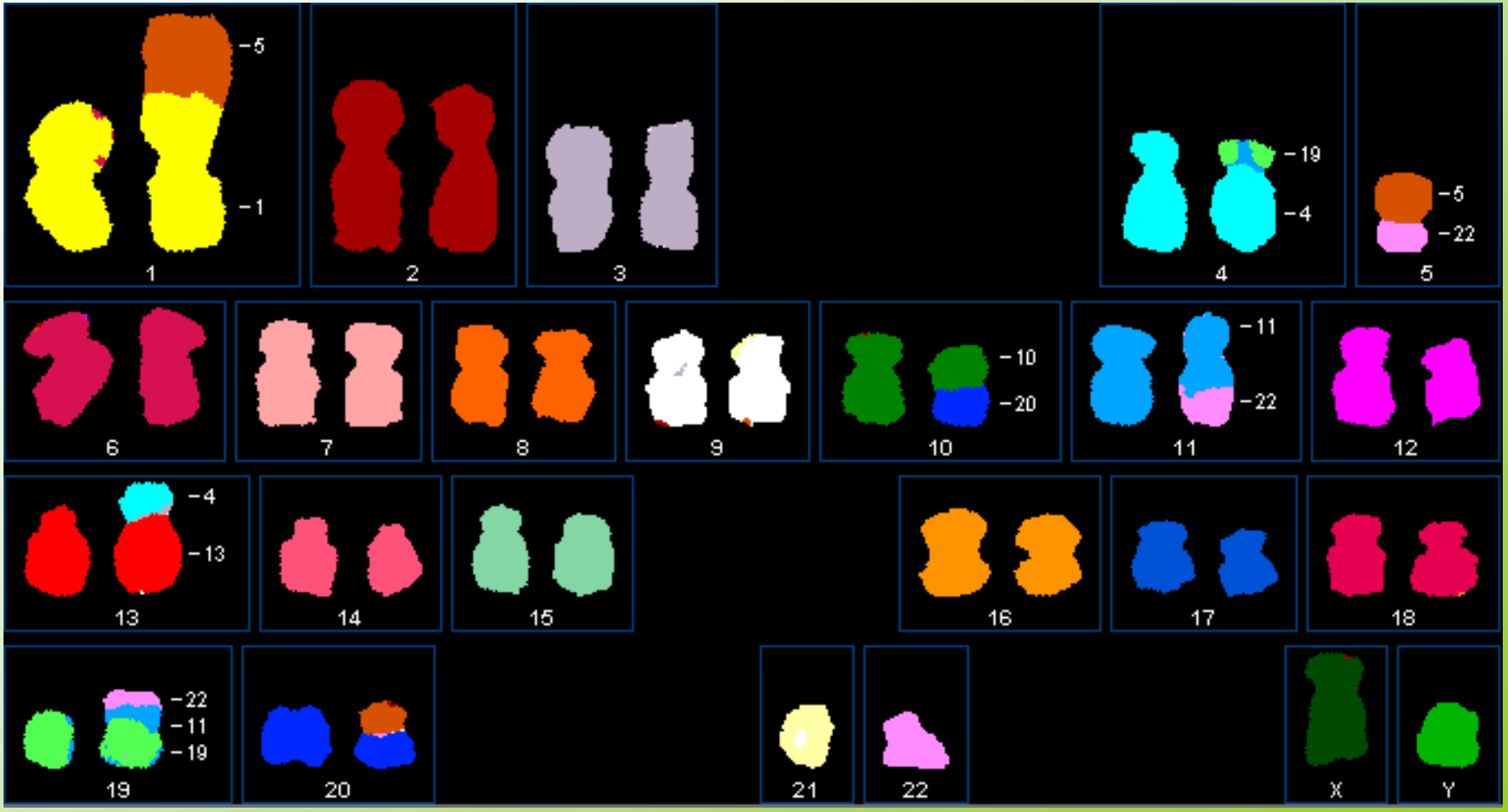
- Diagnosis
- Therapy
- Prognosis
- Minimal residual disease





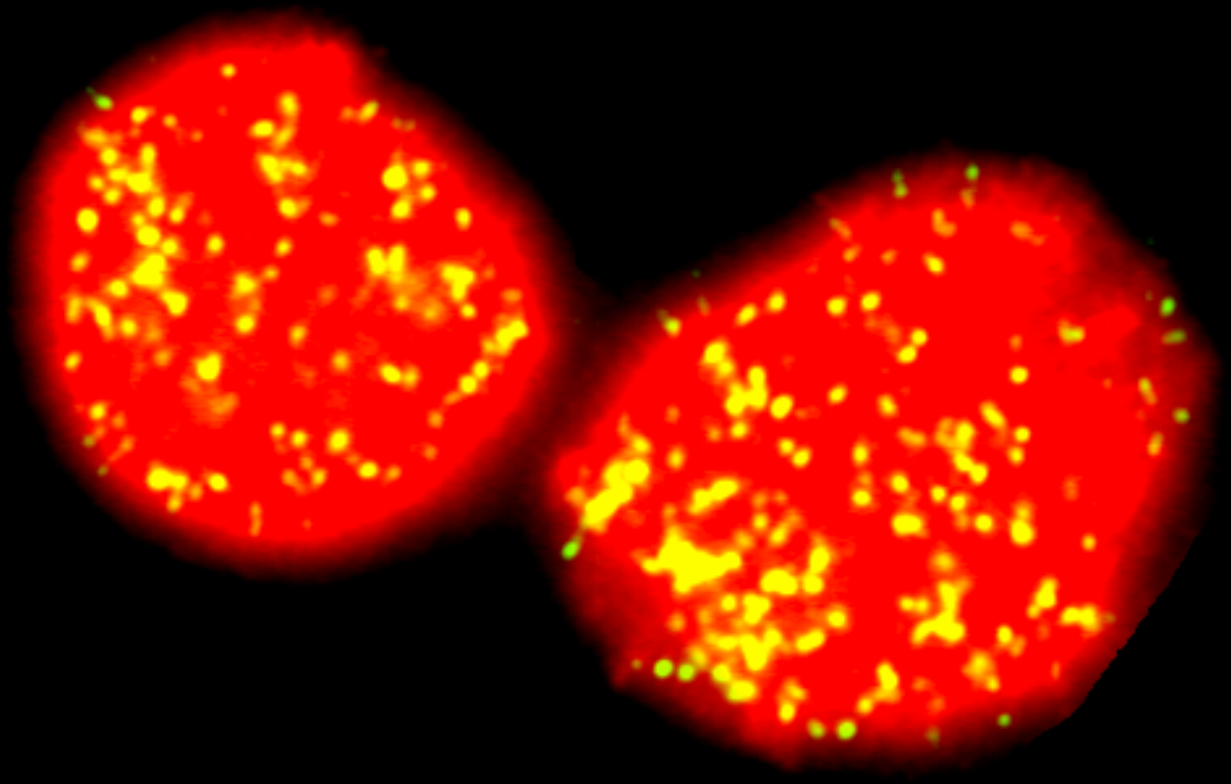
SKY: t(2;13), t(4;8), t(6;16), t(8;11)

a patient with dg. Neuroblastoma
t(11;22) for Ewing sarcoma
spectral karyotyping



N-myc

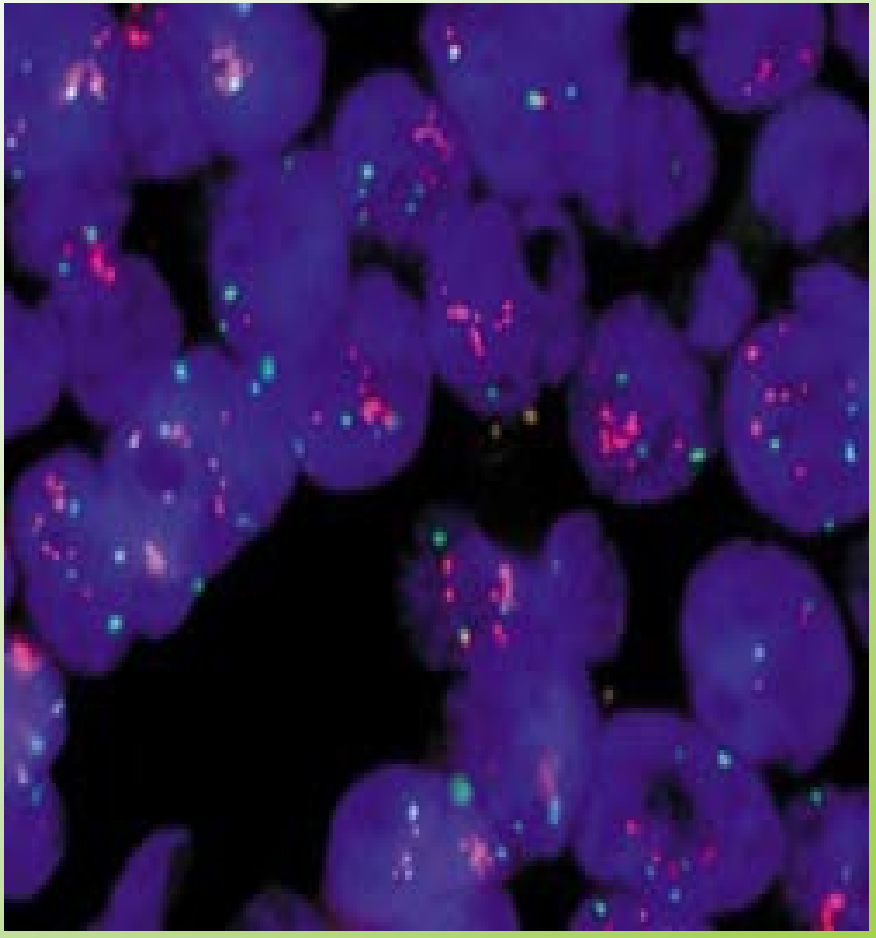
N-myc > 50 copies



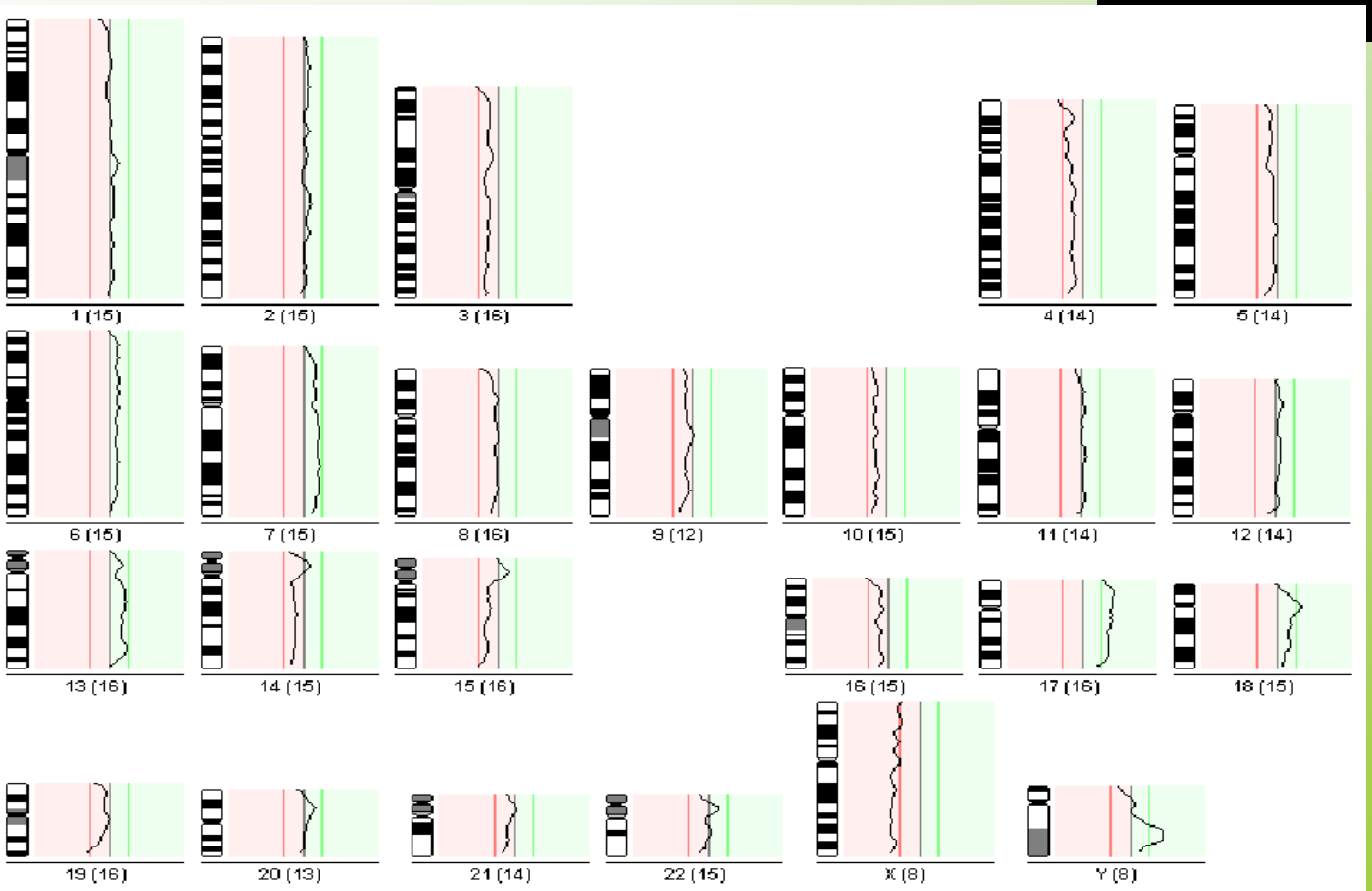
Tumor

Neuroblastoma

HER -2 gene breast cancer

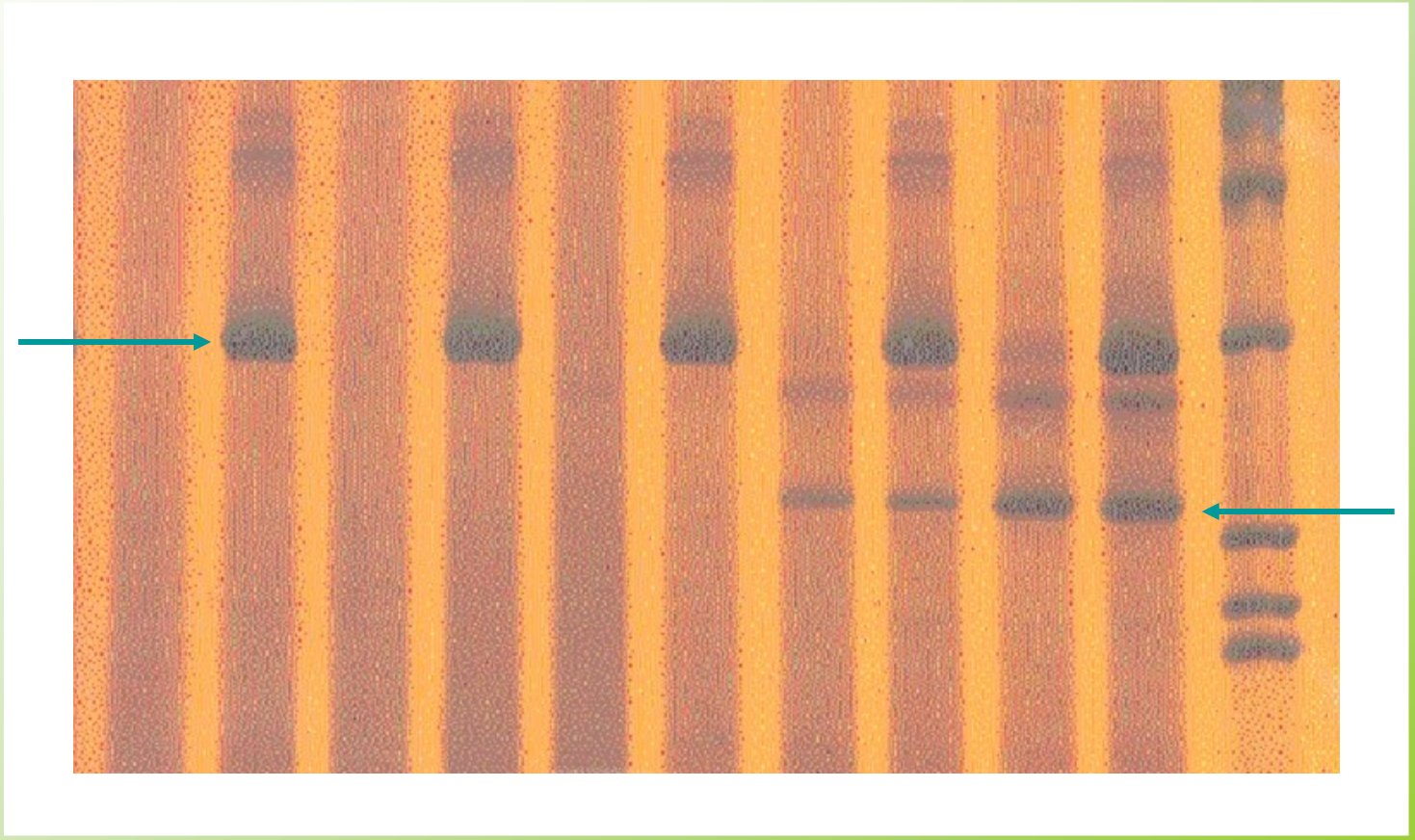


CGH Neuroblastom



rev ish enh (7,13,17,18)
rev ish dim (3,4,14,15,X)

Citlivost detekce TH



Genetic risks in cancer

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

- Embryonal and childhood tumours
- Common malignant tumours of later life

Hereditary tumours

- AD
- Preventive, pre-symptomatic testing
- Assotiated problems
- Prevention
- Brest cancer – BRCA 1 and BRCA 2
- Familial Adenomatous Polyposis coli
- Von Hippel – Lindau syndrome
- Retinoblastoma
- Neurofibromatosis
- Li-Fraumeni syndrome
- Lynch syndrome

Familial tumours following AD inheritance

- Brest cancer – BRCA 1 and BRCA 2
- Familial Adenomatous Polyposis coli
- Von Hippel – Lindau syndrome
- Retinoblastoma (not all)
- Wilms´ tumour (syndromal form)
- Neurofibromatosis
- Li-Fraumeni syndrome
- Lynch syndrome

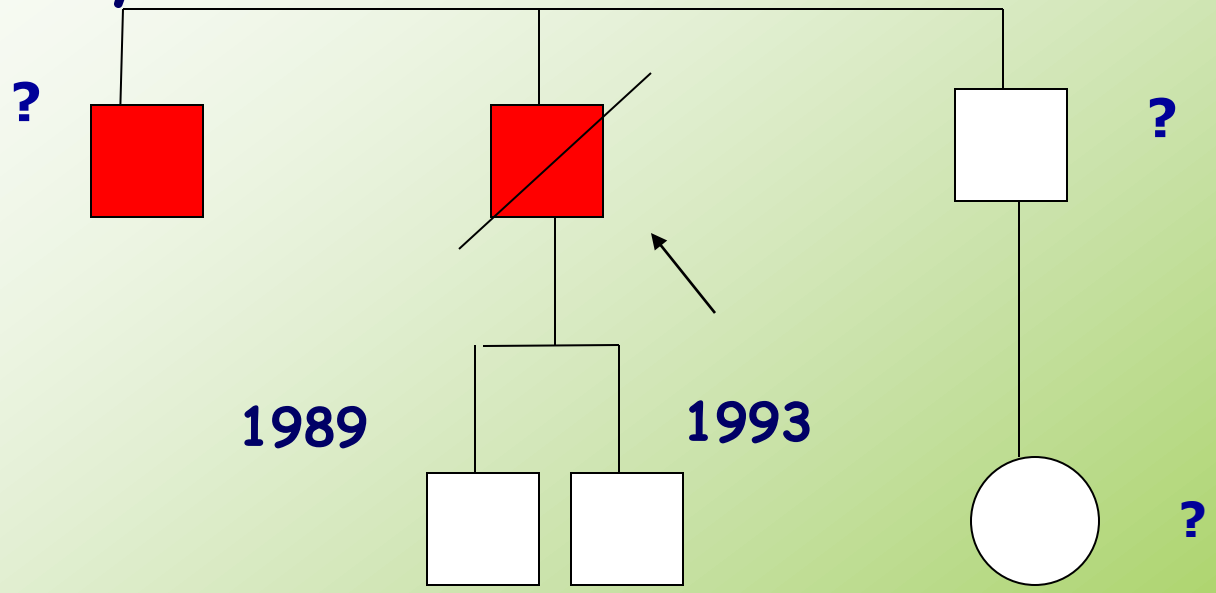
Genetic testing in cancer

- **Tests are voluntary**
- **Mostly in adults only**

- **In children only when prevention in childhood is present and when the risk of tumours is in childhood**

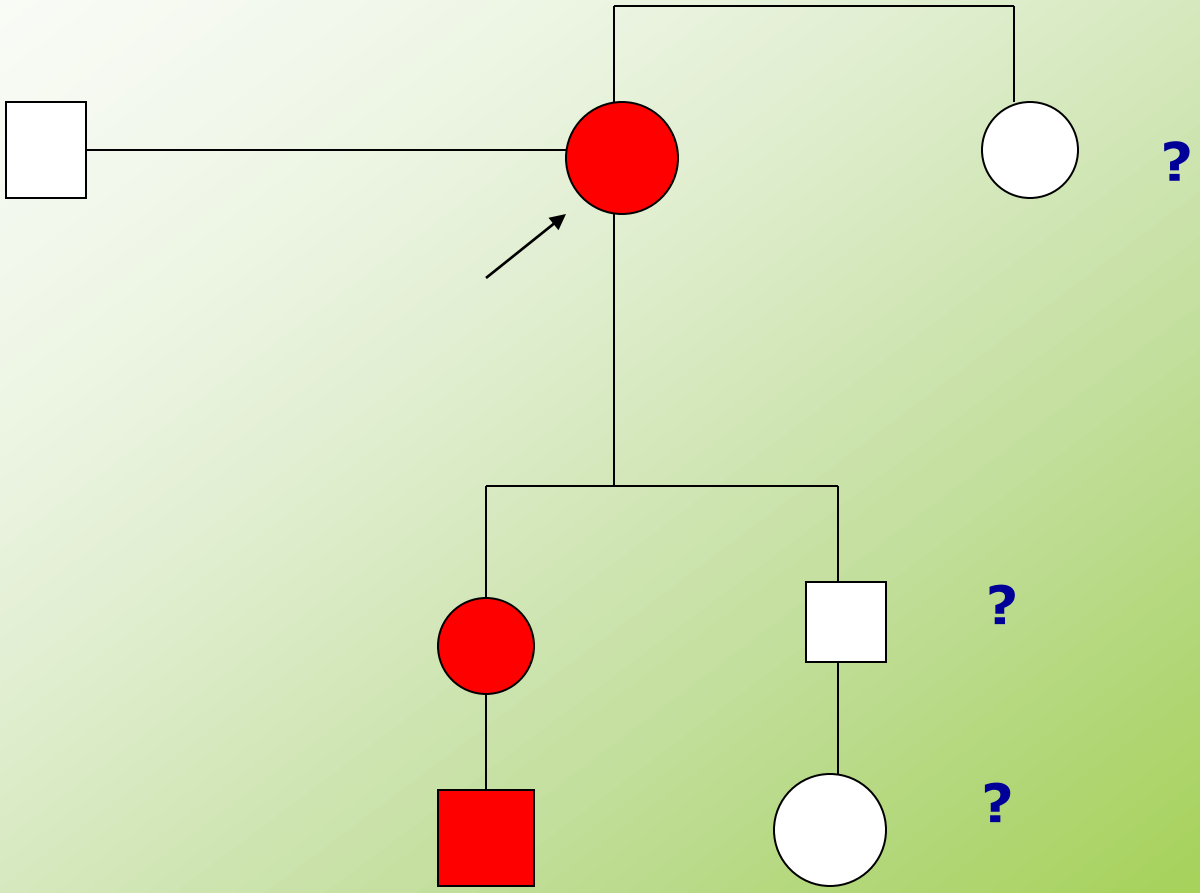
1965-2002
tu mozečku, mozk, kmene,
bil. feochromocytom

1964, amaurosis,
feochromocytom



Von Hippel Lindau , mutation CGG(Arg 167)-CAG(Gln) in father

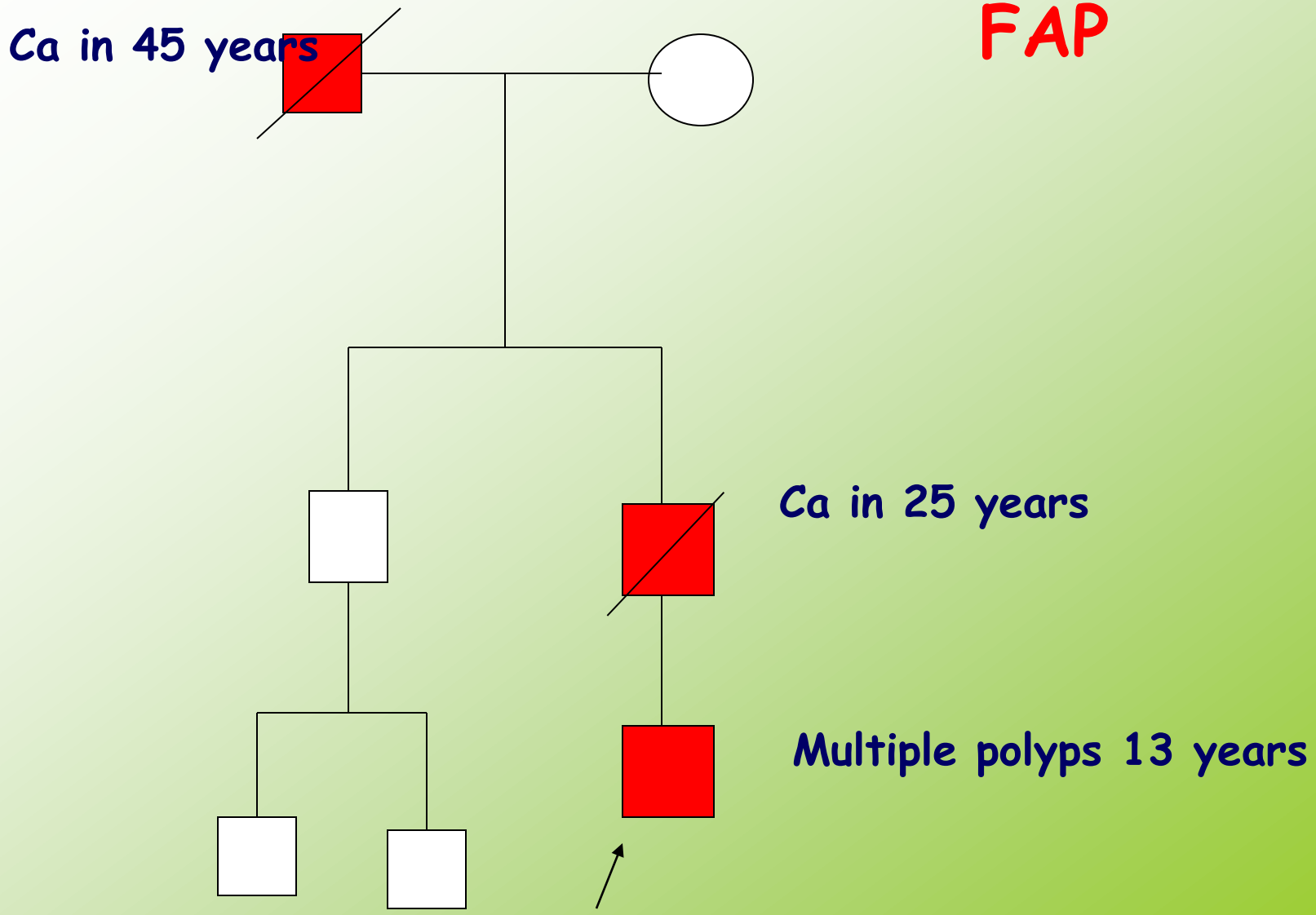
presymptomatic testin in sons - no mutation



VHL

mutation CGG(Arg167)-TGG(Trp)

FAP



Thank you for your attention