Clinical Genetics

Renata Gaillyová

Clinical genetics

- Dept. of medical genetics
- Genetic prevention
- Genetic diseases
- Patients
- Genetic counselling
- 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 laboratories

Prenatal cytogenetics

Postnatal cytogenetics

Molecular – cytogenetics

- Lab. for DNA and RNA analysis (clinical genetics and oncogenetics)
- Oncocytogenetics

Characteristic of Medical Genetics

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

Primary prevention

- **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

- 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

Genetic testing before family planning

? Know we well our health?

? Know we t our partners heal?

? Know we our relatives health?

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 (polygenic or complex) 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 (childless partners), pairs with repeated fetal loss
- Donors (gamets)
- Patients with tumours, oncologic diseases

Children

- Congenital malformations

Children

- Patients with 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

- Abnormal sexual deveplopment
- Precocious or delayed puberty
- Malformations of the external or internal genitalia
- Low or high figure

Children

- Before adoption

Children or adults

- Mental retardation
- Psychomotor retardation
- Developmental delay

Children and adults

- Gender identity disorder

Children and adults

- people with long-term exposure to environmental pollutants (alcohol, cigarettes, drugs, radiation)
- unhealthy lifestyle
- poor working environment
- long-term treatment

Children and adulds

- patients with suspected hereditary cancer
- patients with cancer (sporadic occurrence)

Adults

- Gamete donors

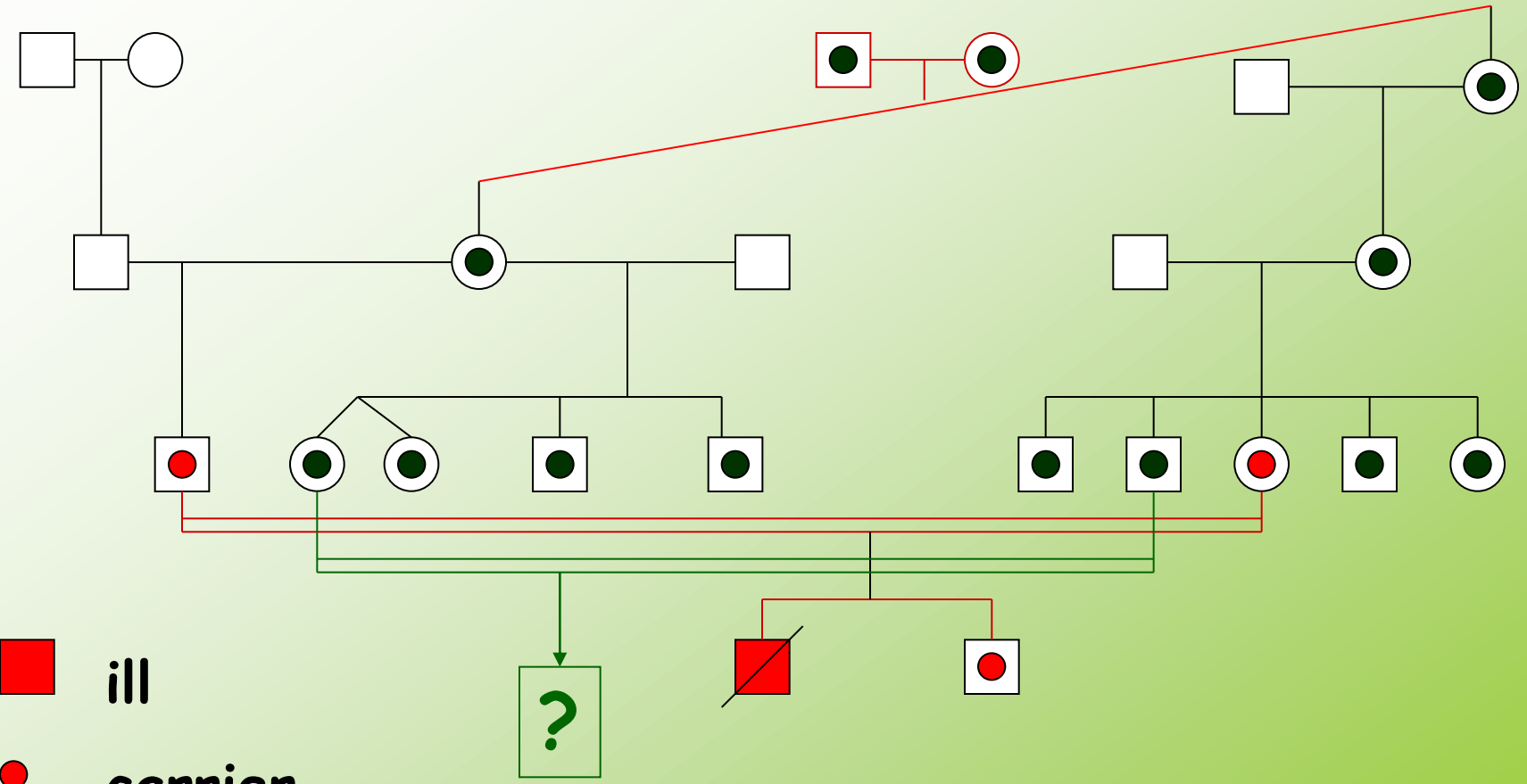
(preventive tests)

Adults

- Related partners

(increased risk for hereditary disease with AR inheritance)

Morbus Pompe



- ill
- carrier
- not DNA analysis – carrier ???

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 screening

- Biochemical tests
- Ultrasonography

(Pathology results)

Pregnant women

- Ultrasound prenatal screening – pathology results
- Congenital malformations in the fetus
- Risk of chromosomal aberrations in the fetus

Pregnant women

- ??? Age of the arents ???

relative indications – 38 years

Genetic clinic

Genetic counselling

- Anamnesis
- 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 of mothers parents
- Relationship
- Jobs - employment risks
- Addictive substances

  alcohol, cigarettes,

  medication ..

Mother

- Health problems from birth until today
- Long-term medication
- Long-term monitoring of a doctor
- Gynecological anamnesis
- The number of births, children, pregnancy, birth weight children, the health status of the children
- The number of abortions, unsuccessful pregnancies
- Unsuccessful attempt to pregnancy

Mother

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

Father

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

  alcohol, cigarettes,

  drugs ..

Father

- Health problems from birth until today
- Long-term medication
- Long-term monitoring of a doctor
- Number of children from any previous partners, 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 records from the attending physician
- Long-term used drugs,
  how long

Child - Patient

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

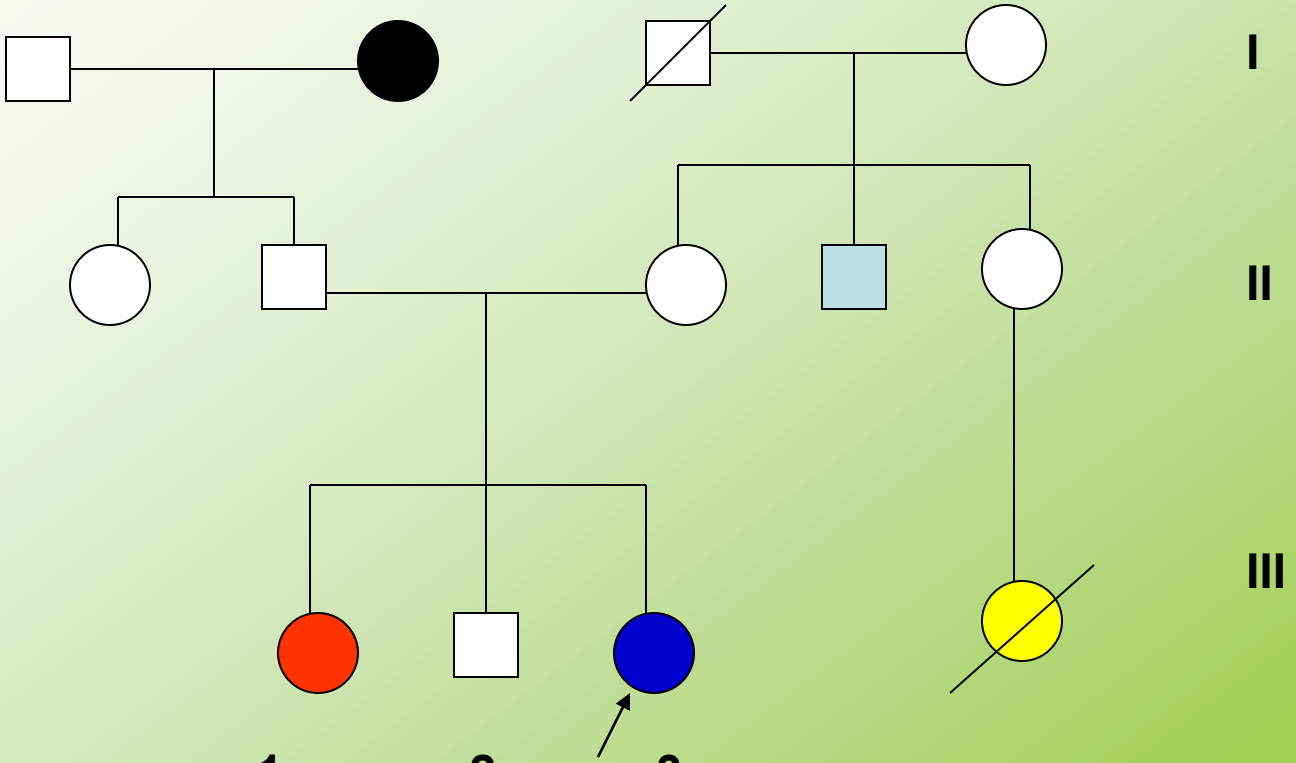
Child

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

Child

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

Pedigree- our patient III/3



Cleft lip

Neonatal death

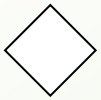
Syndaktilie

Epilepsy

Congenital heart disease

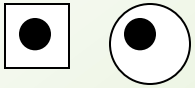
man

woman

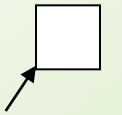


Unknown gender

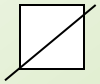
diseased



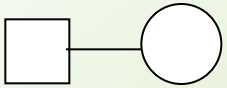
carrier



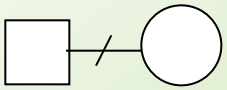
proband



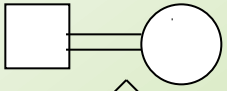
dead person



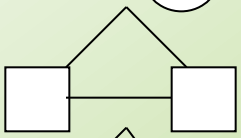
marriage



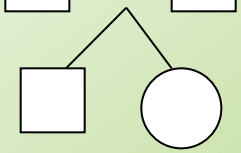
divorce



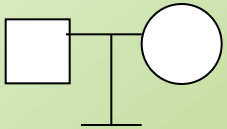
konsanguinity



monozyg. twins



dizygot. twins



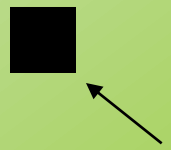
childless

miscarriage

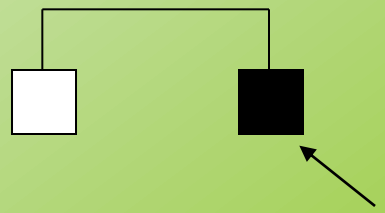
Three-generation pedigree

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

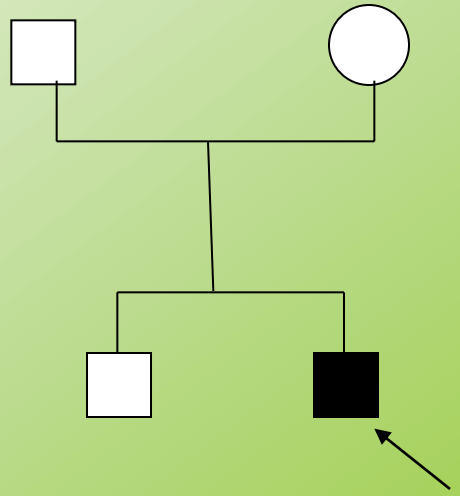
Pedigree



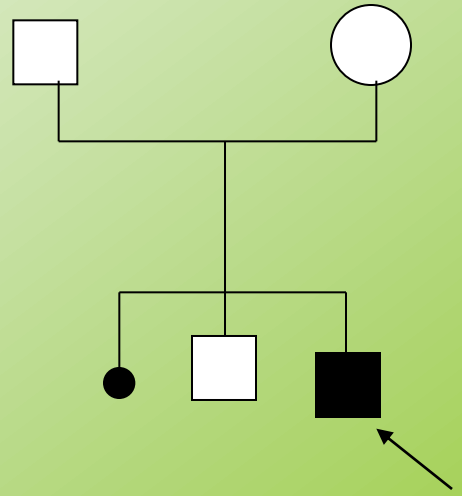
Pedigree - siblings



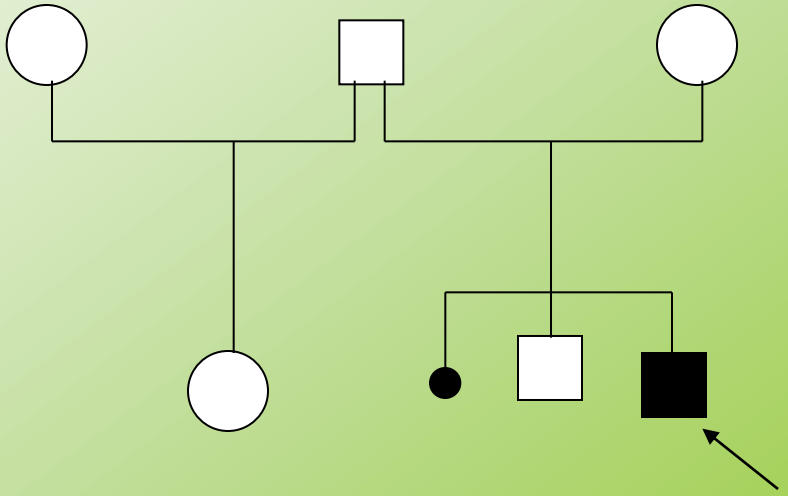
Pedigree - parents



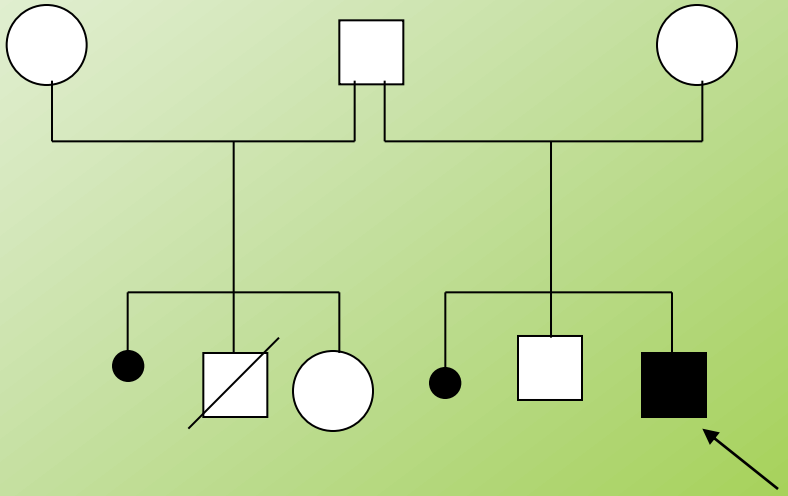
Pedigree - SA



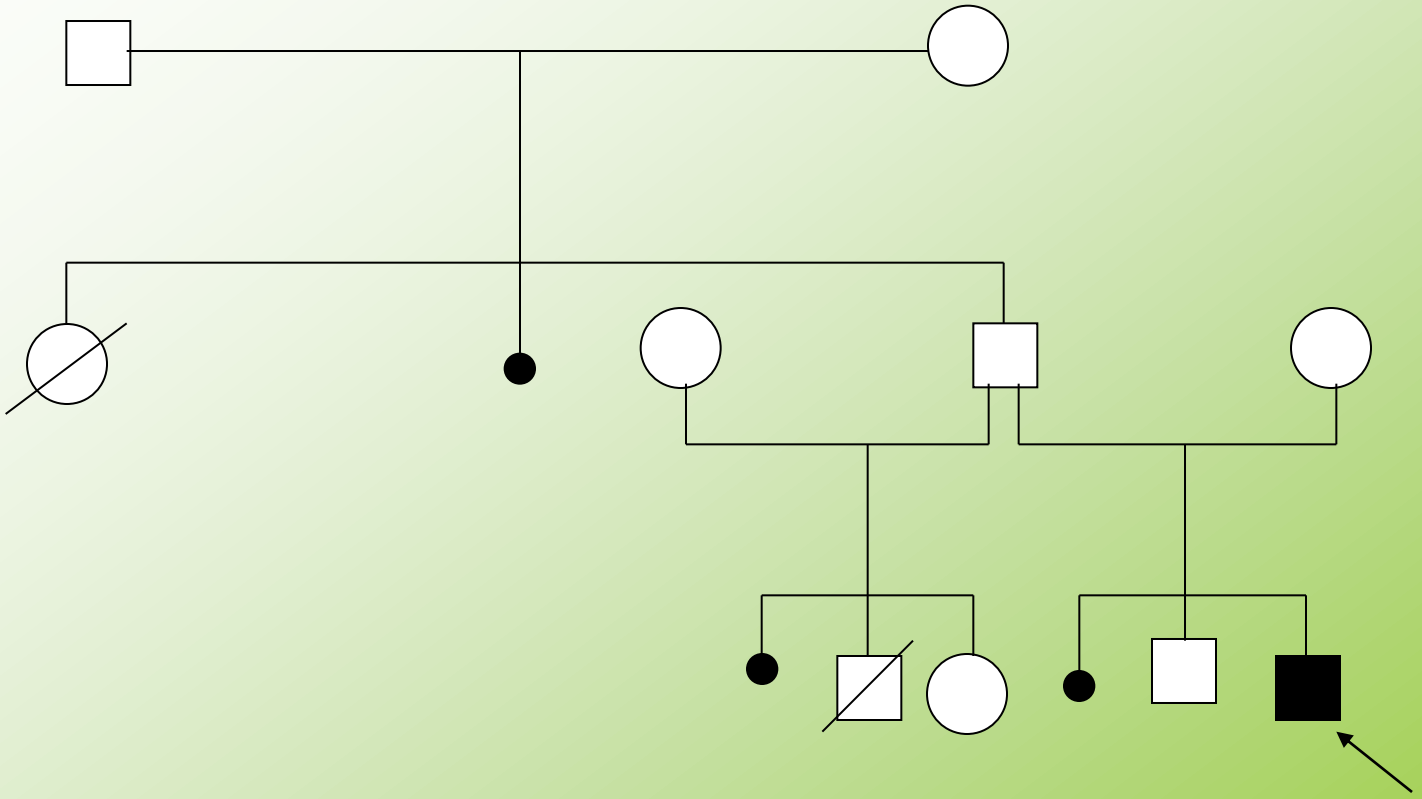
Pedigree - half- siblings



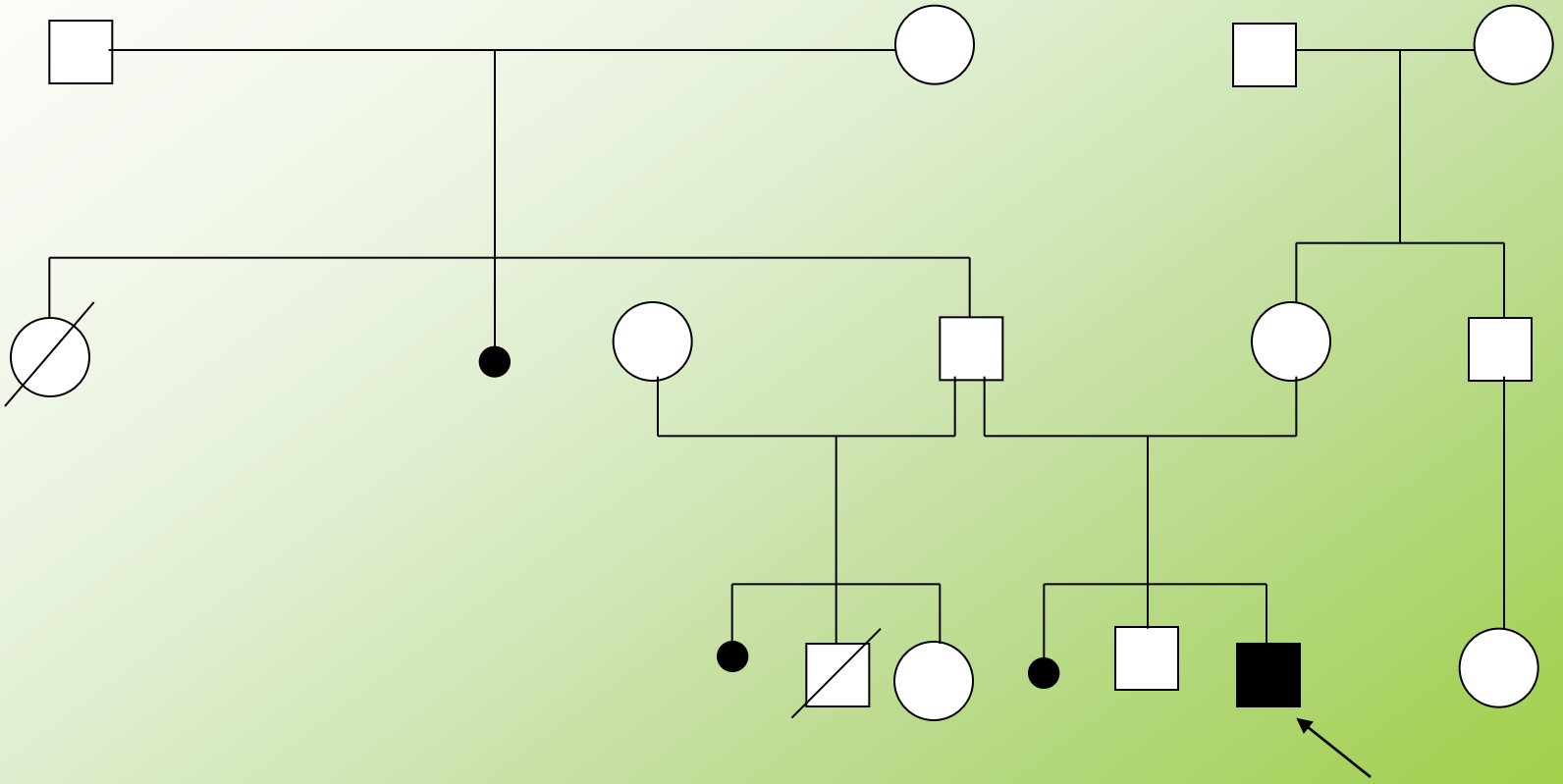
Pedigree



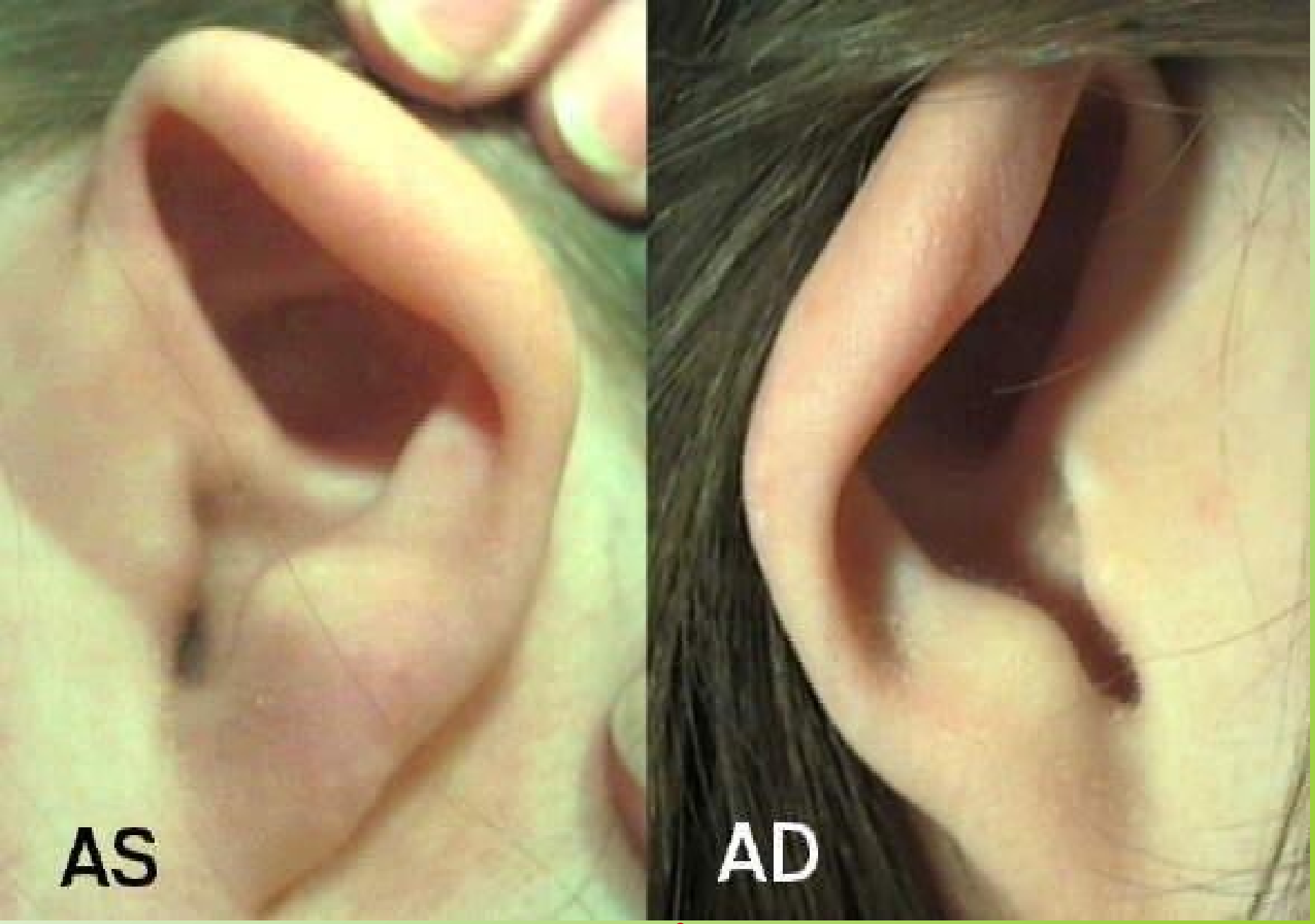
Pedigree – siblings of parents



Pedigree - grandparents

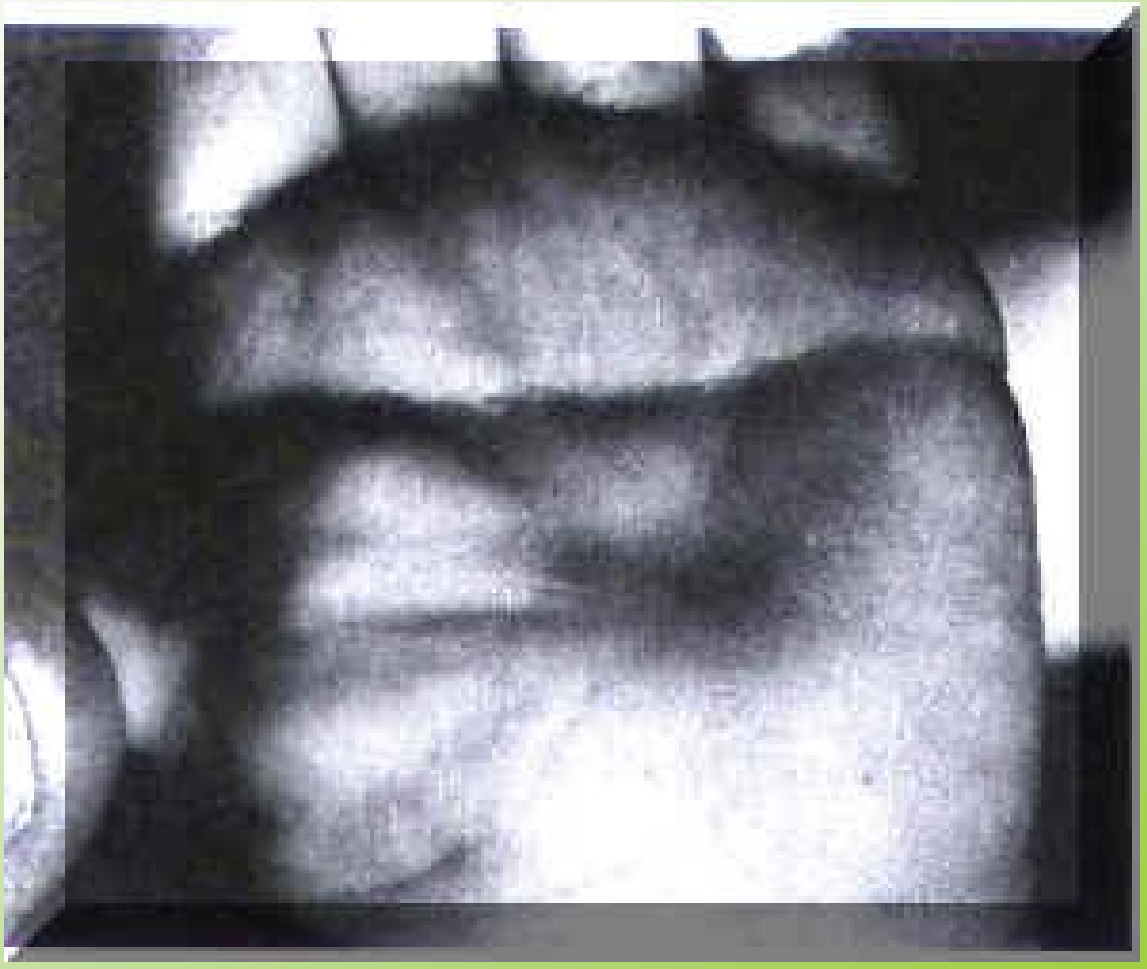


Clinical examination

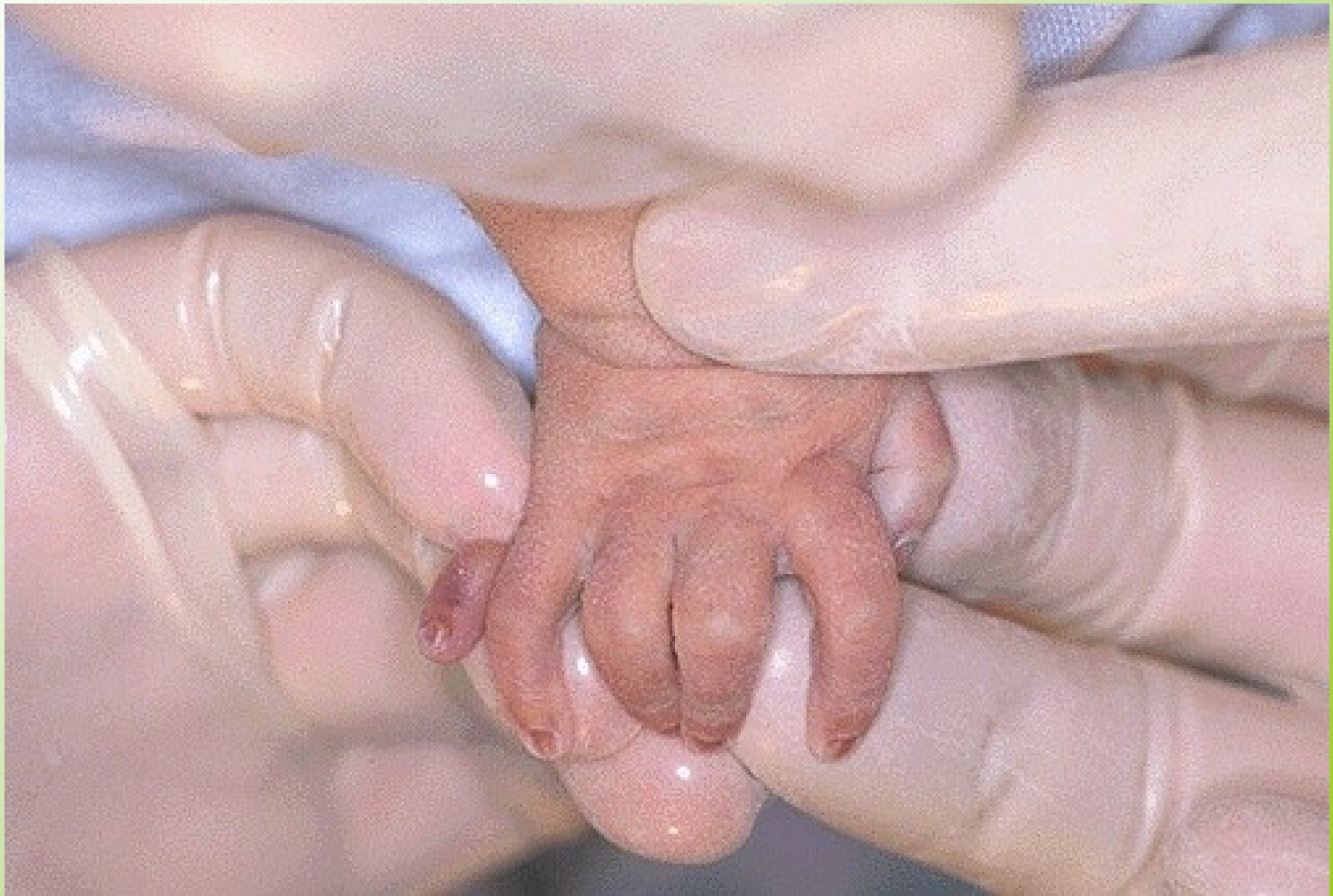


Atypical ears

Dermatoglyfy - grooves on the palms and soles

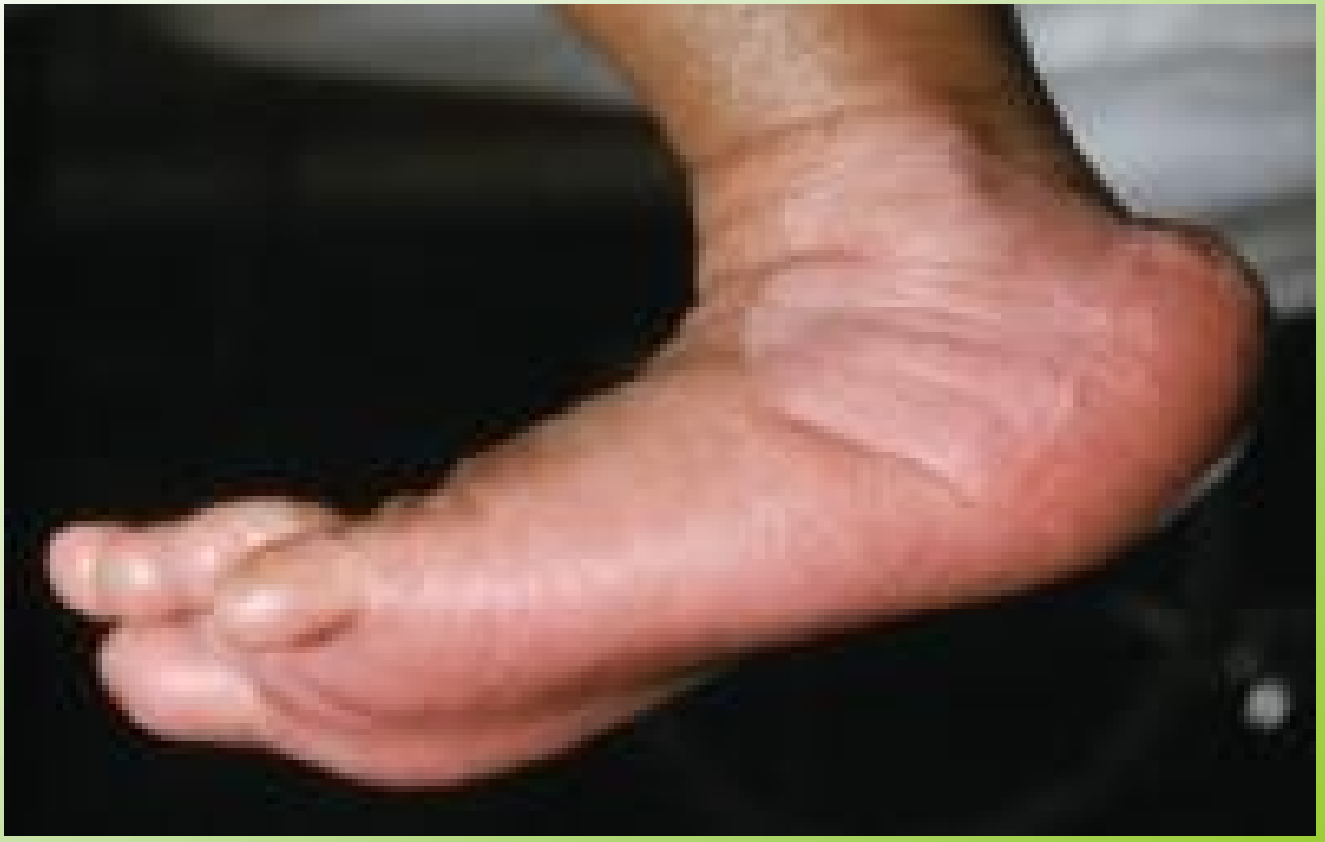


Hexadactylie



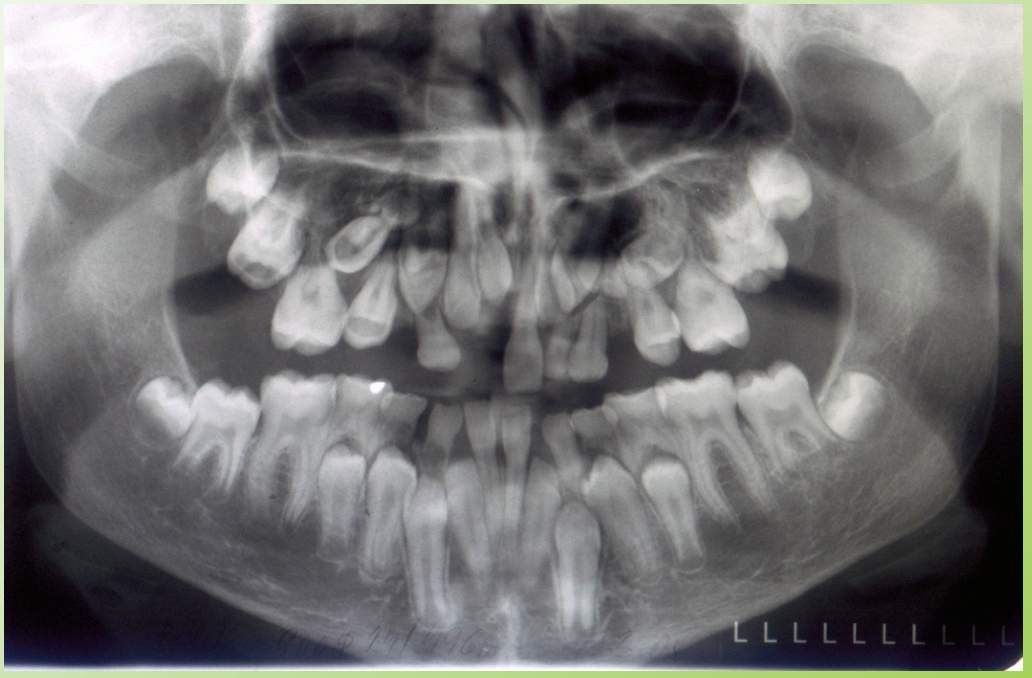
Atipical hand in trisomy 18

Atypical foot in trisomy 18



small figure

Anomalies of teeth



Status eye slits

Atypical face

Next steps

- Recommend the laboratory genetic testing
- Recommend other specialists if needed
- Require medical records
- Make photodocumentation

Genetic counselling

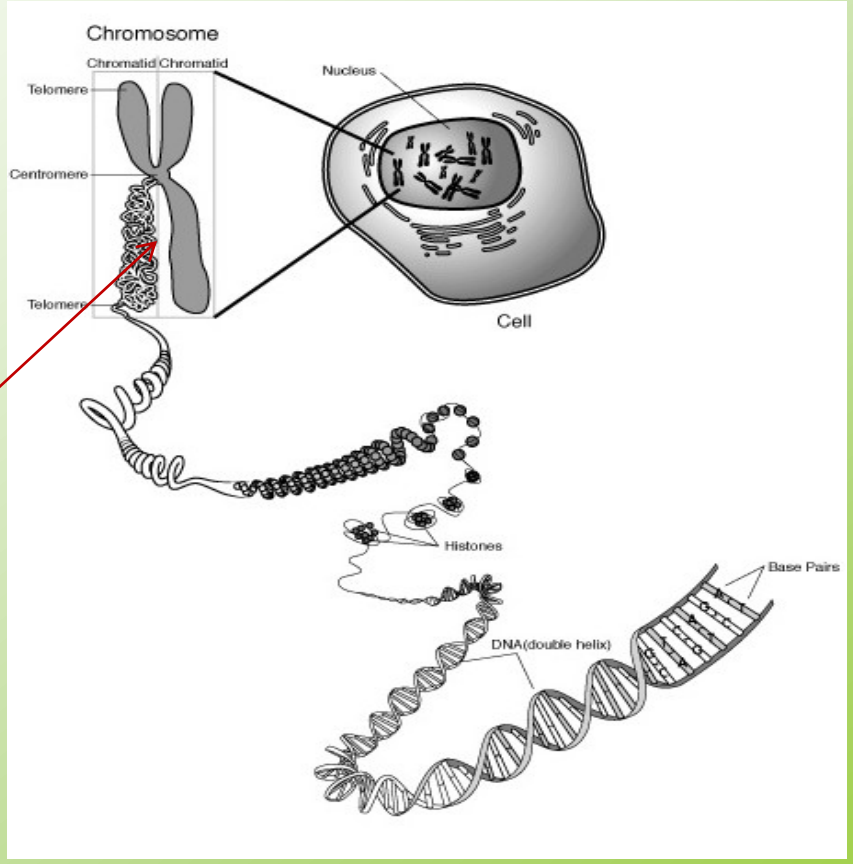
- **Specify exact diagnosis** (if possible)

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

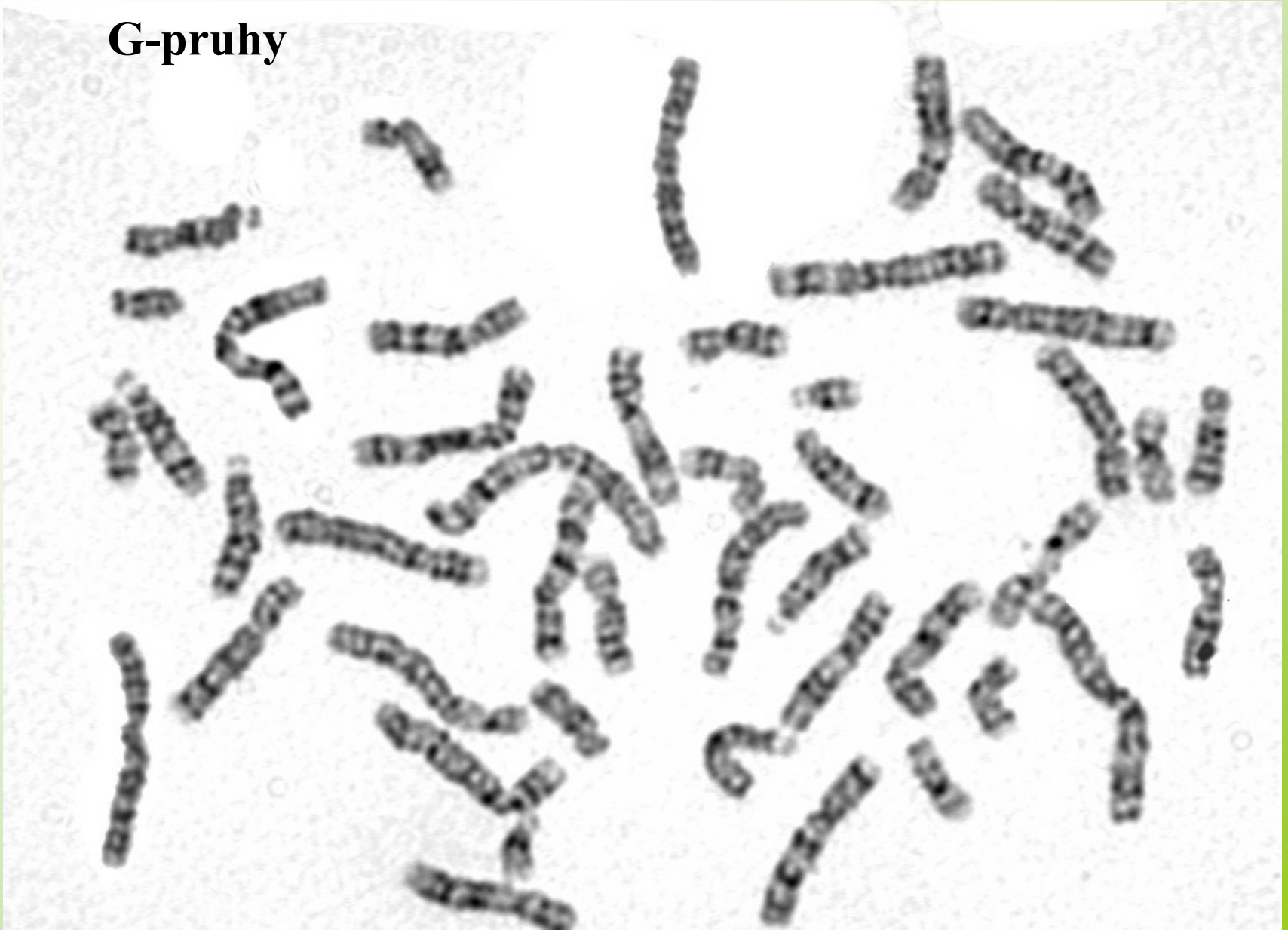
GENOM X GENOTYP

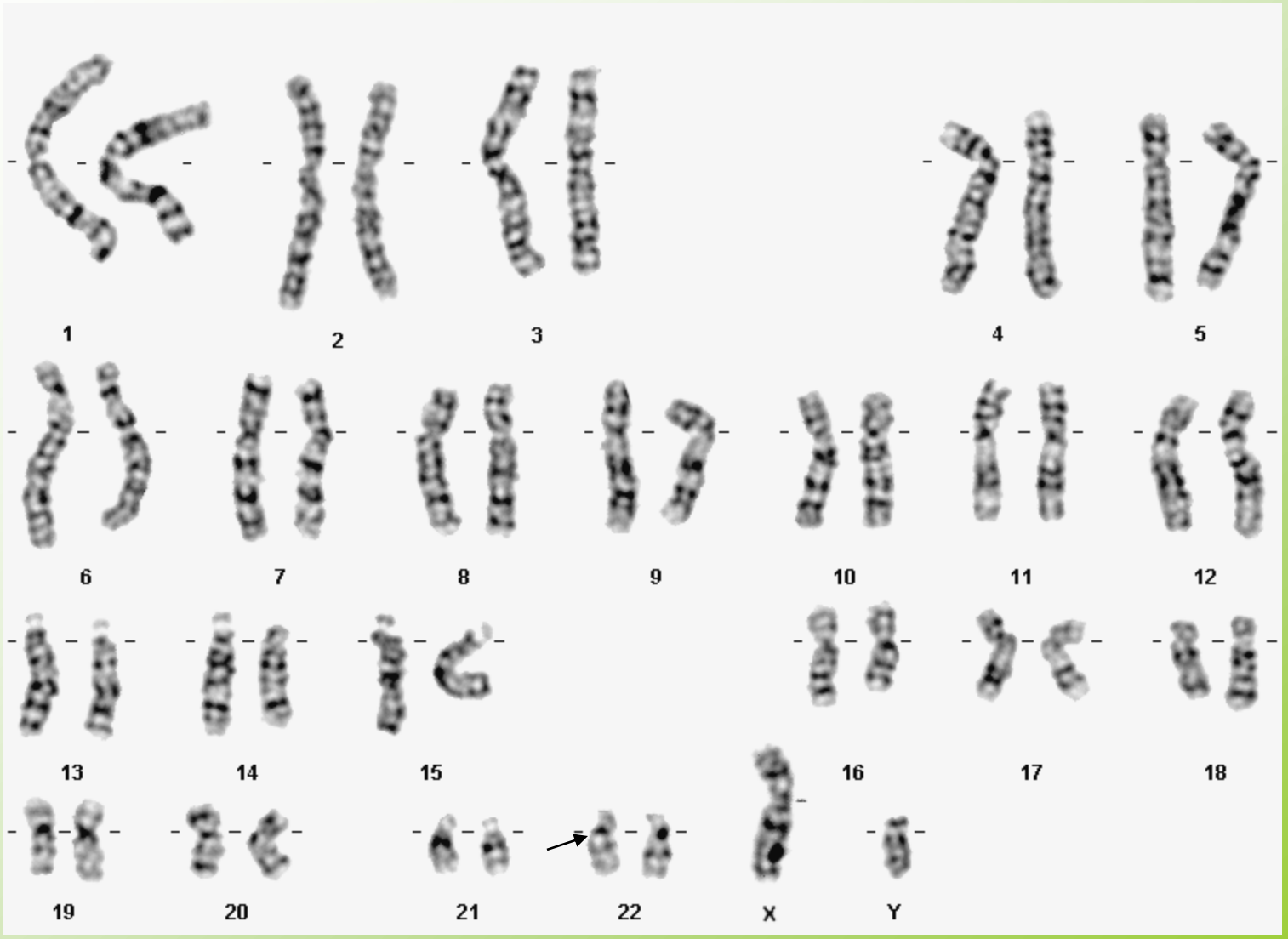
The genome in individuals of the same type is the same
Genotypes of individuals of the same species may be different

Chromosome abnormalities



G-pruhy

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21
22
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 %
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

Risk of Down syndrom (live births)

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

Down syndrome

Happy nature

Vision and hearing disorders

Hypothyroidism

Correlation between positive stimulation and height IQ

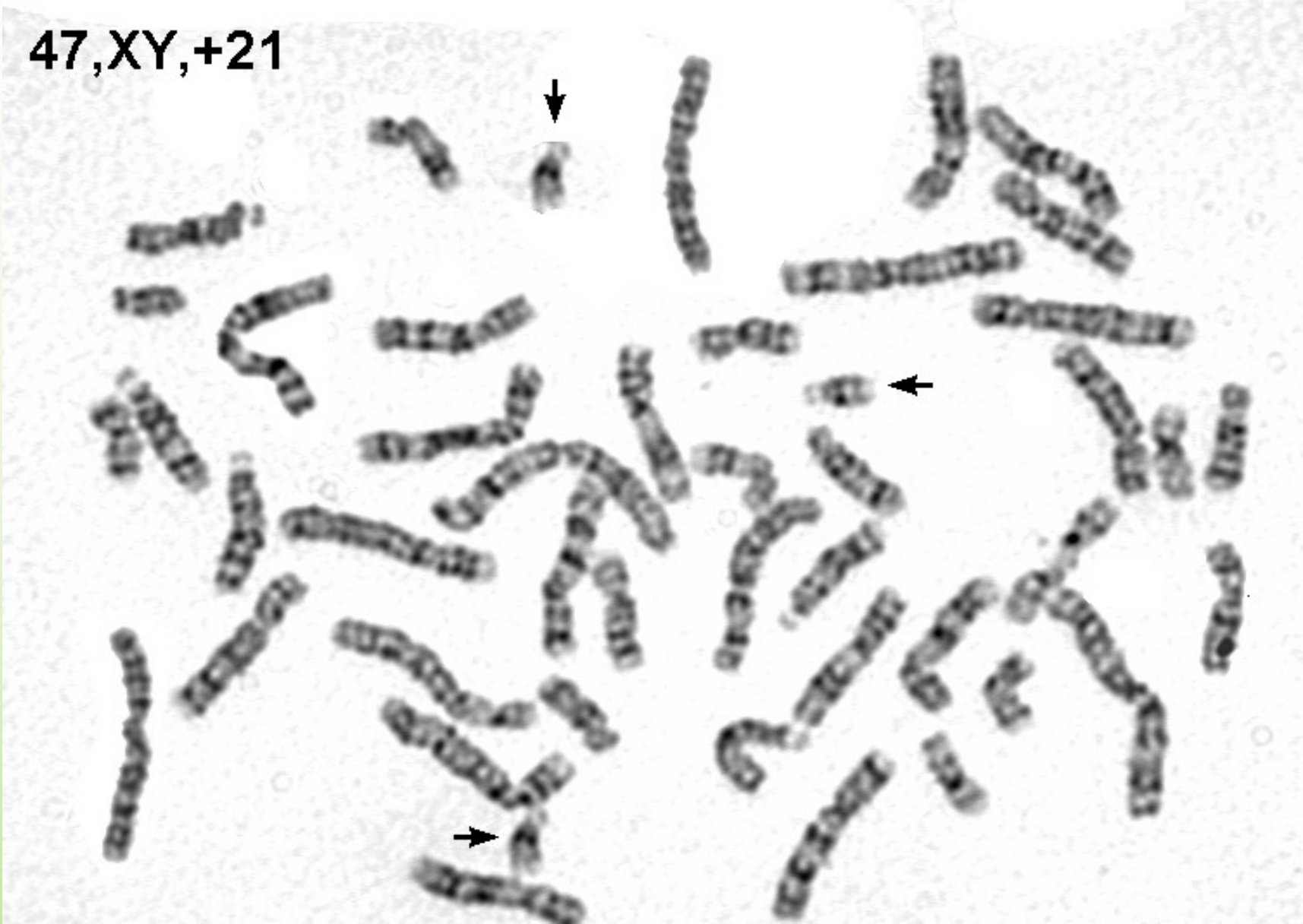
Male sterility

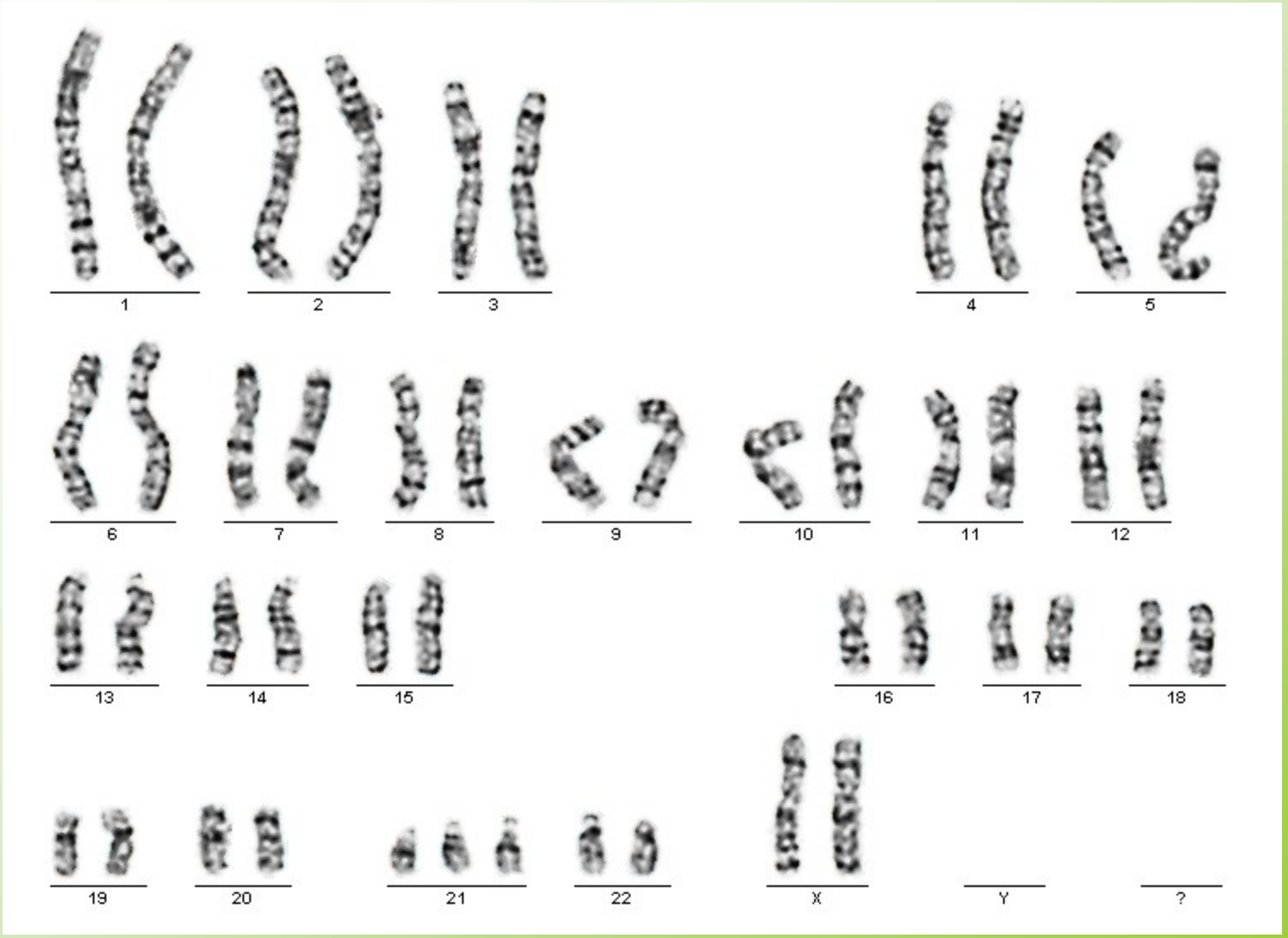
Alzheimer-like symptoms in 40

Down syndrome

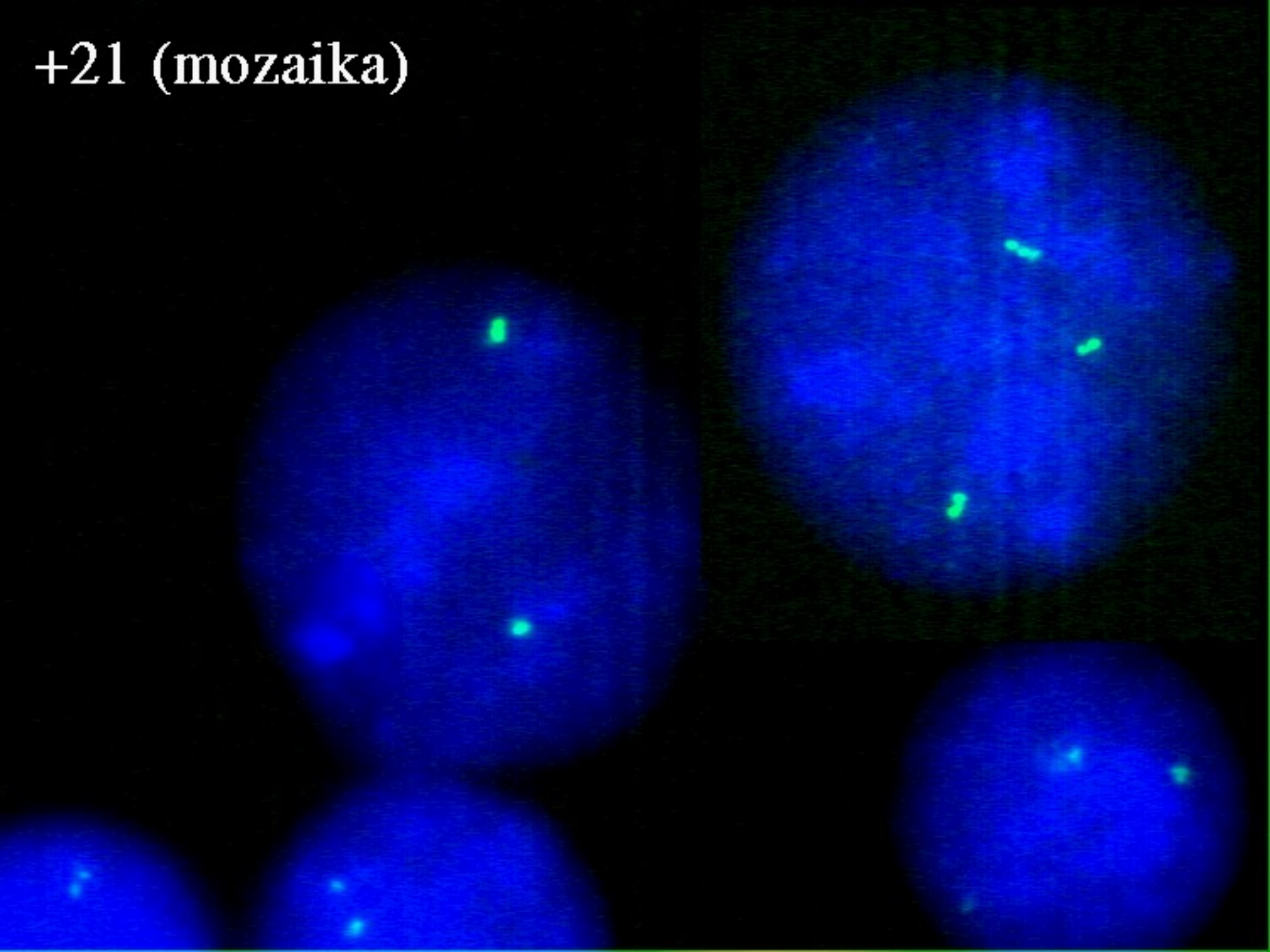
- 47,XX,+21 or 47,XY,+21
- About 1/800-1000 newborns, 1/75 SA
- Hypotonia, joint laxicity, soft skin, flat face, prominent intercanthal folds, slanted palpebral fissurs, specling of the irides (Brushfield´s spots), small, down set ears, small nose, protruding tongue, simian crease in the hands (about 45%), short statue, mental retardation, congenital heart disease (50%), A-V communis

Down syndrome (G-banding)

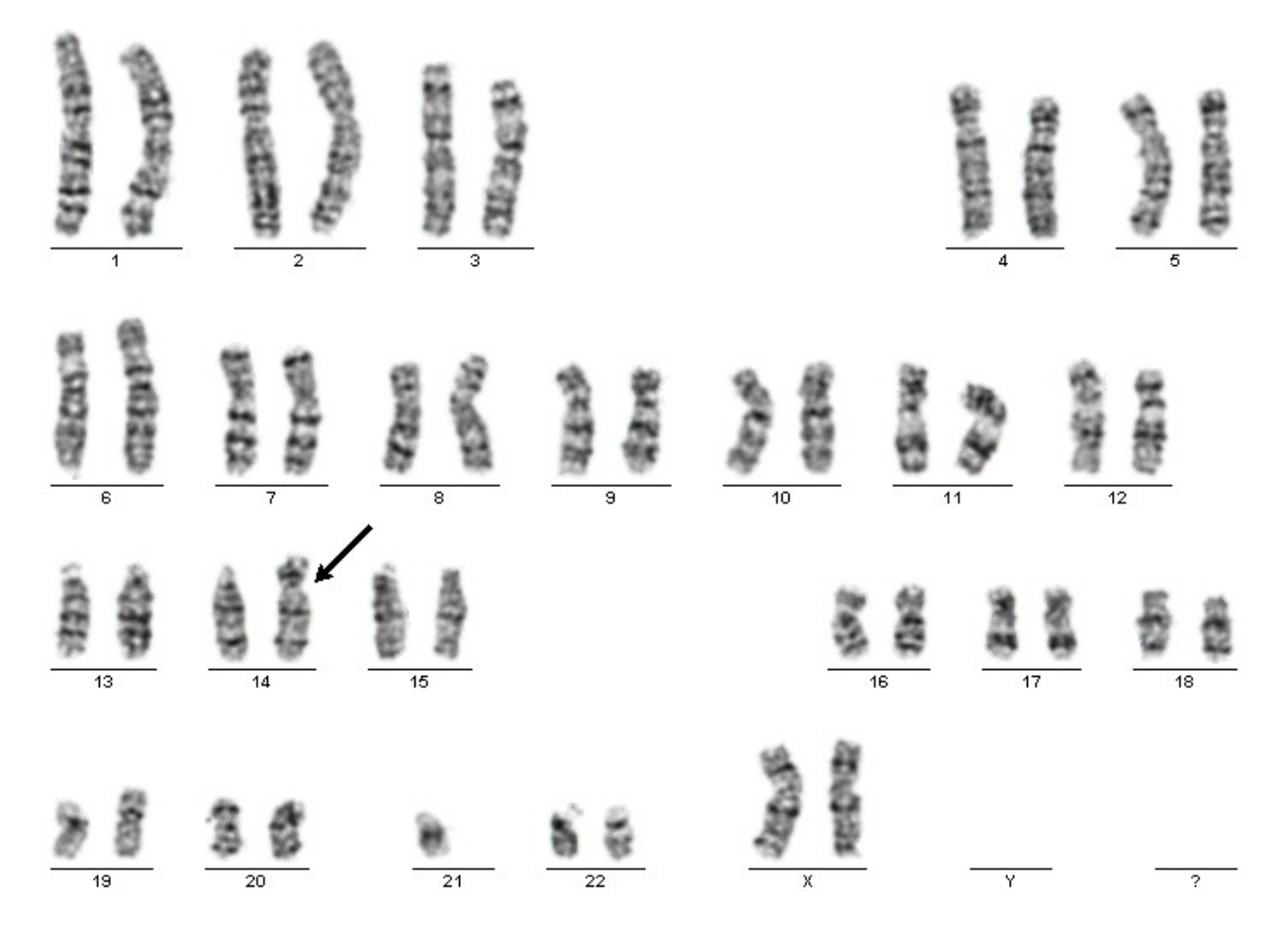




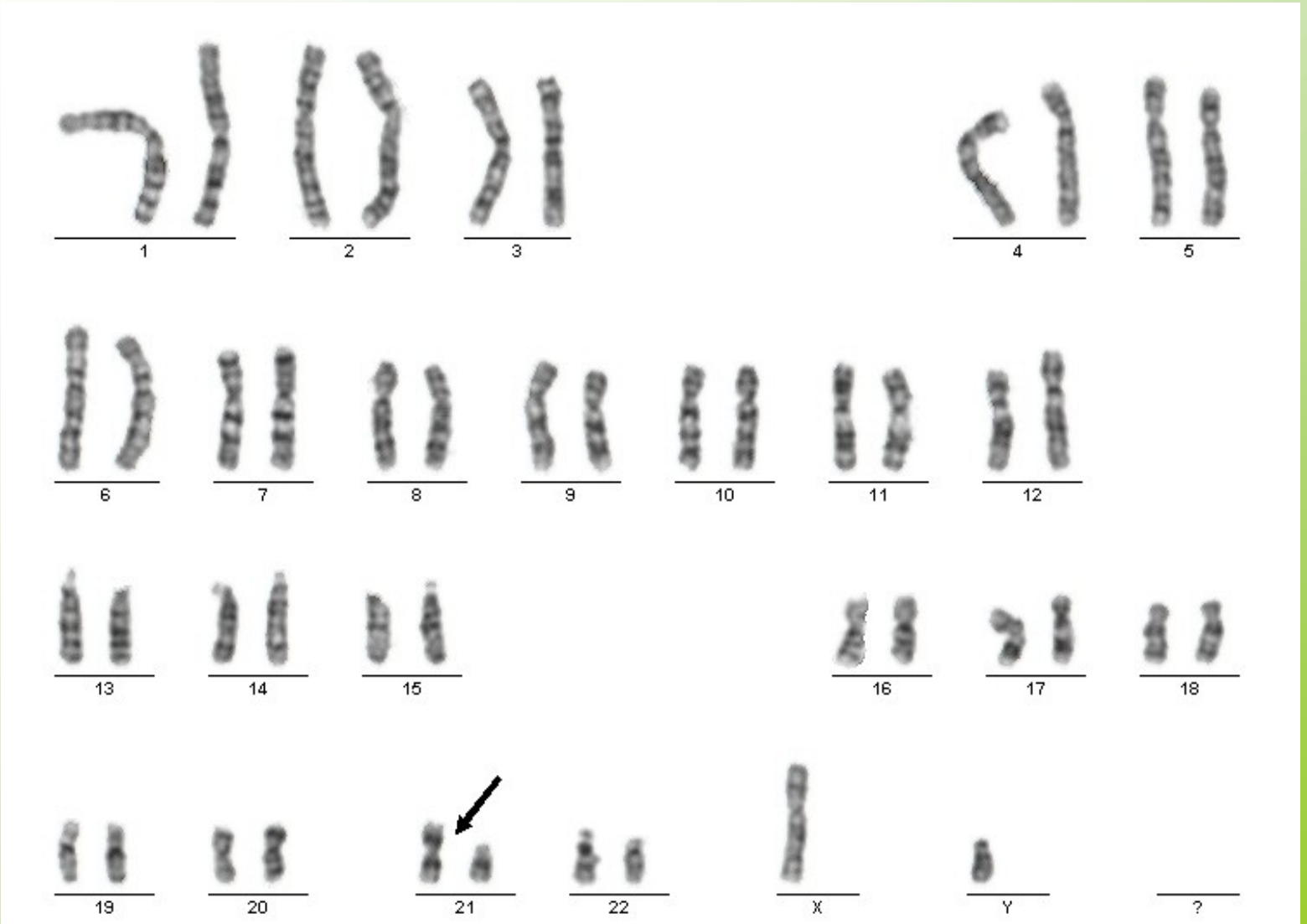
47,XX,+21


+21 (mozaika)

45,XX,t(14;21)



46,XY,t(21;21)



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

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 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

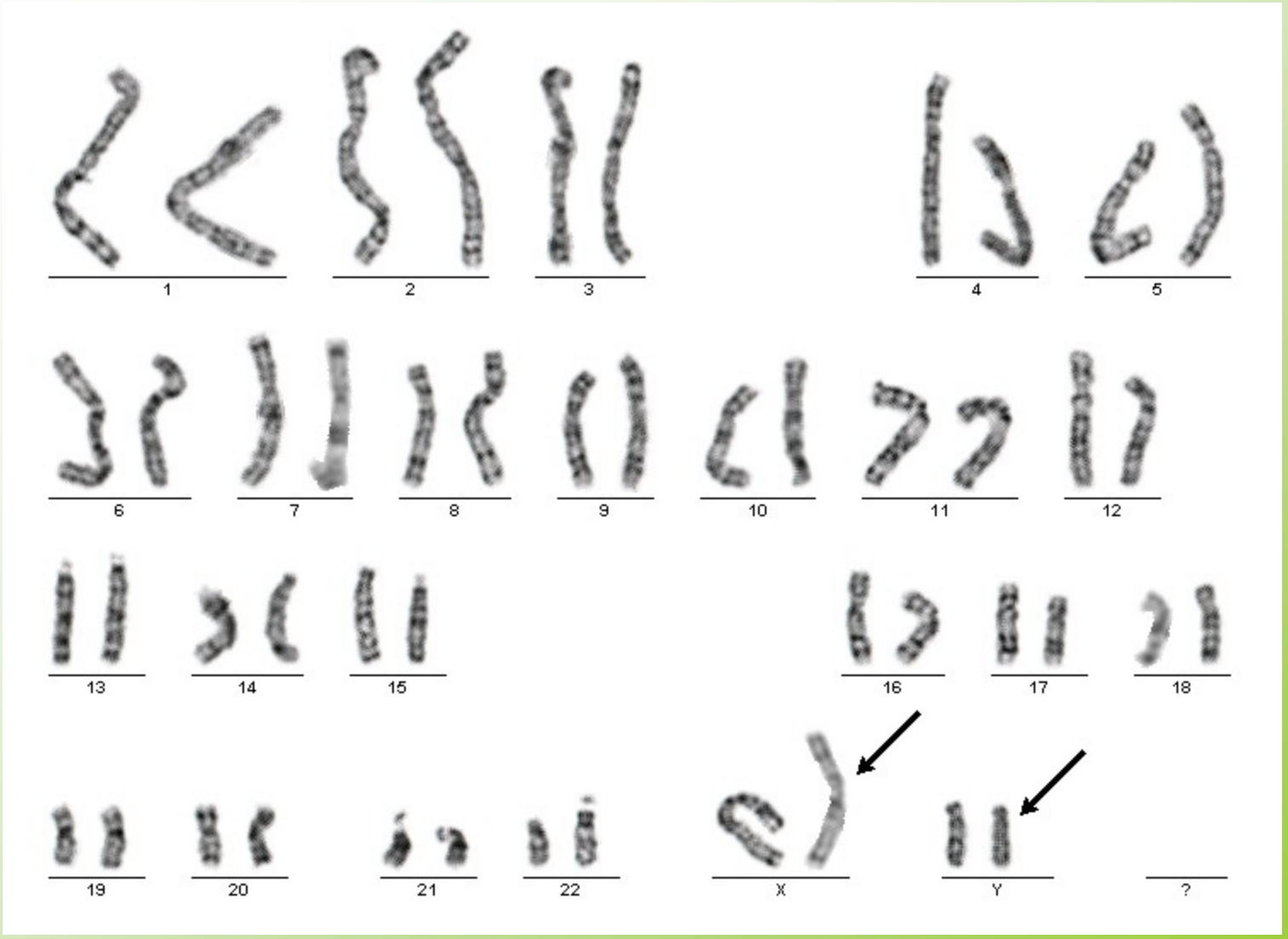
- 1:2000
- hygroma colli
- hydrops
- Low weight in newborns
- Lymfoedema
- Pterygia
- cubiti valgi
- Aortal stenosis
- Small statue
- Sterility

Klinefelter syndrome

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

Others gonoseme abnormalities

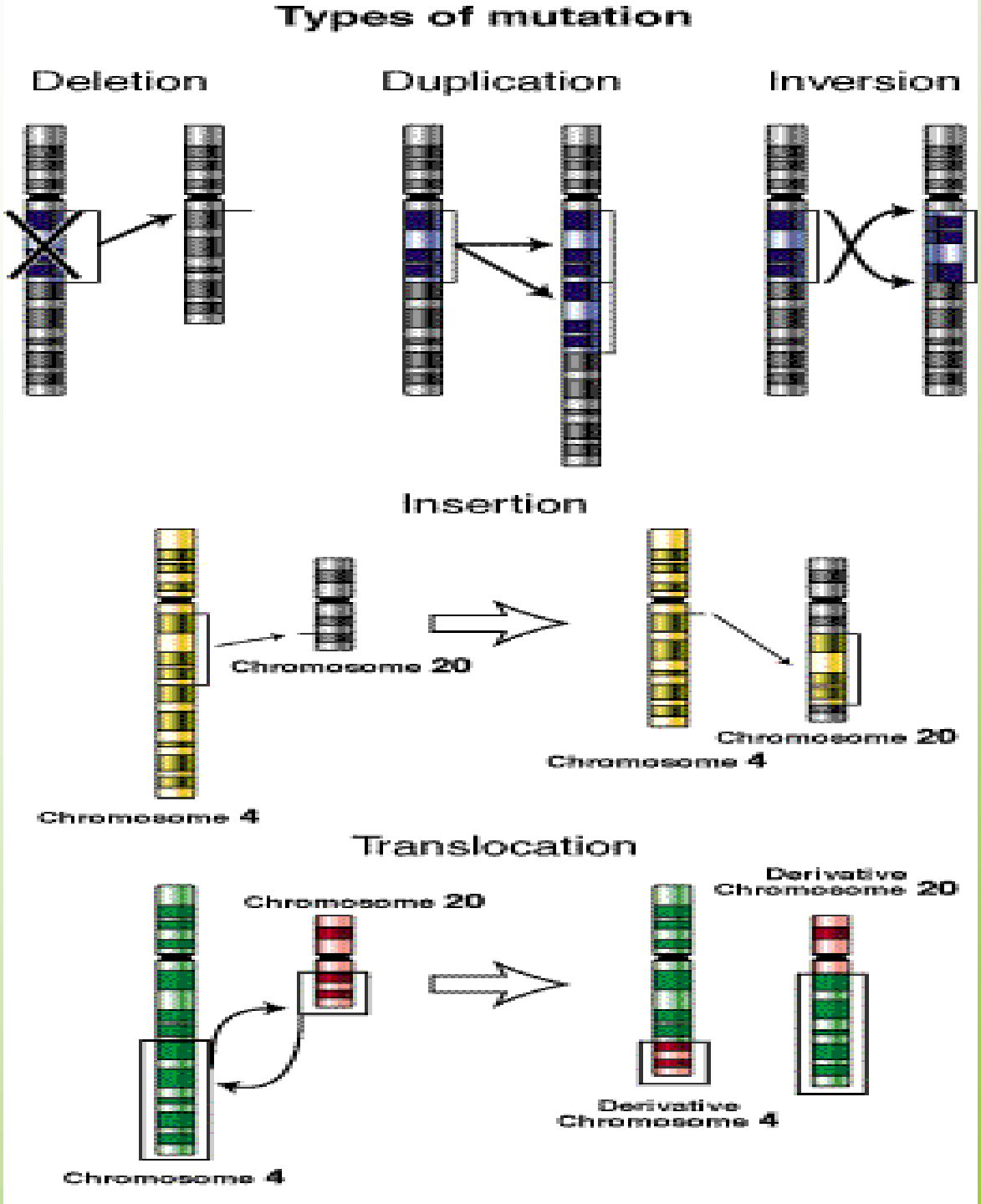
- 47,XXX
- 47,XYY
- 48,XXXX
- 48,XXYY….



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

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 ...

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

IUGR

Hypotonia

Charakteristic face

Heart defects

Hypotonie

Hypotrophie

Severe mental retardation

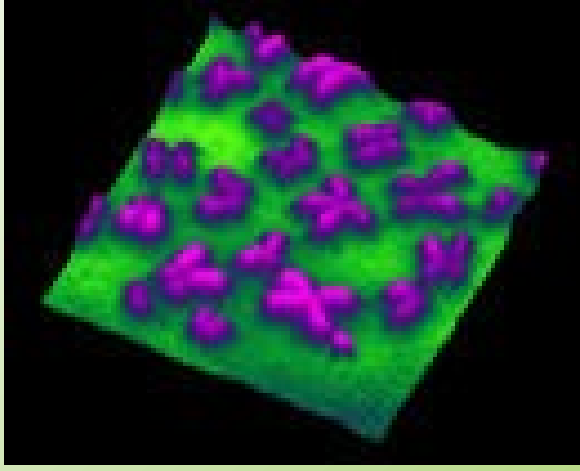
Syndrom Cri du chat 46,XX(XY),5p-

- 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-

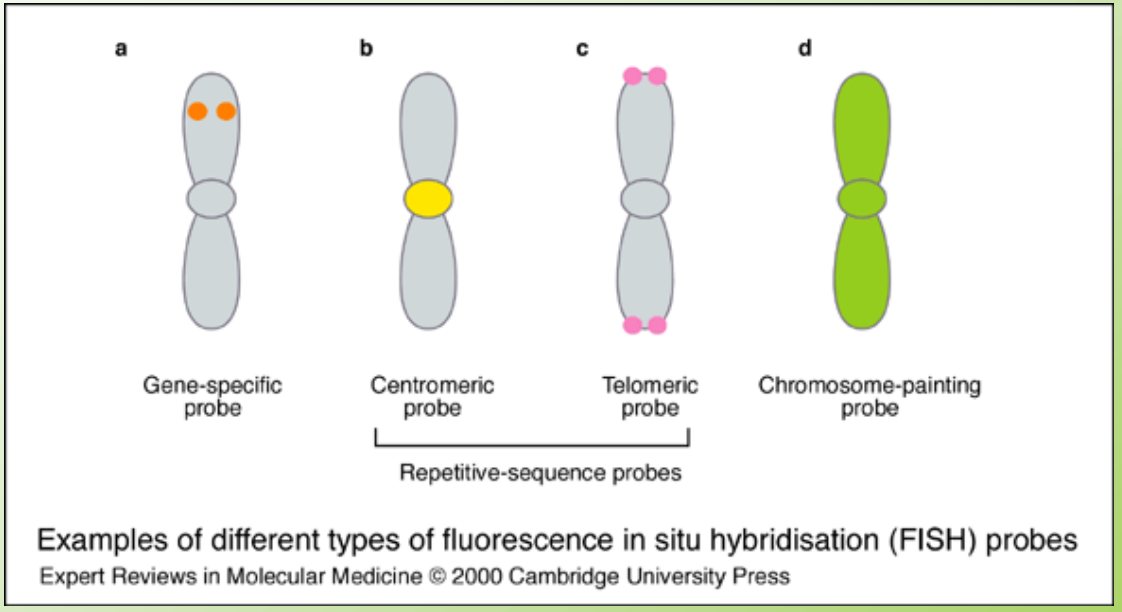
- 1:50 000
- Typicaly cri in newborns
- laryngomalacie
- antimongoloid
- epicanthi
- hypotonie
- hypotrofie

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 prenatal diagnostics …)
- fast methods (possible forprenatal dg)
- metafase and intesfase examination

FISH



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

Microdeletions

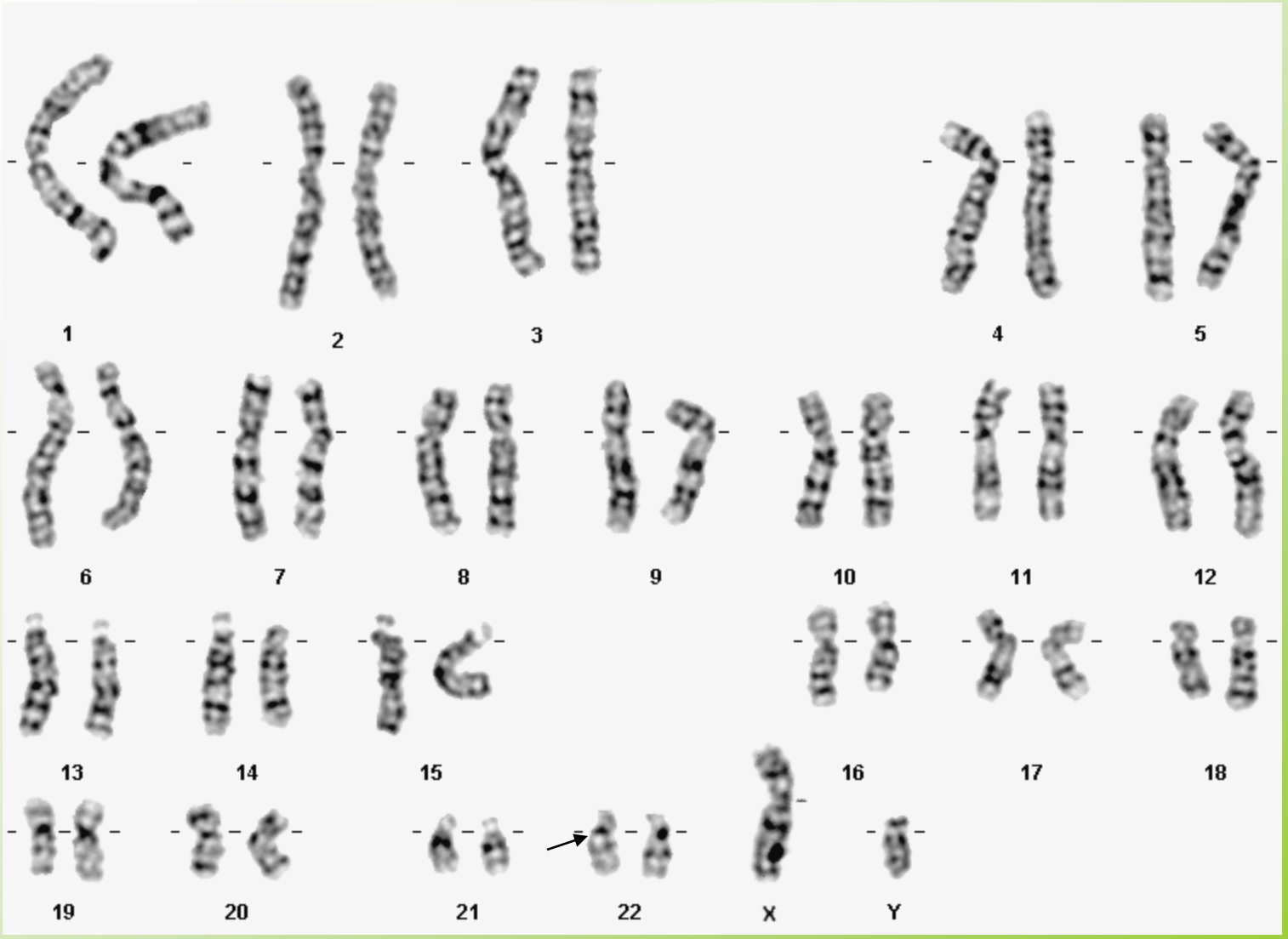
- Di George syndrome
  (del 22q11)

- 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


1
2
3
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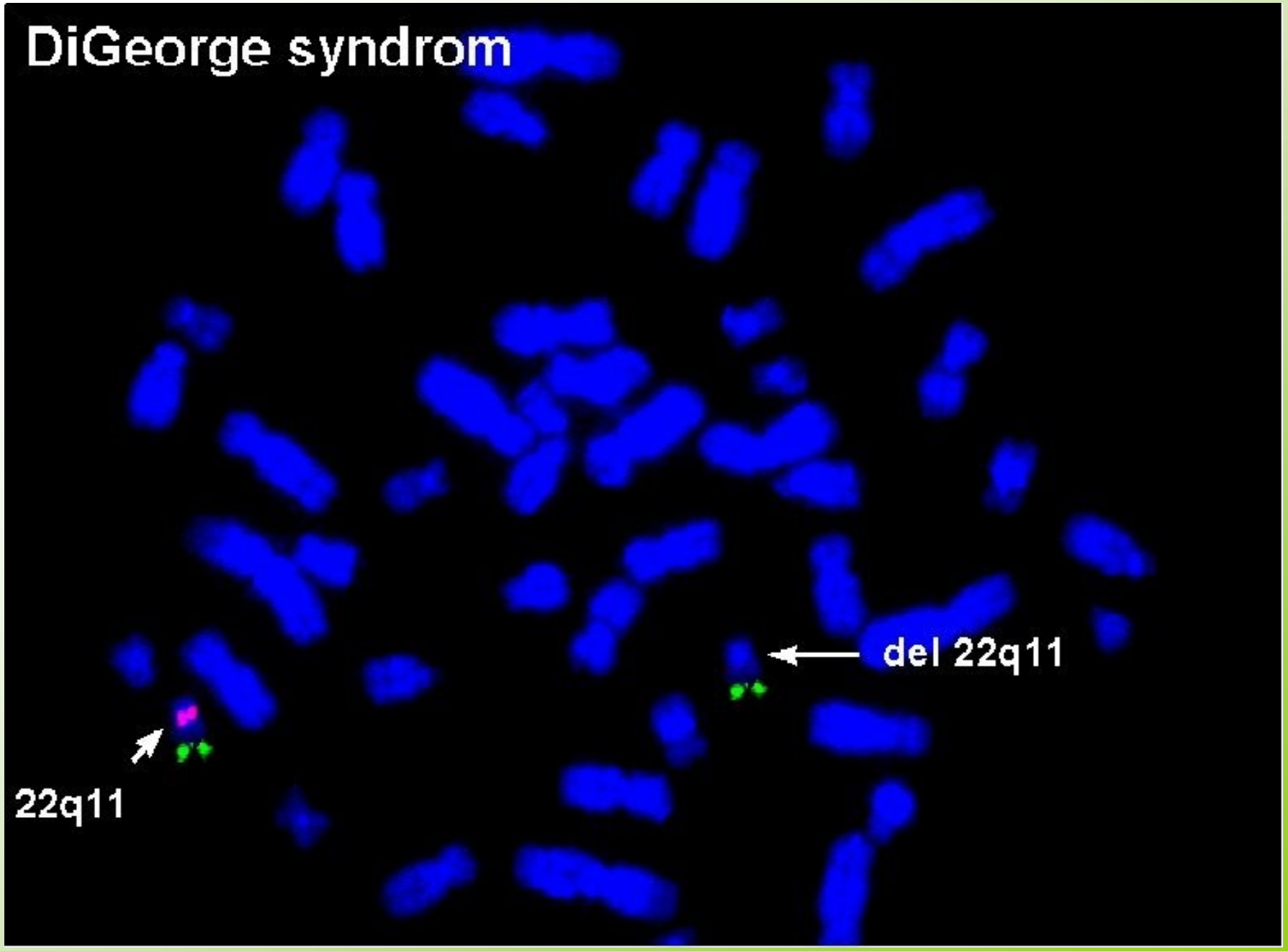
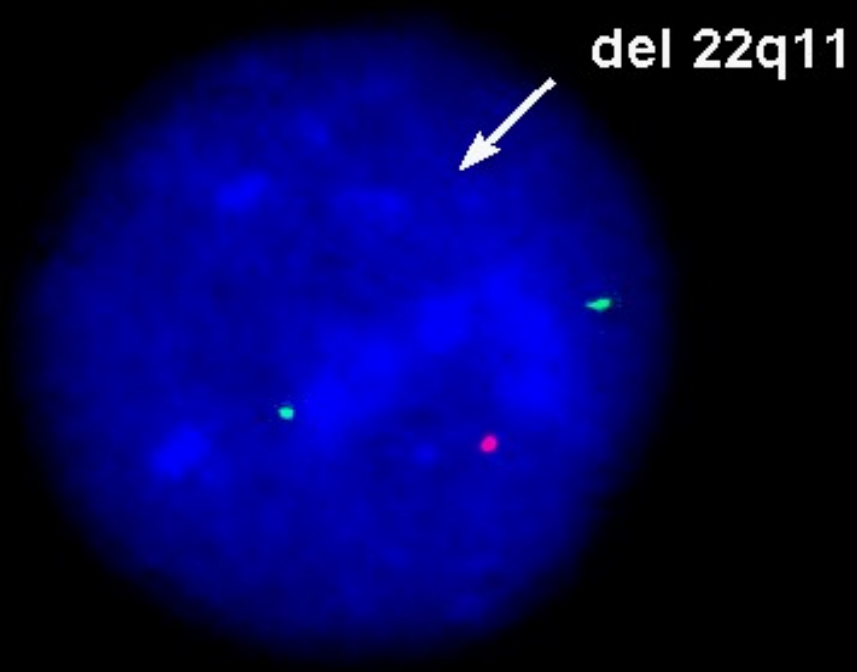
17
18
19
20
21
22
X
Y


DiGeorge syndrom
del 22q11
22q11

DiGeorge syndrom



Williams - Beuren syndrom

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

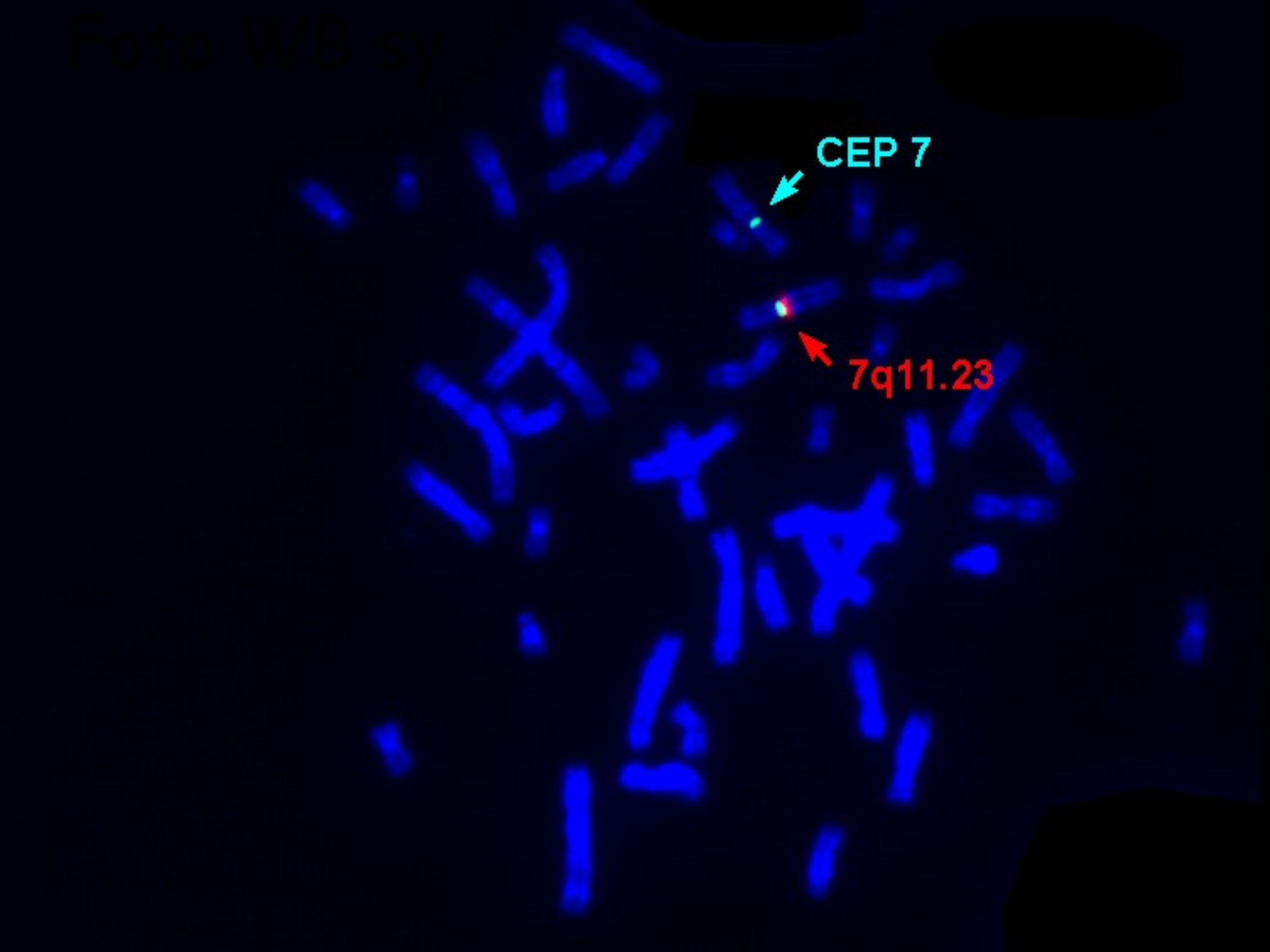


Foto WB sy
CEP 7
7q11.23

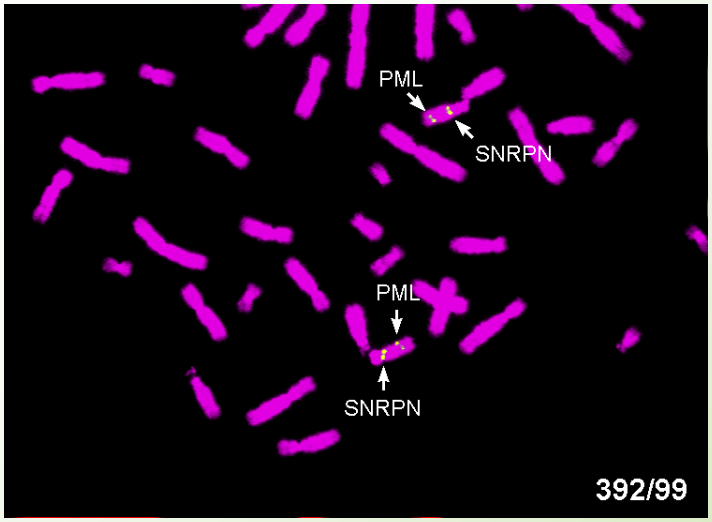
Prader-Willi syndrom

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

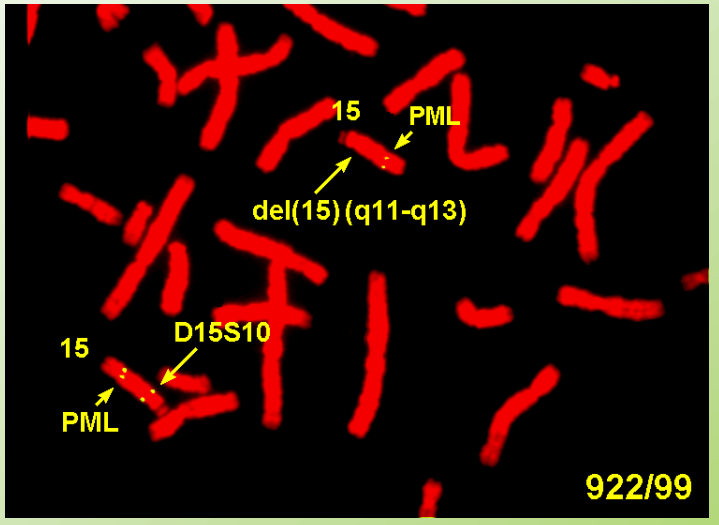
Angelman syndrom

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

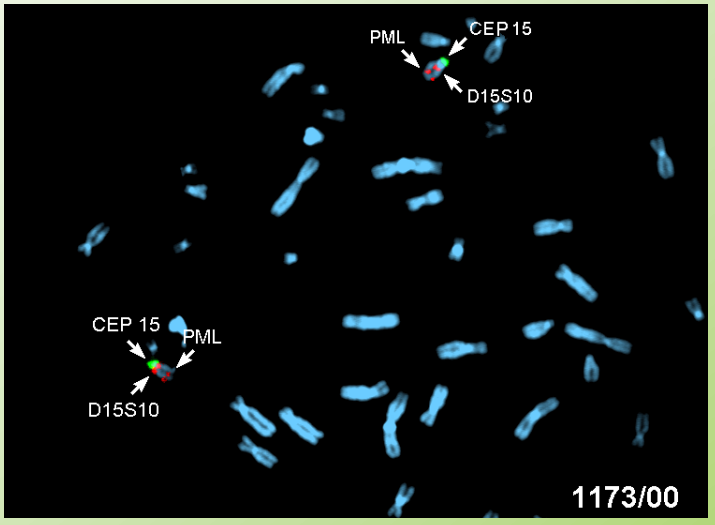
Obr.1: ONCOR -negative



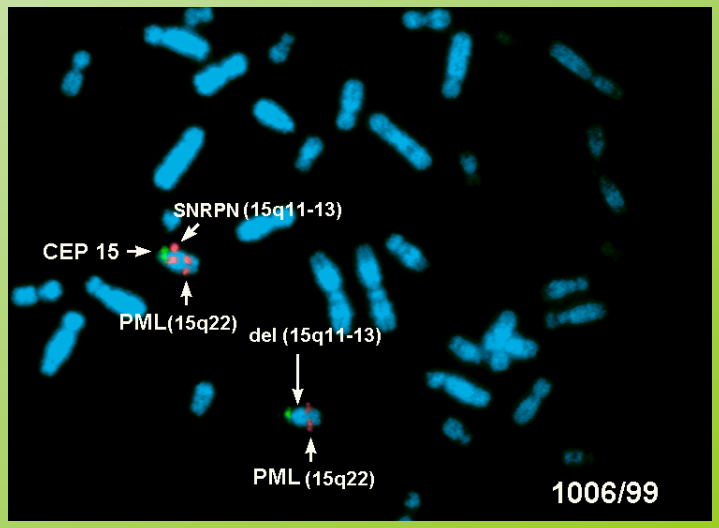
Obr.2: ONCOR- positive



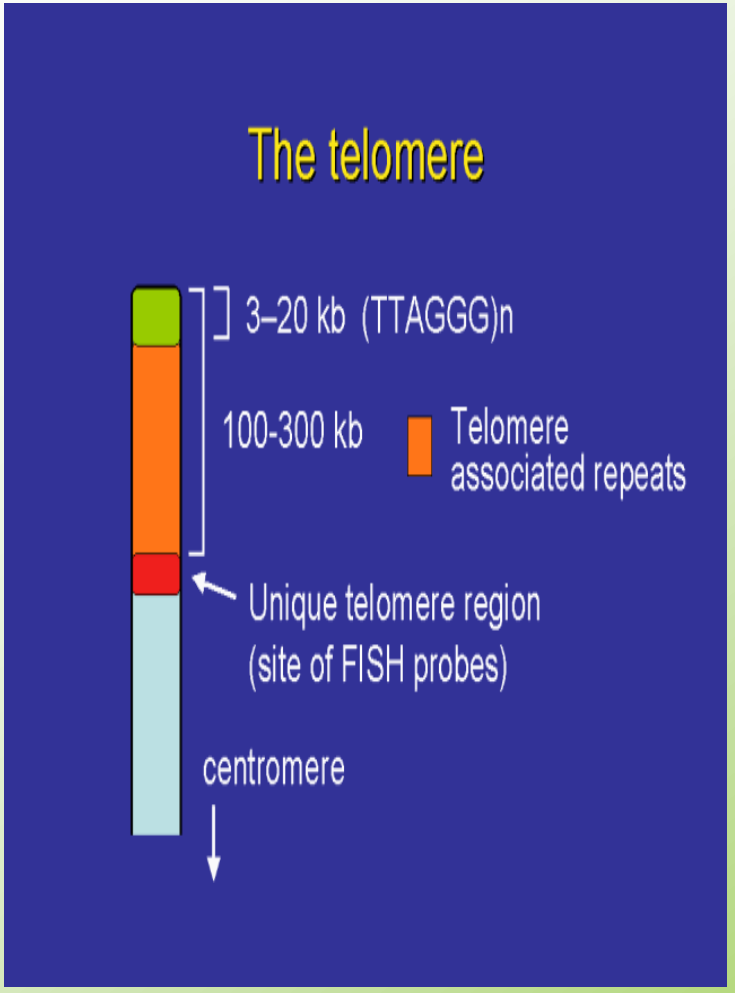
Obr.3: VYSIS - negative



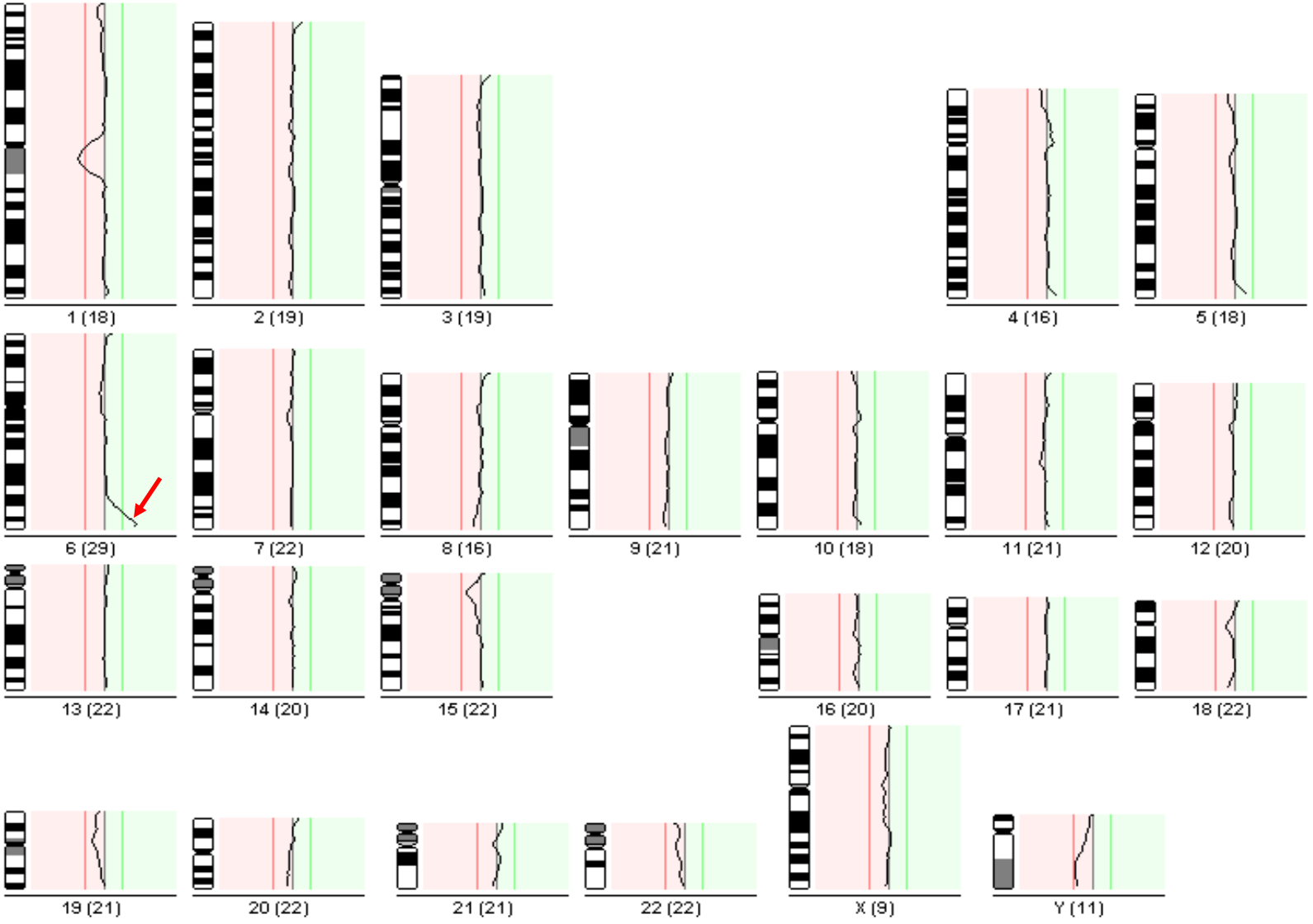
Obr.4: VYSIS - positive



The telomere



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


1 (18)
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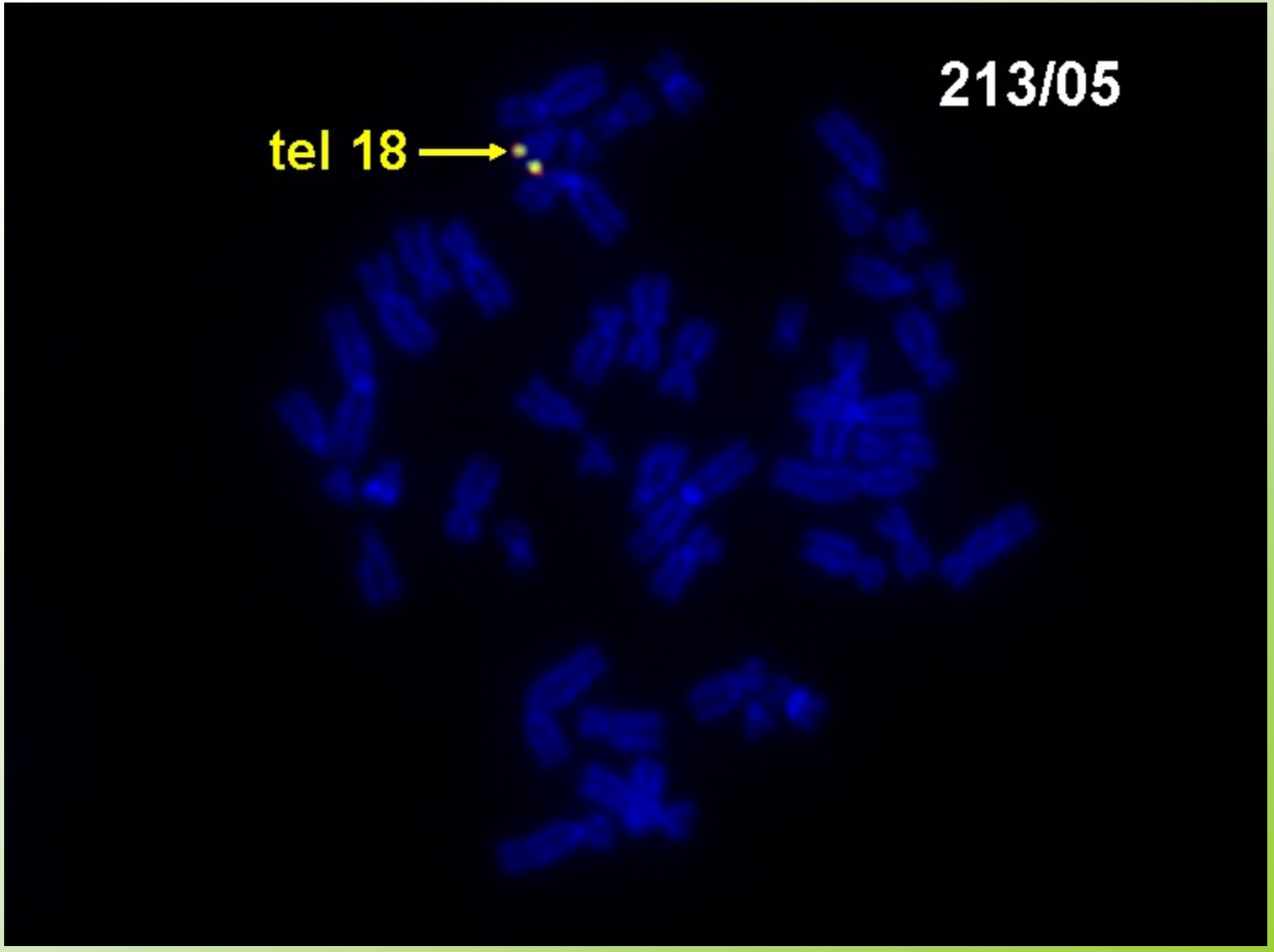
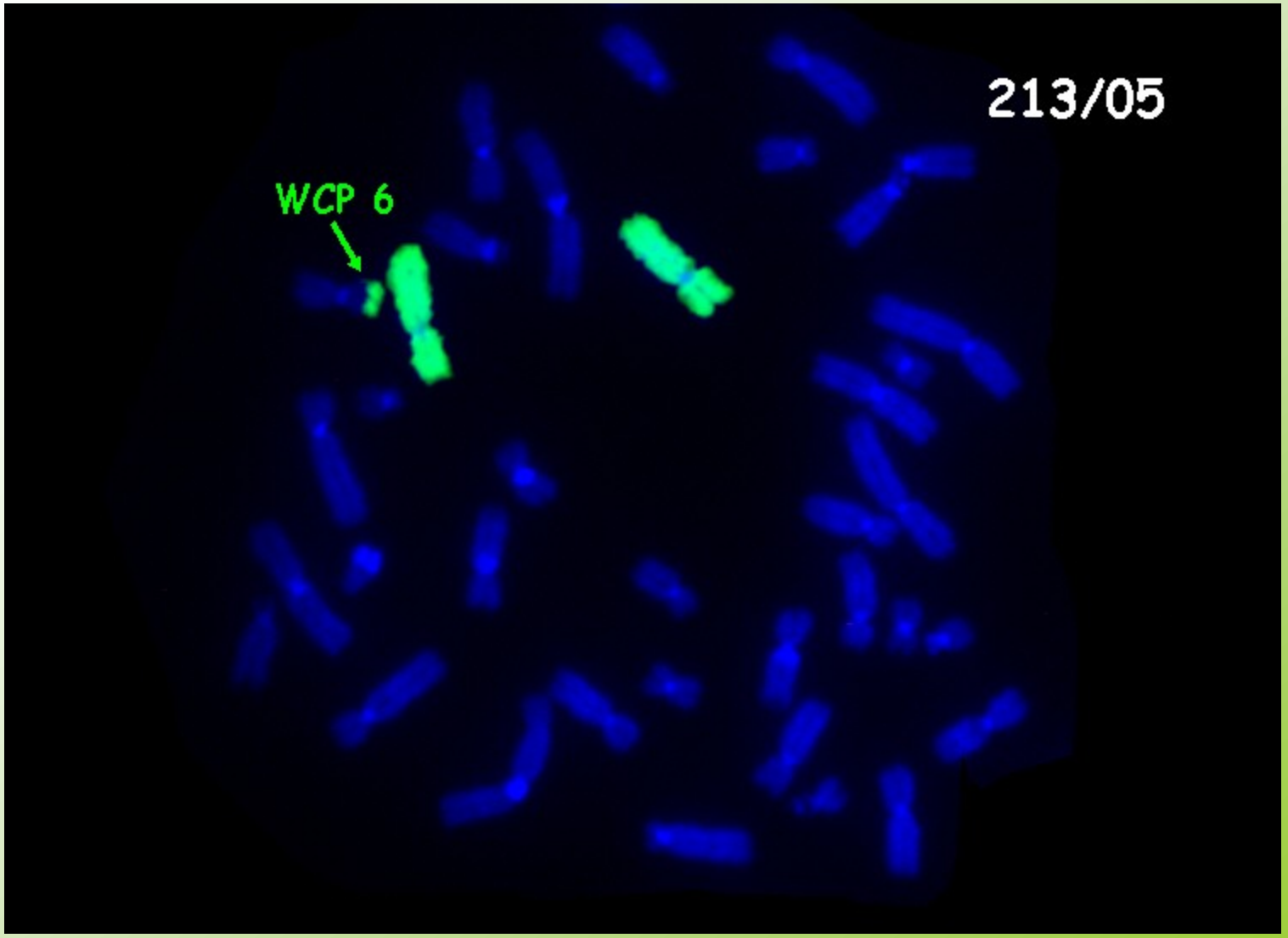
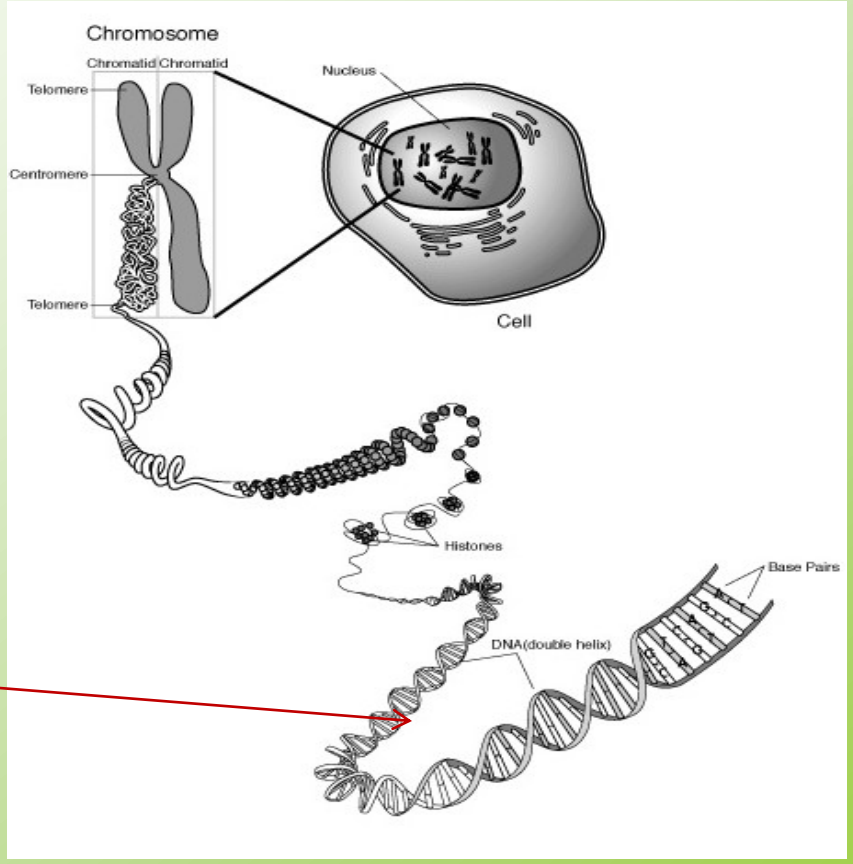
22 (22)
X (9)
Y (11)


213/05
tel 18


213/05
WCP 6

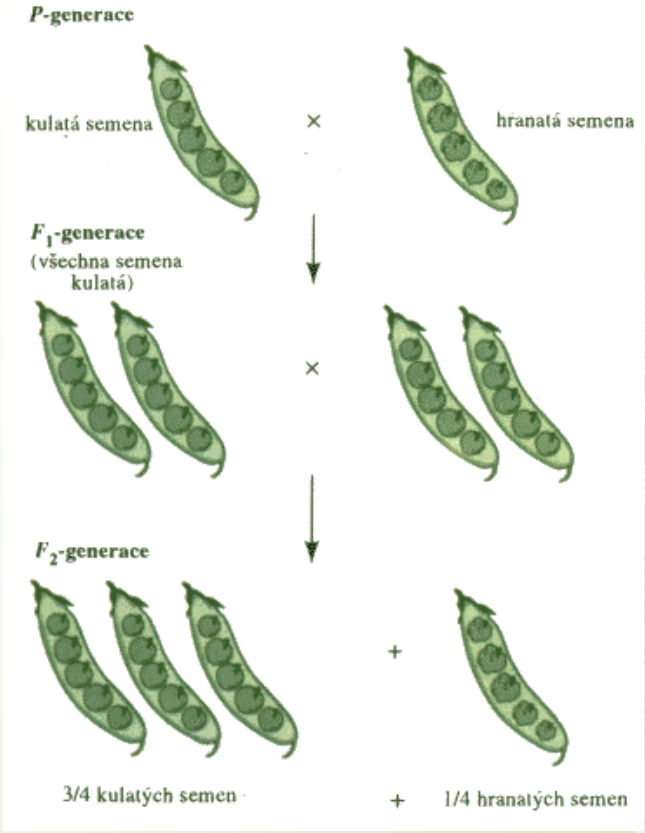
Monogenetic diseases

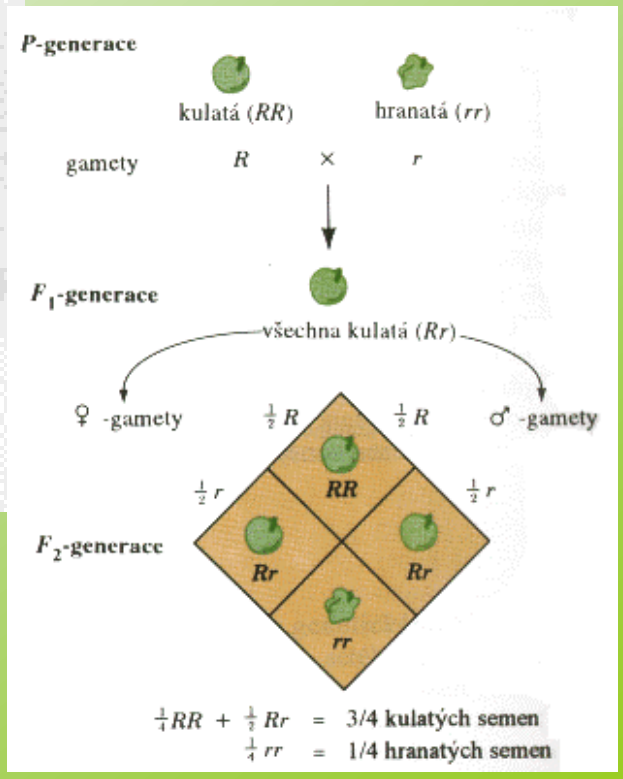


Mendelian inheritance

http://www.ncbi.nlm.nih.gov/omim

OMIM® - Online Mendelian Inheritance in Man®


P-generace
kulatá semena
×
hranatá semena
F1-generace
(všechna semena
kulatá)
×
F2-generace
+
3/4 kulatých semen
+
1/4 hranatých semen

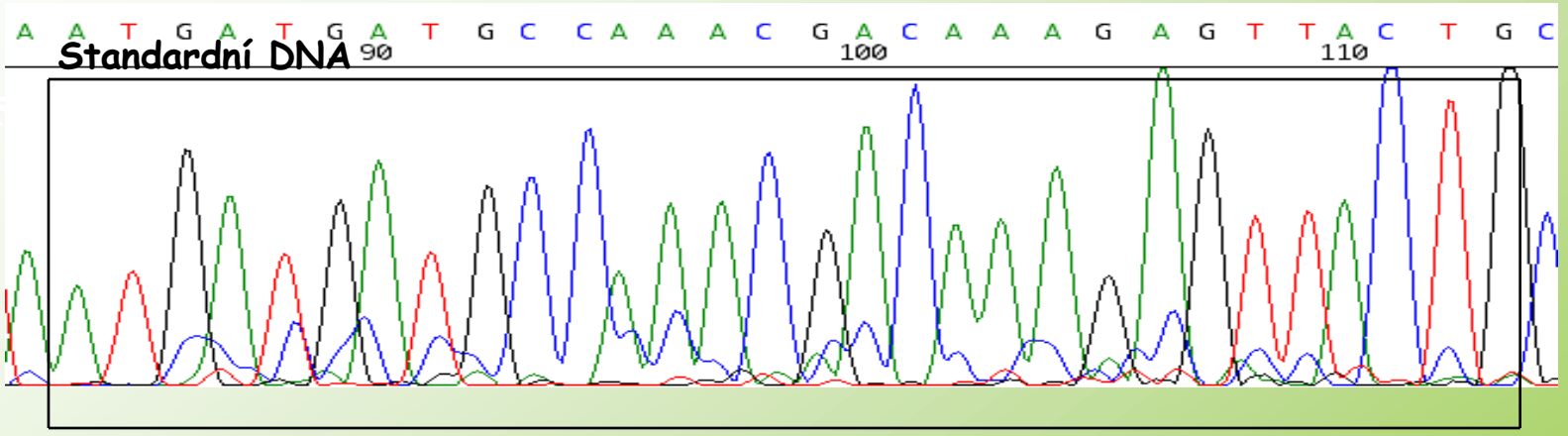

P-generace
kulatá (RR)
hranatá (rr)
gamety
R
×
r
F1-generace
všechna kulatá (Rr)
♀-gamety
½ R
½ R
♂-gamety
½ r
½ r
RR
Rr
Rr
rr
F2-generace
¼RR + ½Rr = 3/4 kulatých semen
¼ rr = 1/4 hranatých semen

Mendel muzeum, MU Brno

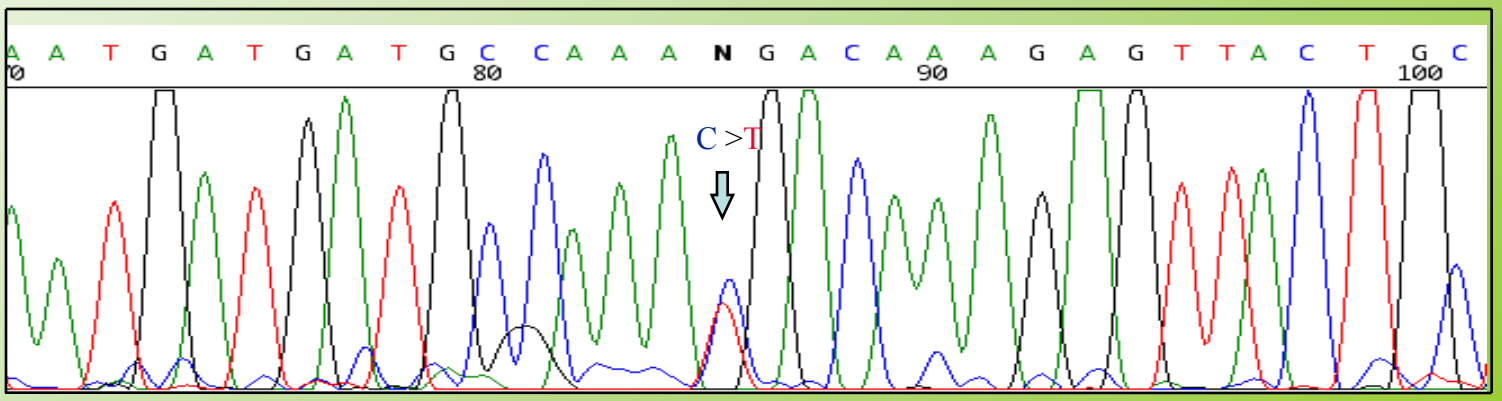
Mendlovo náměstí 1a, Brno

Tuesday to Sunday
10 am.-18 p.m.

DNA analysis



DNA NF1 pacienta, mt C5839T (Arg > STOP)

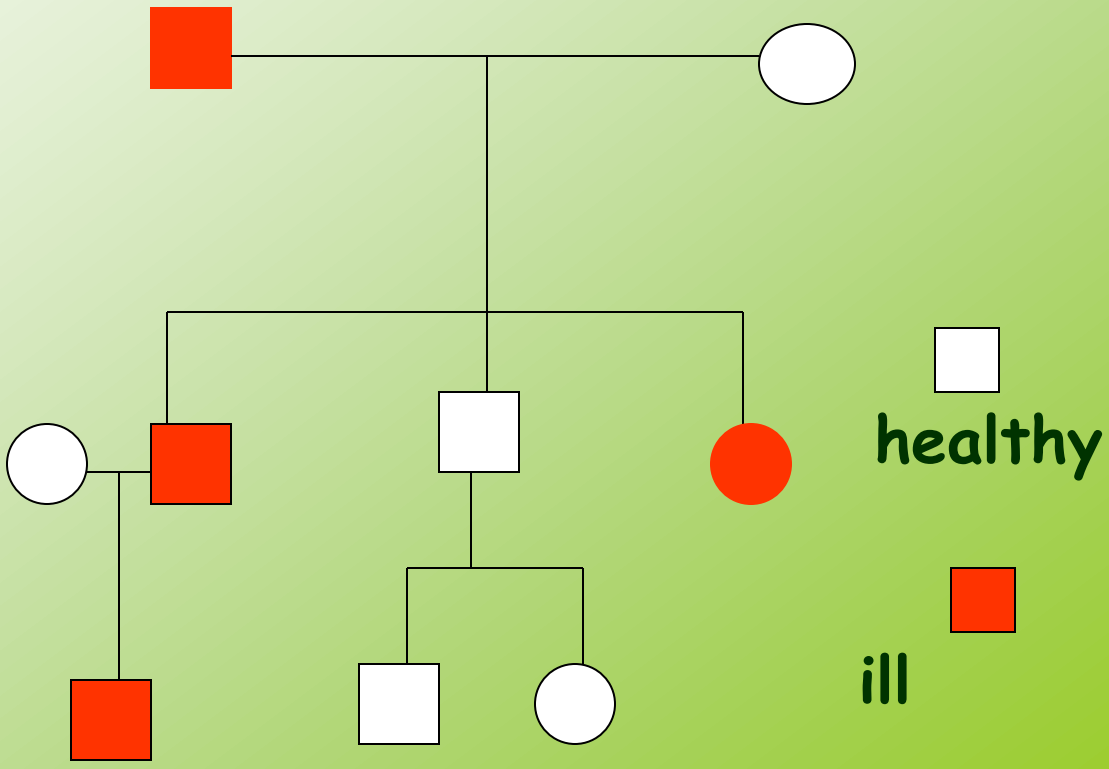


Autosomal Dominant

- 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

Myotonic dystrophy
http://omim.org/entry/160900

Molecular Basis - Caused by a trinucleotide repeat expansion (CTG)n in the dystrophia myotonica-protein kinase gene , 19q13.32 ,OMIM 160900

MYOTONIC DYSTROPHY 1; DM1

- Cataract, Heart Atrial arrhythmias,Heart block,EKG abnormalities
  Biliary Tract Cholelithiasis,Recurrent intestinal pseudoobstruction
  Dysphagia, Poor feeding (congenital form)
  Internal Genitalia (Male) Hypogonadism,Testicular atrophy ,Uncoordinated uterine contraction
  Myotonia (delayed muscle relaxation after contraction)
  Weakness
  Electromyography shows myotonic discharges
  Wasting, especially temporal, neck, and facial muscles
  Respiratory distress (congenital form)
  Bilateral facial weakness (congenital form)
  Absence of myotonia in infancy (congenital form)
  Mild cognitive deterioration in adults,Speech disability
  Excessive daytime sleepiness, Reduced sleep latency, Sleep-onset REM
  Hypotonia (congenital form), Severe mental retardation (congenital form)
  Poor feeding (congenital form form)
  Prenatal Manifestations -Reduced fetal movements (congenital form)
  Amniotic Fluid Polyhydramnios (congenital form)
  Miscellaneous - Genetic anticipation occurs
  Prevalence of in 1 in 8,000

Neurofibromatosis 1,17q11.2
http://omim.org/entry/162200

Neurofibromatosis 1,17q11.2

- Macrocephaly
  Sphenoid dysplasia
  Lisch nodules (iris hamartomas), Glaucoma, Hypertelorism
  Renal artery stenosis, Hypertension
  Scoliosis, Spina bifida, Pseudoarthrosis,Thinning of long bone cortex
  Local bony overgrowth
  Skin Neurofibromas, Plexiform neurofibroma, Cafe-au-lait spots
  Axillary freckling, Inguinal freckling
  Mental retardation, 30% learning disabilities, 10% mild mental retardation
  Aqueductal stenosis, Hydrocephalus
  Neoplasia - Optic glioma, Meningioma, Hypothalamic tumor, Neurofibrosarcoma, Rhabdomyosarcoma, Duodenal carcinoid Somatostatinoma, Parathyroid adenoma, Pheochromocytoma Pilocytic astrocytoma, Malignant peripheral nerve sheath tumors Tumors at multiple other sites including CNS

- Miscellaneous - 50% of cases are caused by new mutations

- Molecular Basis - Caused by mutations in the neurofibromin gene (NF1, OMIM 162200)

ANKYLOBLEPHARON-ECTODERMAL DEFECTS-CLEFT LIP/PALATE, 3q28

- Hay-Wells
- Autosomal dominant
  Scalp erosions
  Oval face
  Maxillary hypoplasia
  Conductive hearing loss, Atretic external auditory canal
  Cup-shaped auricle, Ankyloblepharon filiforme adnatum
  Lacrimal duct atresia, Sparse to absent eyelashes
  Conjunctivitis, Blepharitis
  Broadened nasal bridge
  Cleft lip, Cleft palate, Conical teeth, Widely spaced teeth
  Hypodontia, Selective tooth agenesis
  Ventricular septal defect, Vascular Patent ductus arteriosus
  Supernumerary nipples
  (Male) Hypospadias, Micropenis
  (Female) Vaginal dryness

ANKYLOBLEPHARON-ECTODERMAL DEFECTS-CLEFT LIP/PALATE, 3q28

Feet 2-3 toe soft tissue syndactyly

Skin Red, cracking, peeling skin at birth, Palmar and plantar, keratoderma, Hyperkeratosis, Hyperpigmentation, Partial anhidrosis
Scalp erosions, Absent nails, Dystrophic nails, Hyperconvex nails
Wiry, sparse hair, Patchy alopecia, Sparse to absent eyelashes
Sparse body hair, Patchy alopecia
Normal intelligence

- Miscellaneous - Allelic to EEC3 (604292), SHFM4 (605289), ADULT syndrome (103285), limb-mammary syndrome (603543), and Rapp-Hodgkin syndrome (129400)

- Molecular Basis - Caused by mutations in the tumor protein p63 gene (TP63)

Achondroplasia
http://omim.org/entry/100800

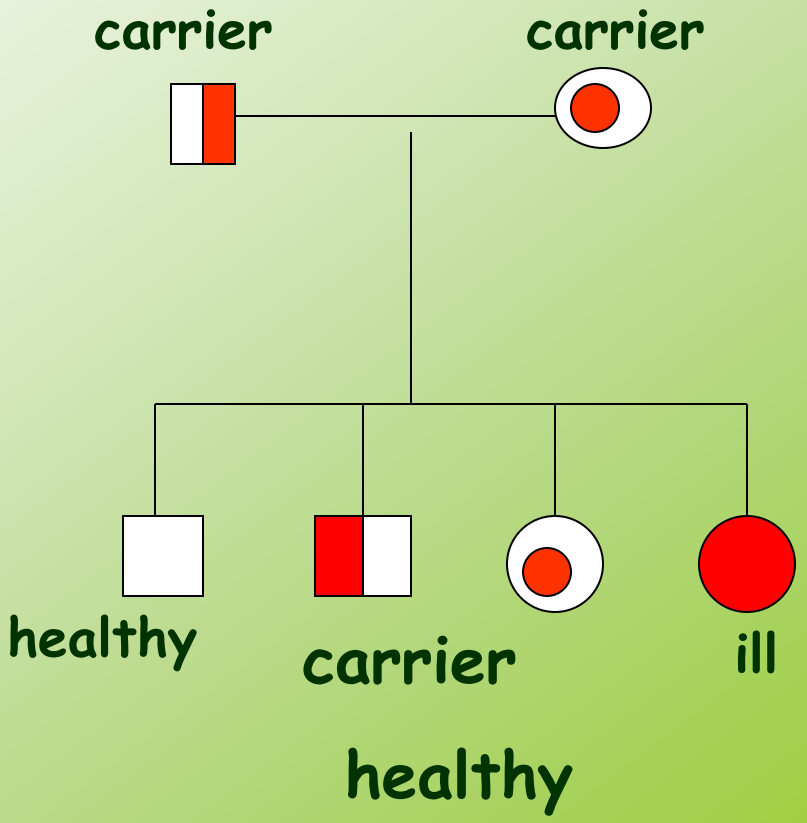
- Autosomal dominant with complete penetrance
- 80% cases new mutations
- 99+% of the mutations are FGFR3, G380R
- Paternal age effect
- Caused by mutation in the fibroblast growth factor receptor-3 gene (FGFR3)

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)

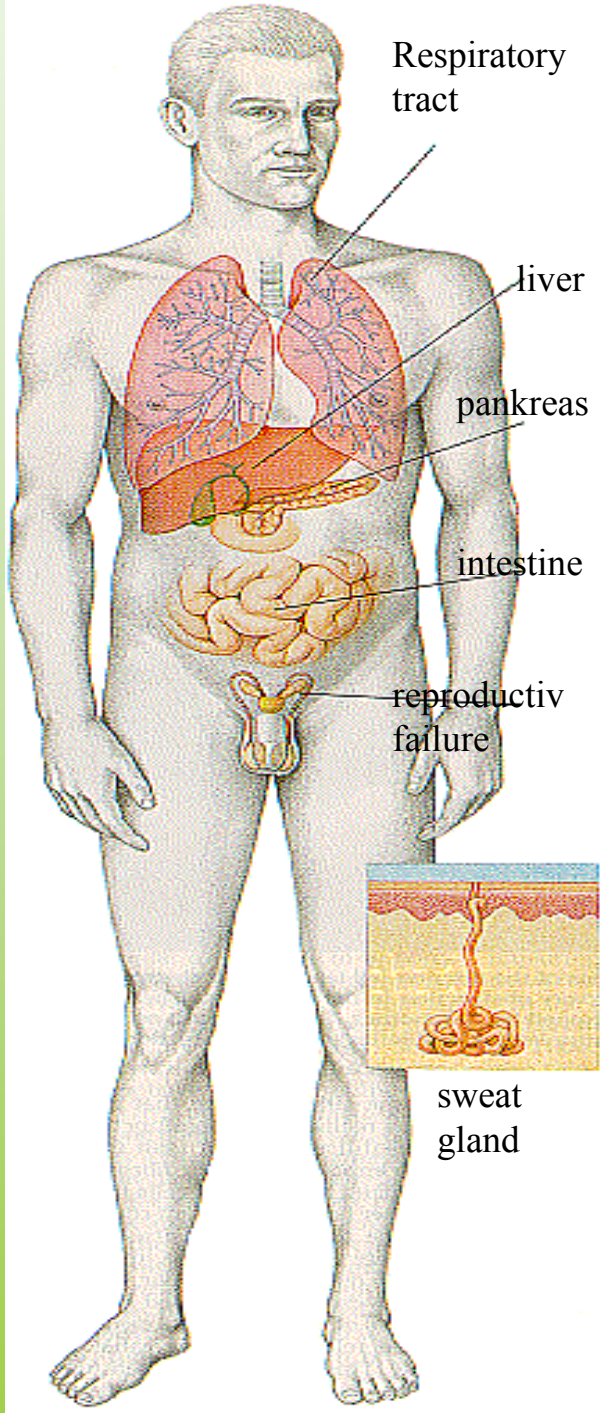
- Phenylketounria (1/40)
- Congenital adrenal hyperplasia (1/40)
- Spinal muscular atrophy (1/60-80)

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

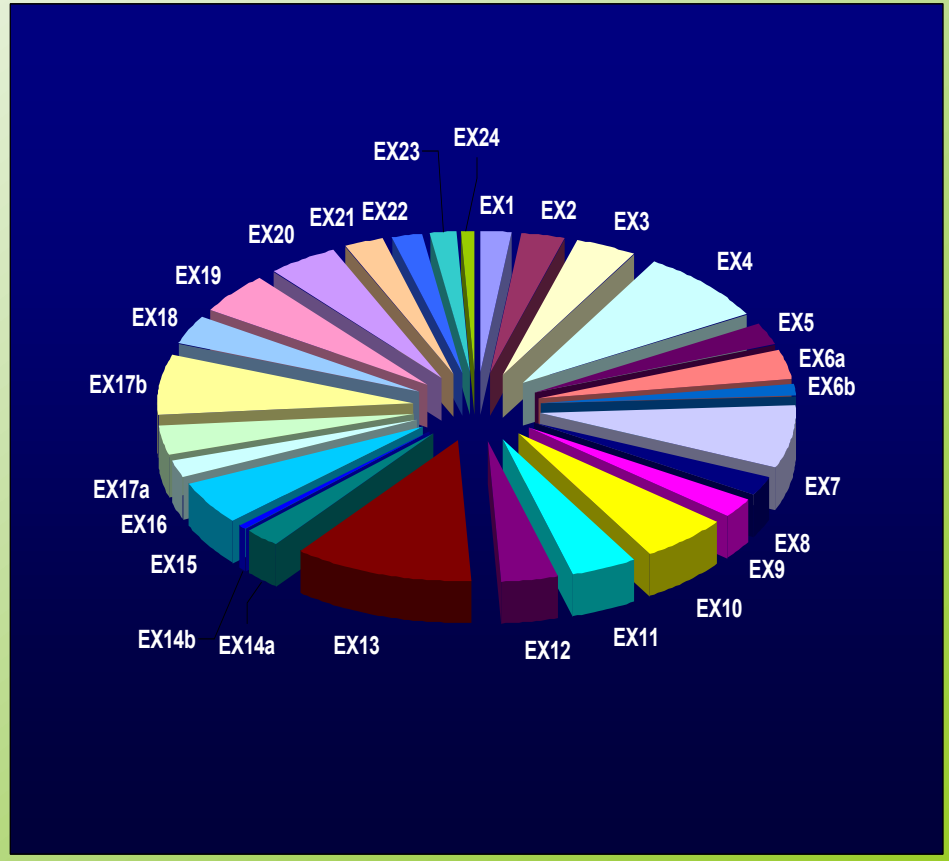
Cystic fibrosis http://omim.org/entry/602421

- disease affecting multiple organs



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

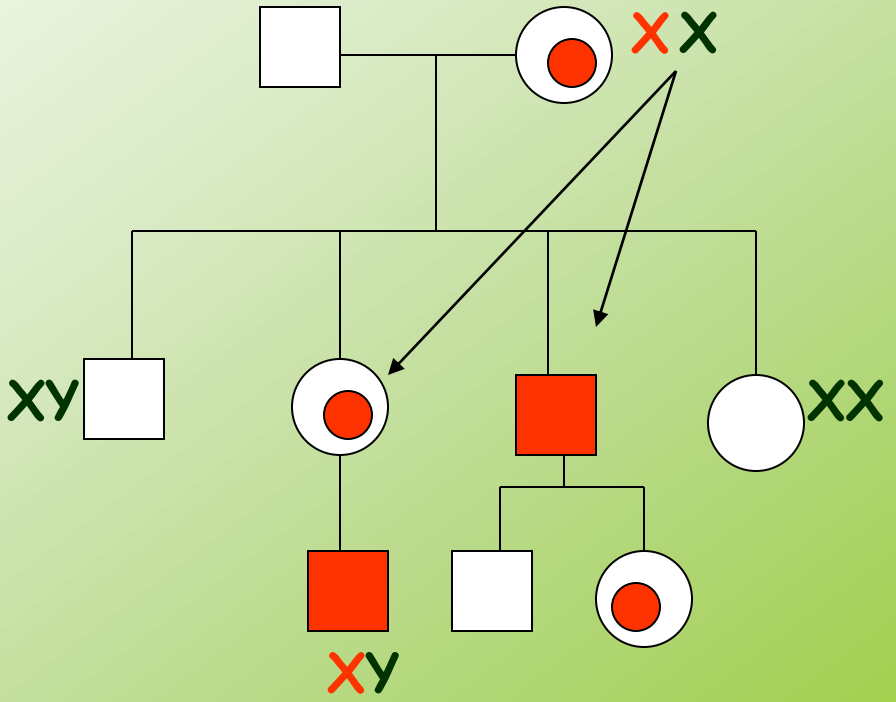
- Females are not affected as severaly as males or are not affected
- An affected male cannot transmit the train to his sons, becose the trait is on X-chromosome, and the father must necessarily transmit his Y-chromosome to a son
- All of the daughters of an affected male must be carriers, because the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

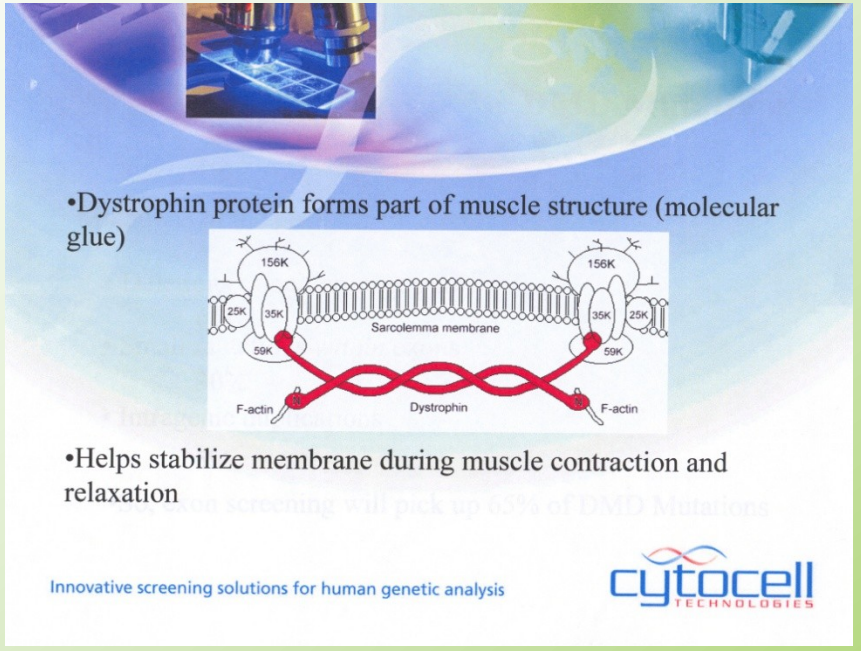
X- recesive inheritance

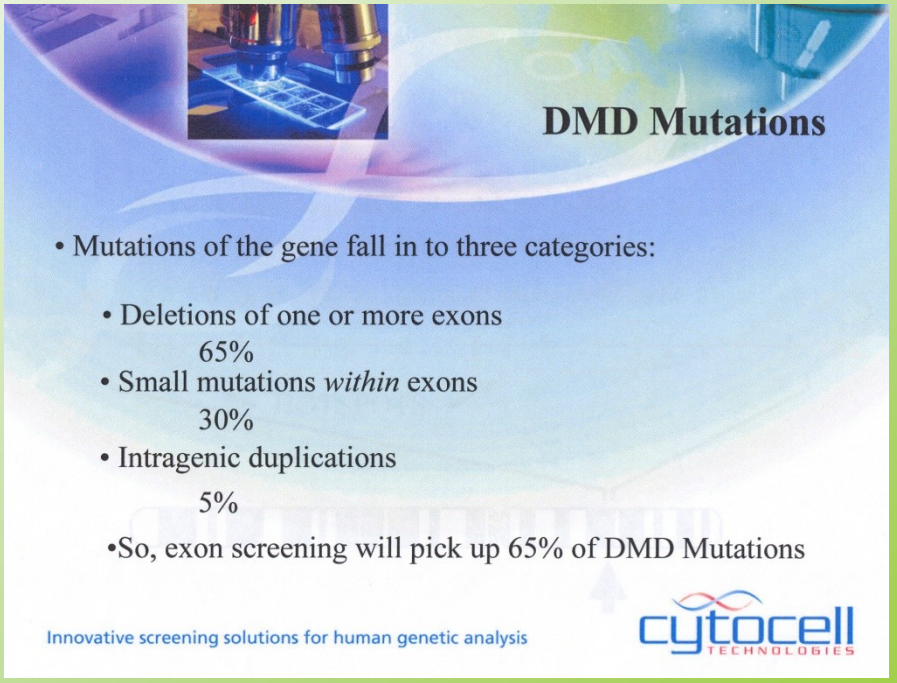


XR - diseases

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

Muscular dystrophy Duchenn/Becker
http://omim.org/entry/310200
Xp21,2-Xp21,1





DMD

- X-linked recessive
  Red-green color defect in many patients with deletion downstream of exon 30
  Cardiomyopathy, dilated, Congestive heart failure
  Pulmonary hypoventilation, Respiratory failure
  Increased lordosis, Scoliosis, Limbs Flexion contractures
  Calf muscle pseudohypertrophy, Weakness
  Mental retardation, mild (20% have more severe mental retardation)
  Hypotonia, Waddling gait, Hyporeflexia, Positive Gowers sign
  Laboratory Abnormalities - High serum creatine kinase
  Abnormal electrocardiogram
  Absent dystrophin on muscle biopsy
  Usual onset before age 6 years and death by age 20/40
  Incidence of 1 in 3,500 boys
  About 20% of female mutation carriers may show mild muscle weakness
  About 8% of female mutation carriers develop dilated cardiomyopathy
  Caused by mutation in the dystrophin gene (DMD)

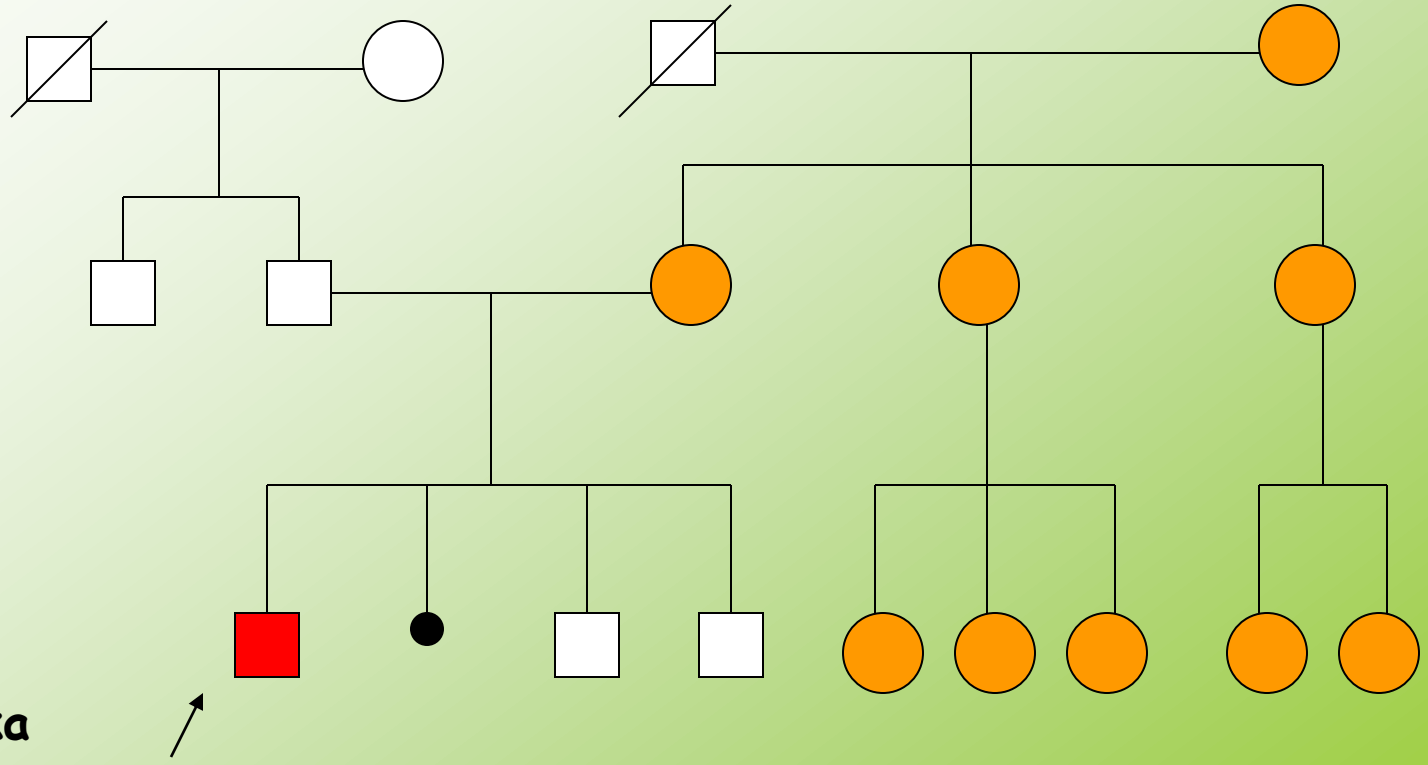
Hemophilia A, Xq28
http://omim.org/entry/306700

- X-linked recessive

- Limbs – Hemarthroses, Degenerative joint disease
  Skin Ecchymoses common
  Petechiae and purpura do not occur
  Laboratory Abnormalities - Factor VIII deficiency
  PTT prolonged
  PT normal
  Bleeding time normal
  Platelet count normal
  Platelet function normal
  Partial factor VIII deficiency in heterozygous carriers
  Persistent bleeding after trauma

- Molecular Basis - Caused by mutations in the coagulation factor VIII gene (F8)

Hemophilia A



proband

přenašečka

susp. přenašečka

není přenašečka

Pedegree

I
II
III
IV
V
VI
VII
VIII
Albert
Victoria
31
2
33
23
21
56
4
Alexei
14
31
20
Elizabeth II
Charles
= hemophilia
= age at death
= carrier for hemophilia

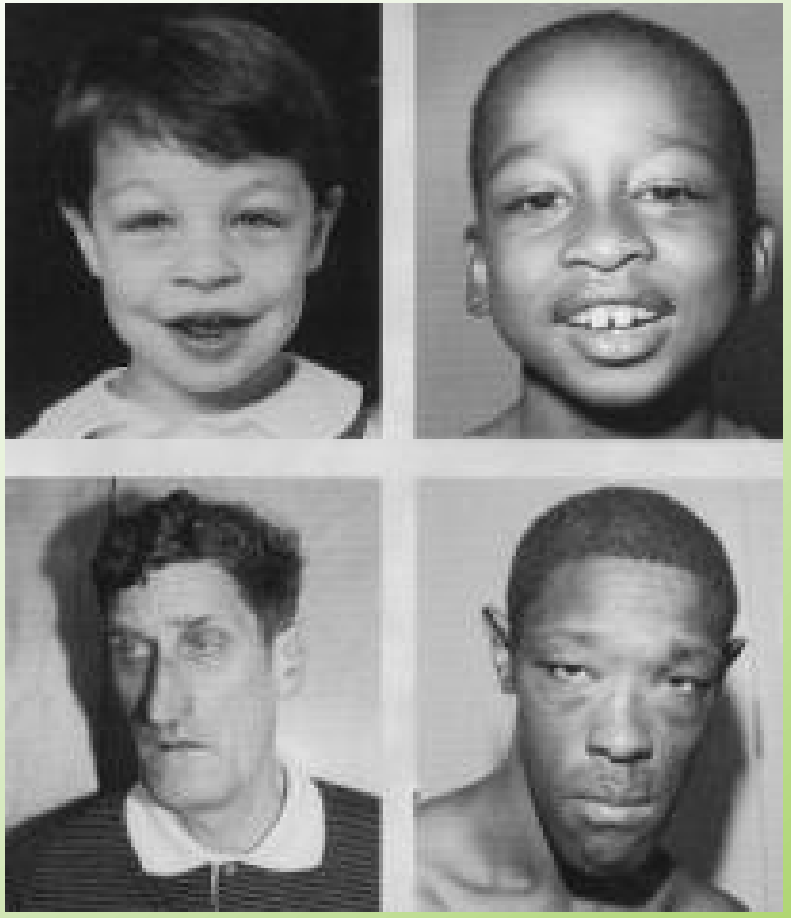
Hemophilia B, Xq27.1
http://omim.org/entry/306900

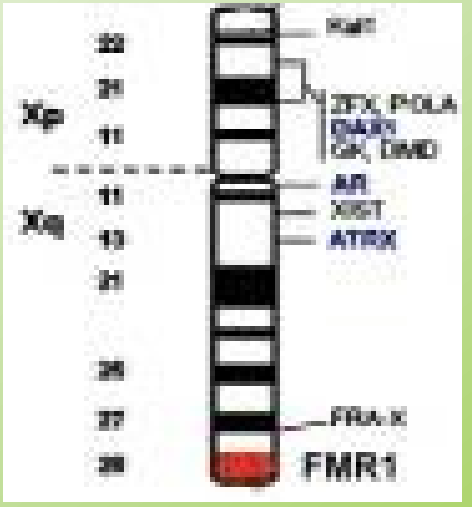
- X-linked recessive

- Hematology - Factor IX deficiency
  Laboratory Abnormalities - Factor IX deficiency
  PTT prolonged
  PT normal
  Platelet count normal
  Platelet function normal
  Miscellaneous - Patient with factor IX Leyden variants have bleeding in childhood that improves or resolves after puberty
  Patients with hemophilia B(M) variants also have prolonged PT
  Phenotypically indistinguishable from hemophilia A (306700)

- Molecular Basis - Caused by mutation in the coagulation factor IX gene (F9)

Fragile X chromosome
X-linked mental retardation





X-linked dominant

- Incontinentia pigmenti
- http://omim.org/entry/308300
- Familial incontinentia pigmenti (IP) is a genodermatosis that segregates as an X-linked dominant disorder and is usually lethal prenatally in males.
- In affected females it causes highly variable abnormalities of the skin, hair, nails, teeth, eyes, and central nervous system. The prominent skin signs occur in 4 classic cutaneous stages: perinatal inflammatory vesicles, verrucous patches, a distinctive pattern of hyperpigmentation, and dermal scarring. Cells expressing the mutated X chromosome are eliminated selectively around the time of birth, so females with IP exhibit extremely skewed X-inactivation.

- Familial incontinentia pigmenti is caused by mutations in the NEMO gene and is here referred to as IP2, or 'classical' incontinentia pigmenti. Sporadic incontinentia pigmenti, the so-called IP1, which maps to Xp11, is categorized as hypomelanosis of Ito

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 firstdegree relatives	50
Sib of isolated case	2 - 3
Second-degree relatives	1 – 2
Offsprin- affected father	2 - 3
Offsprin – 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

Teratogeny

- 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 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 microcephaly
- 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

Prenatal diagnosis

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

Prenatal screening (ČR)

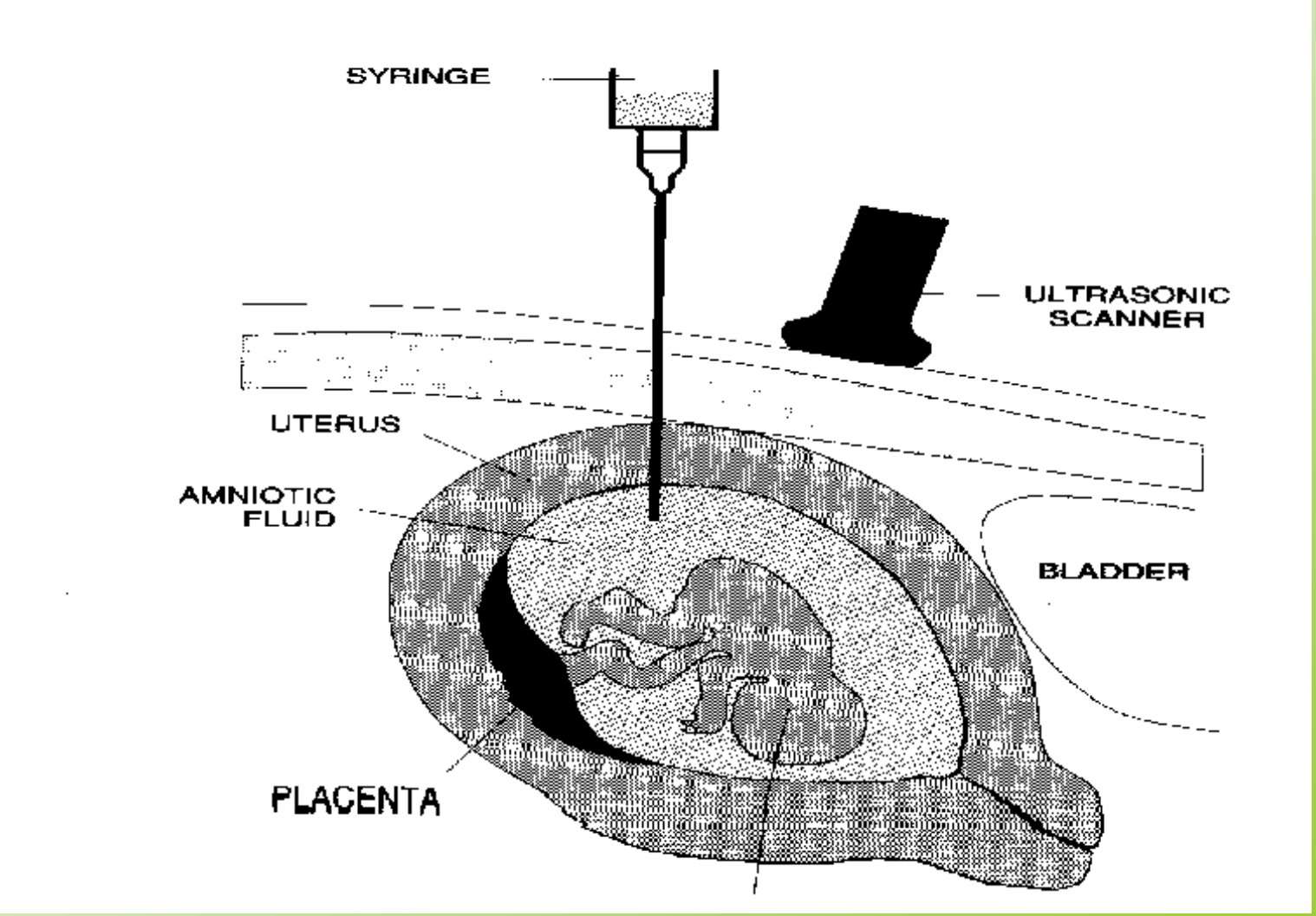
- Ultrasound (12. - 2 0. - 33. week)
- Ultrasound 20.week – cong. defect
- Ultrasound 20-22. week – cong. heart defect

- Free beta hCG, PAPP-A, US-NT:10-14. week of gestation
- AFP, hCG, uE3 - 16.-18.week of gestation

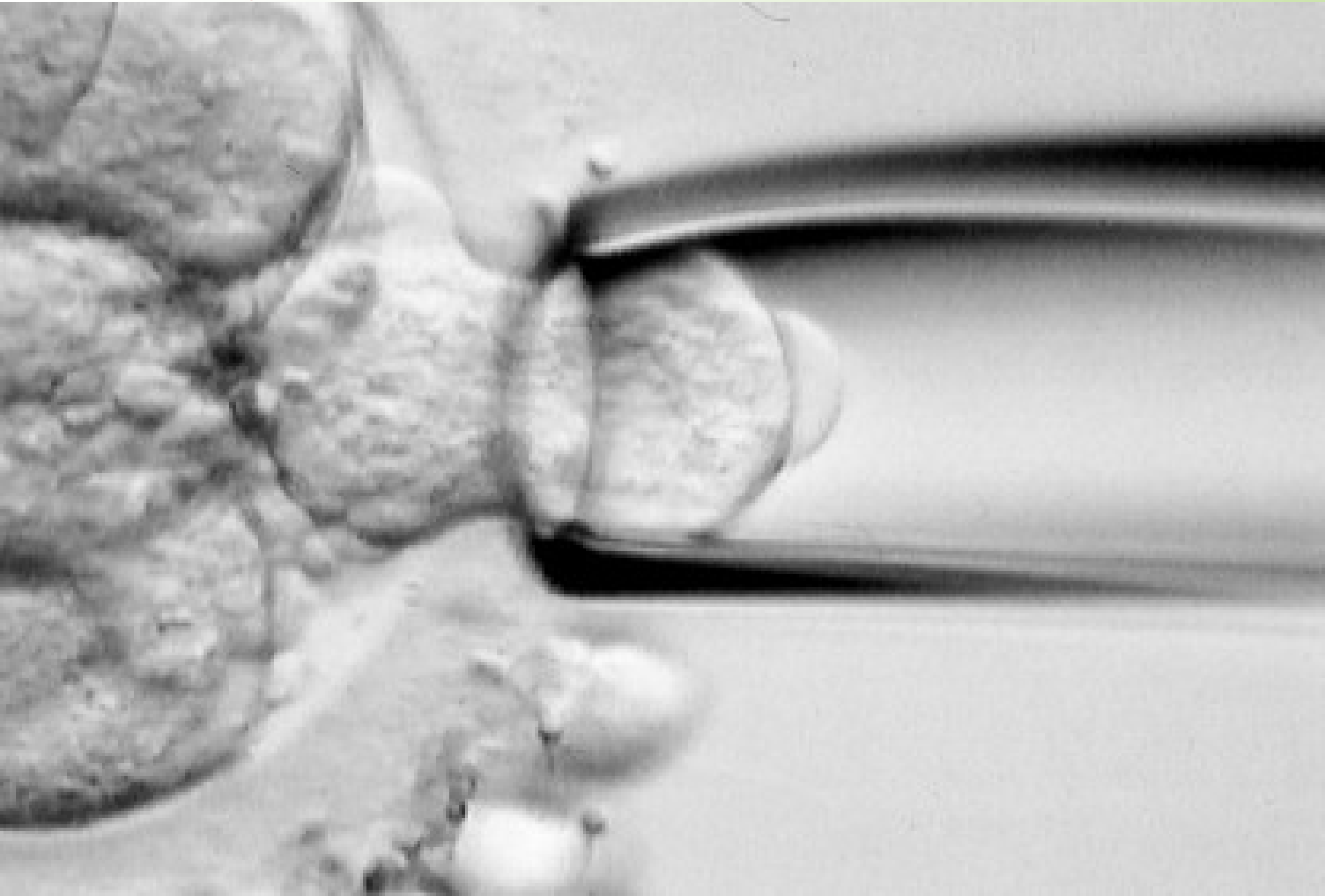
Indications for prenatal diagnosis / counselling

- Advanced maternal age (35)
- Risk factors – US – 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

Amniocentesis



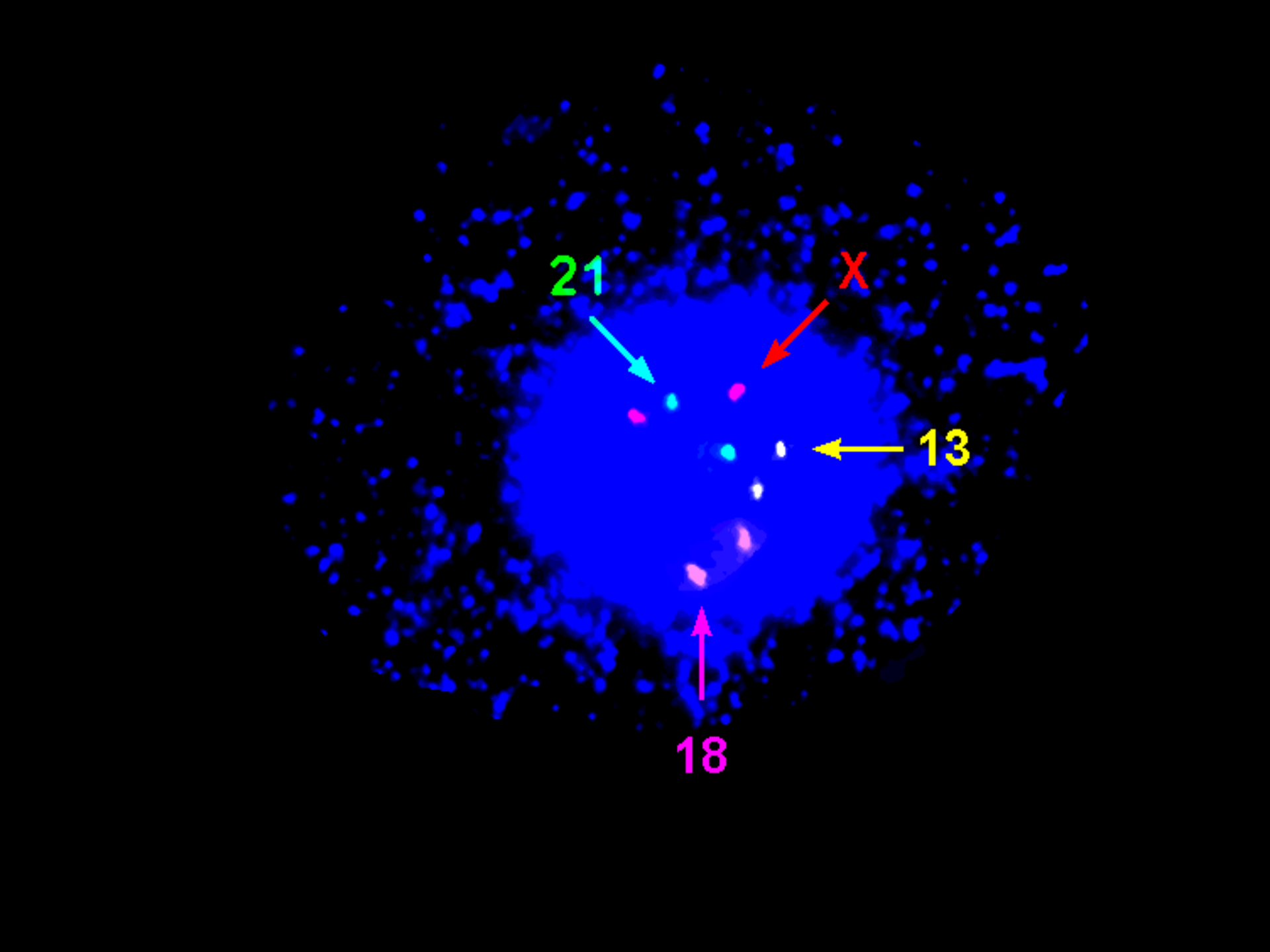
Preimplatation Genetic Diagnostics



PG Diagnostic
X
PG Screening

- PGD high genetic risk

- PGS frequent aneuploidies


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?

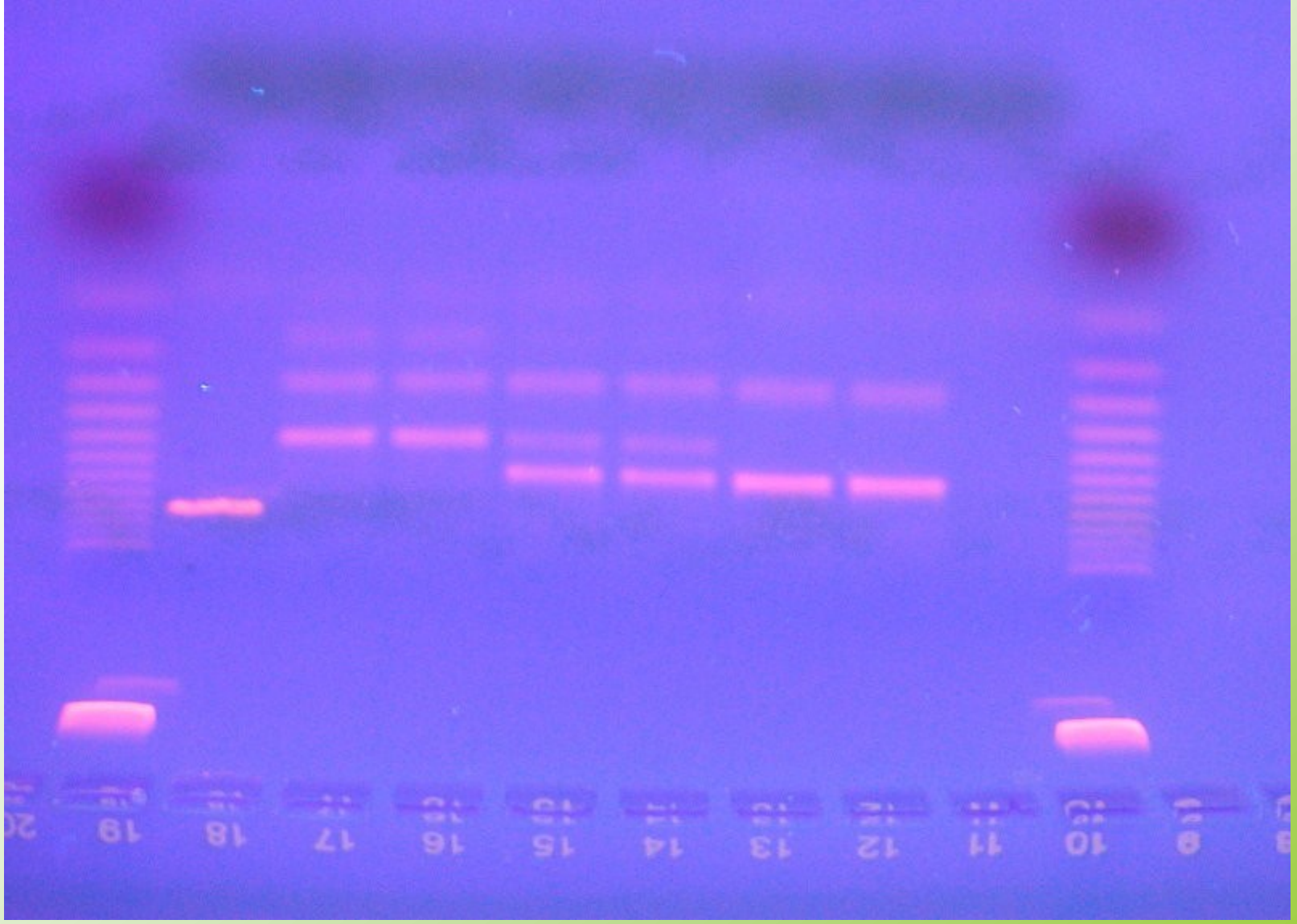
- Genetic testing before use of metods of asisted reproduction.

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.

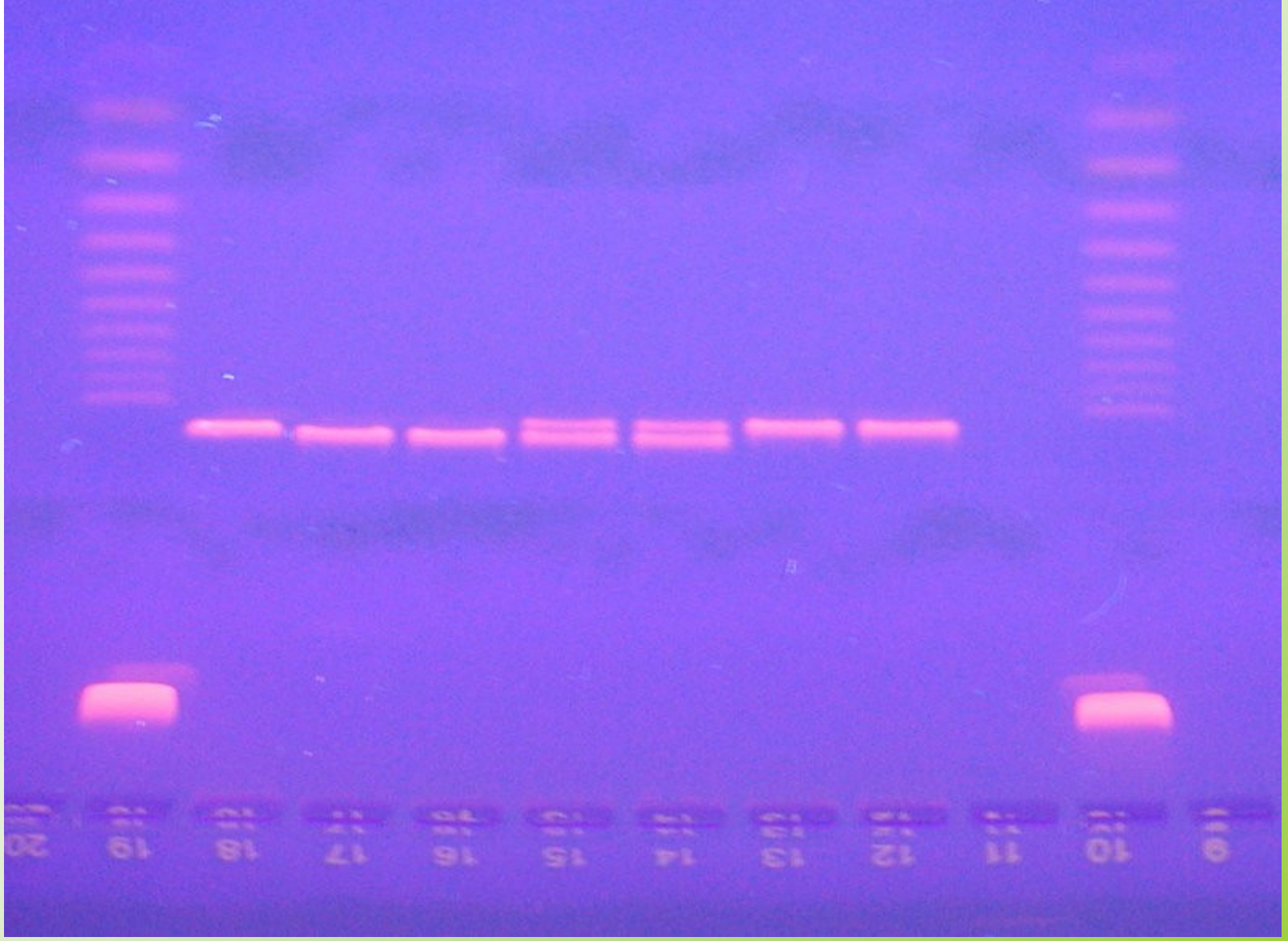
Infertility

- 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 - mutation G1691A f II:

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

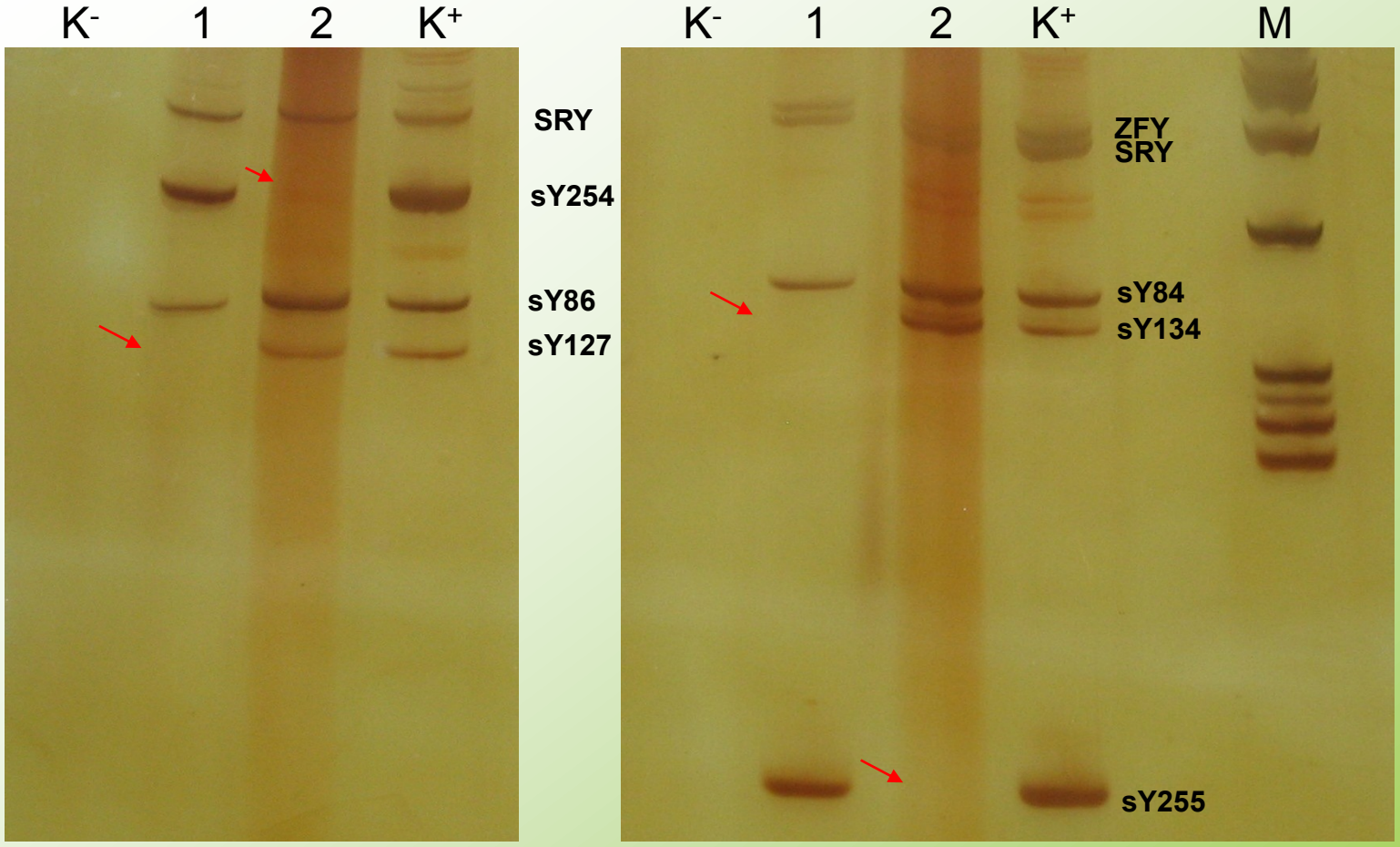


Mutation G20210A factor II (Prothrombin):

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

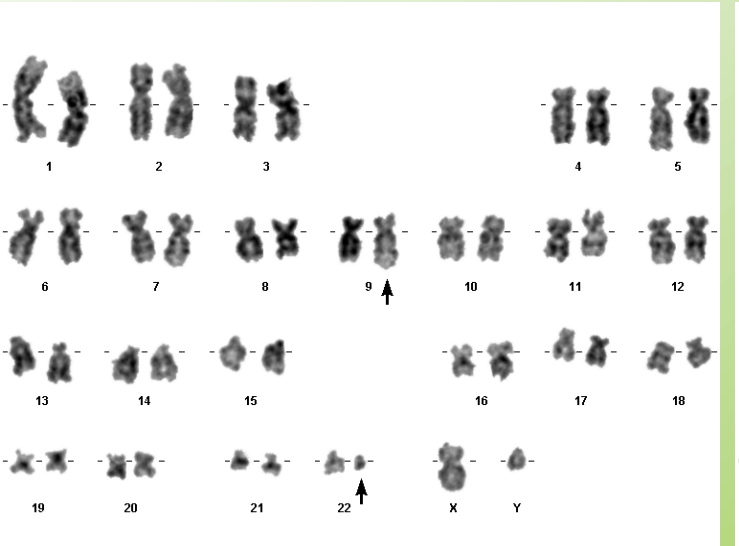
AZFc: sY254, sY255

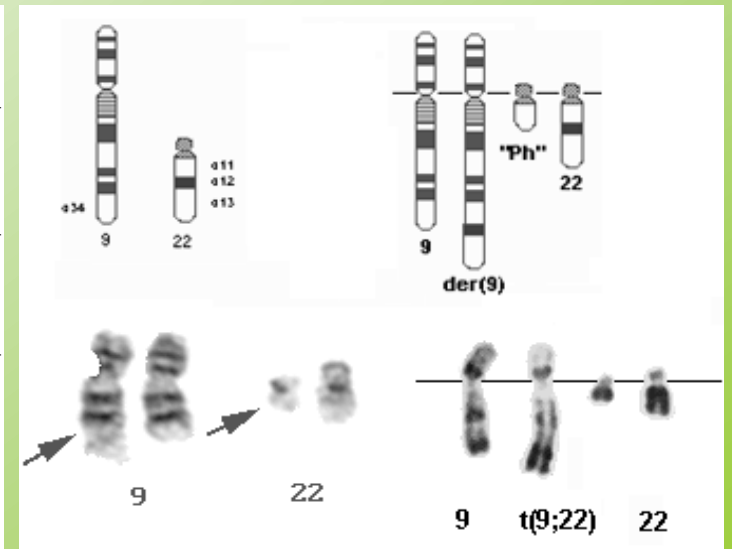
pacient	1	2
delece	AZFb	AZFc

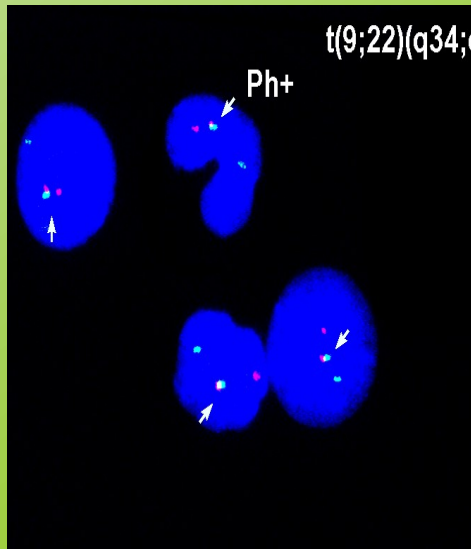
Genetic risk in cancer

Genetic testing in oncologic patients

- Diagnosis
- Therapy
- Prognosis
- Minimal residual disease



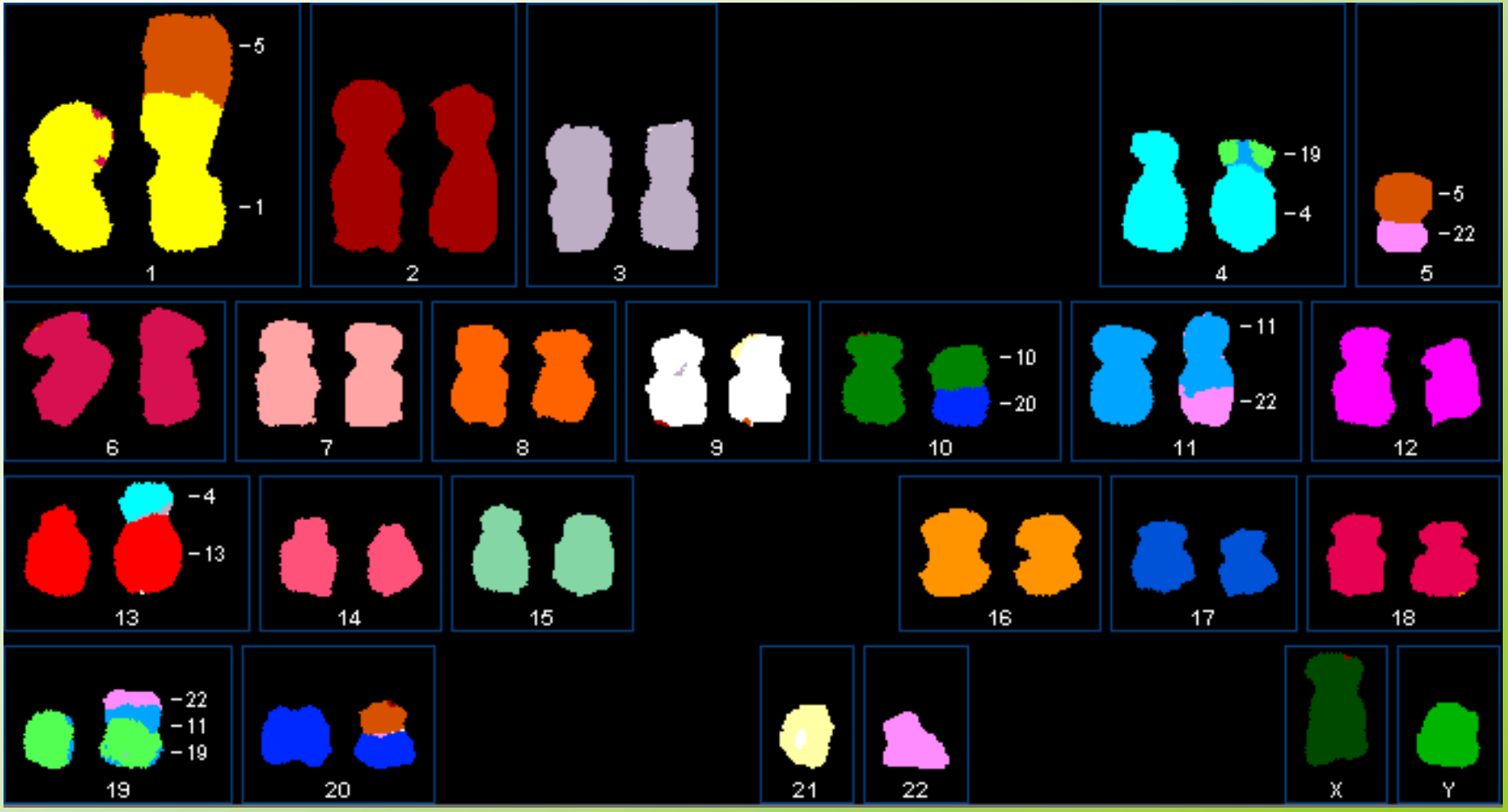




SKY: t(2;13), t(4;8), t(6;16), t(8;11)

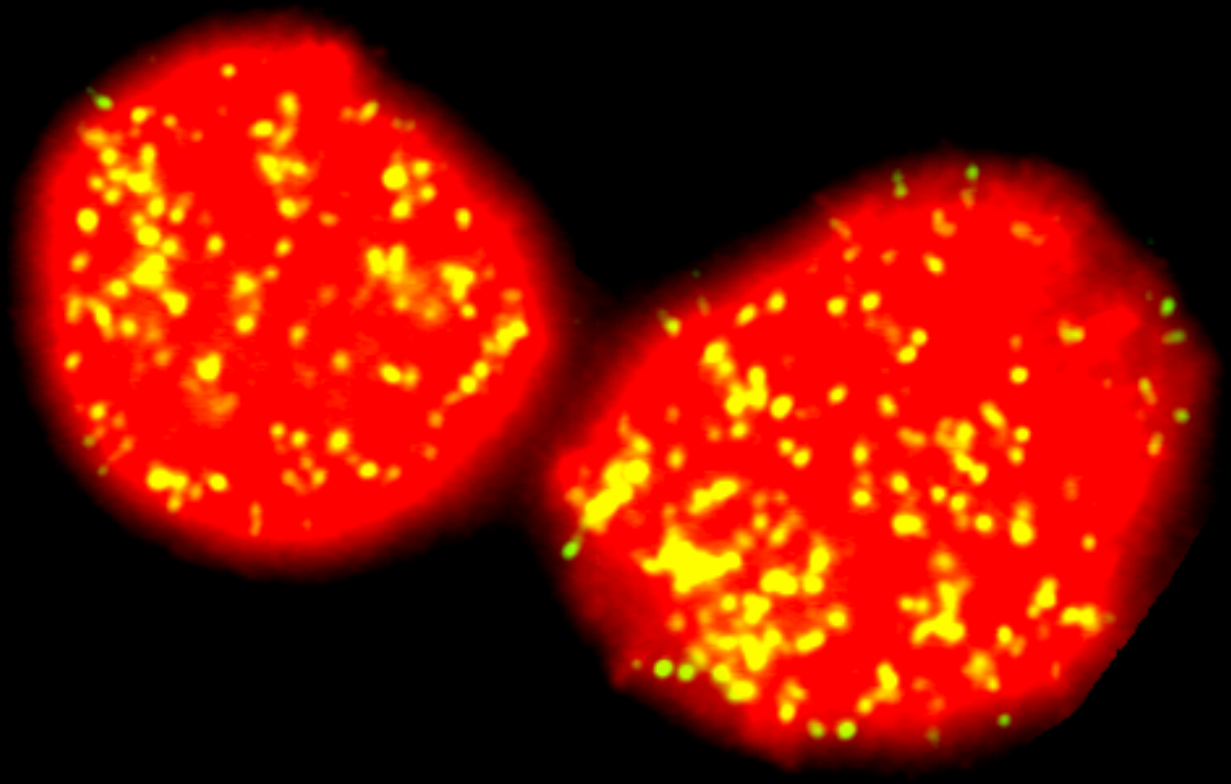
a patient with dg. Neuroblastoma
t(11;22) is typical change in Ewing sarcoma

Spectral karyotyping



N-myc

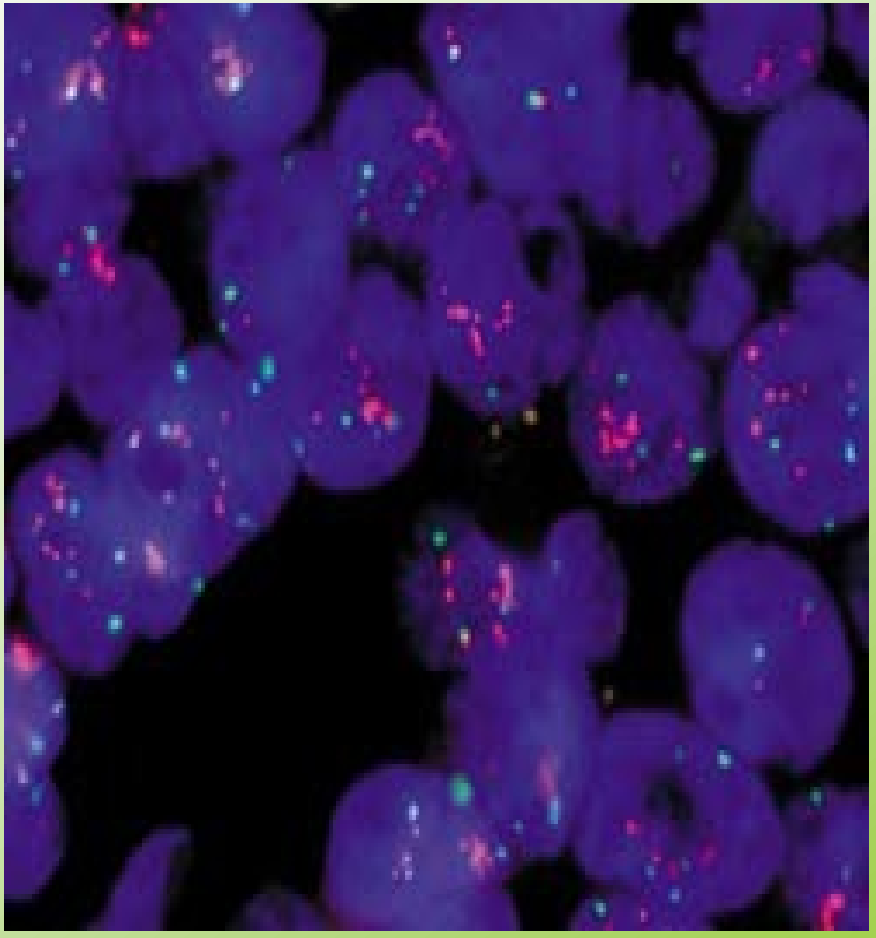
N-myc > 50 copies



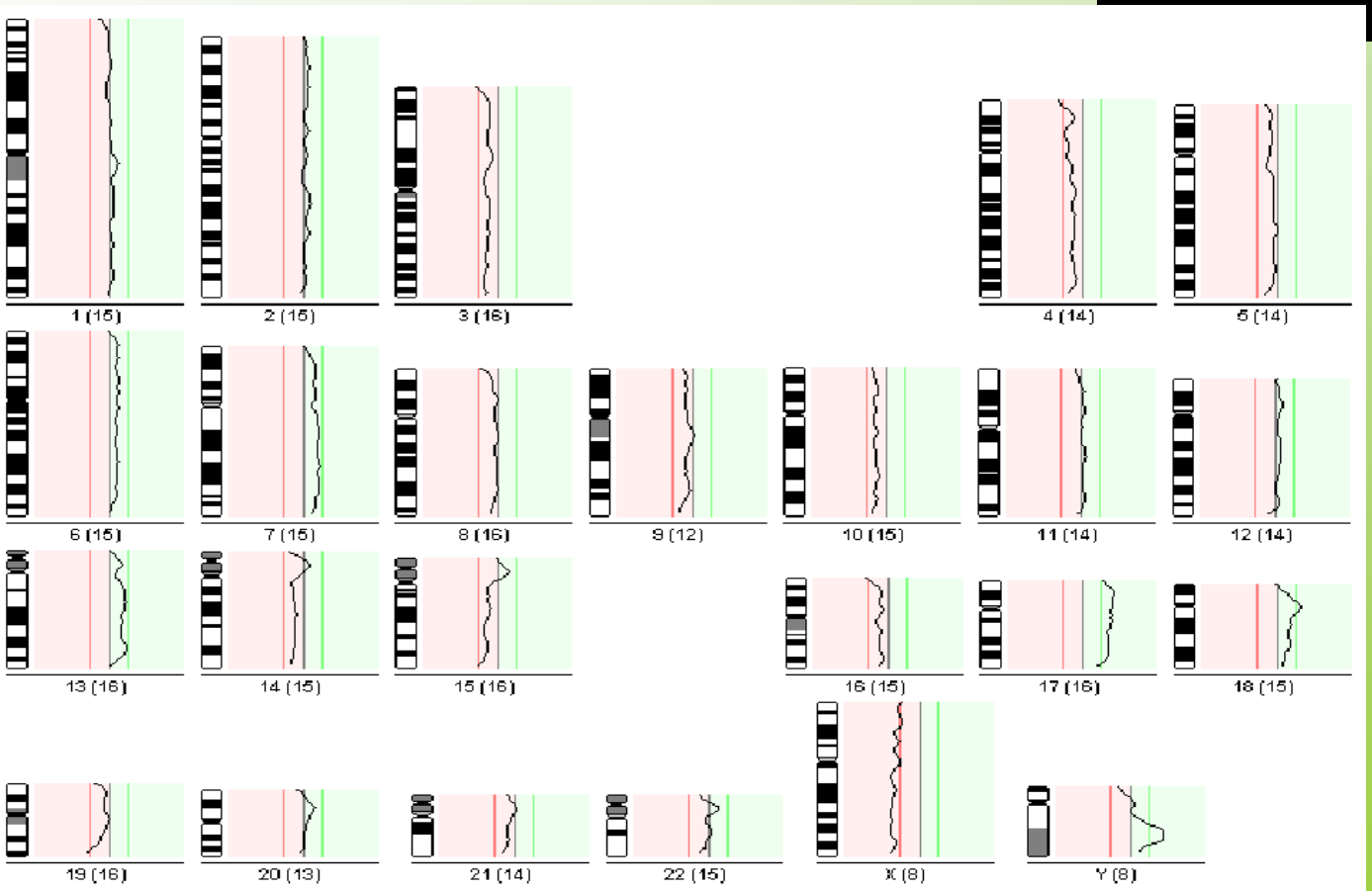
Tumor

Neuroblastoma

HER -2 gene breast cancer

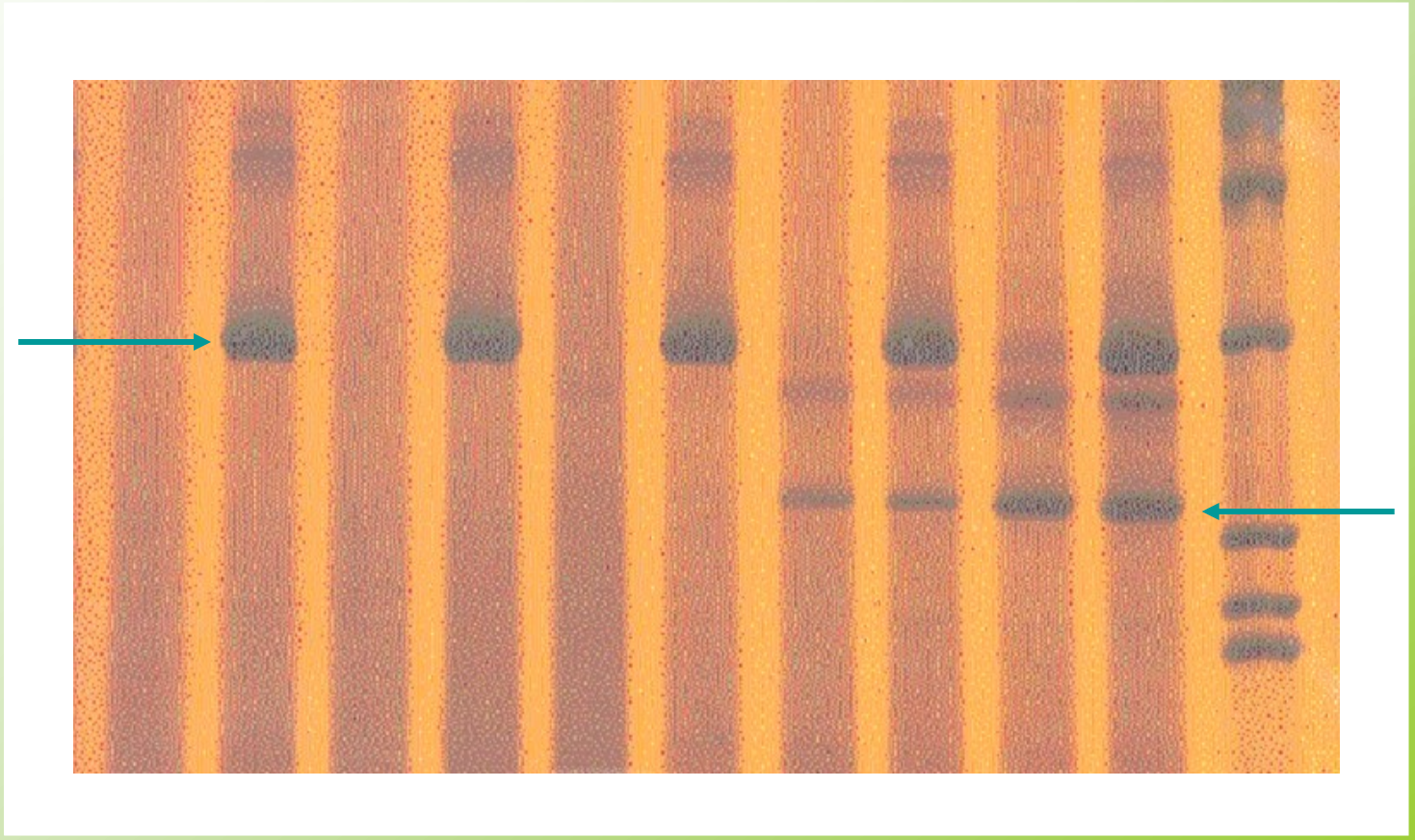


CGH Neuroblastom



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 cancer syndromes

- AD inheritance
- Preventive, pre-symptomatic testing
- Assotiated problems
- Prevention

Hereditary cancer syndromes following AD inheritance

- Brest cancer – BRCA 1 and BRCA 2
- Familial Adenomatous Polyposis coli - FAP
- Von Hippel – Lindau syndrome- VHL
- Retinoblastoma
- Neurofibromatosis- NF1, NF2
- Li-Fraumeni syndrome
- Lynch syndrome – hereditary non polypous colon cancer - HNPCC

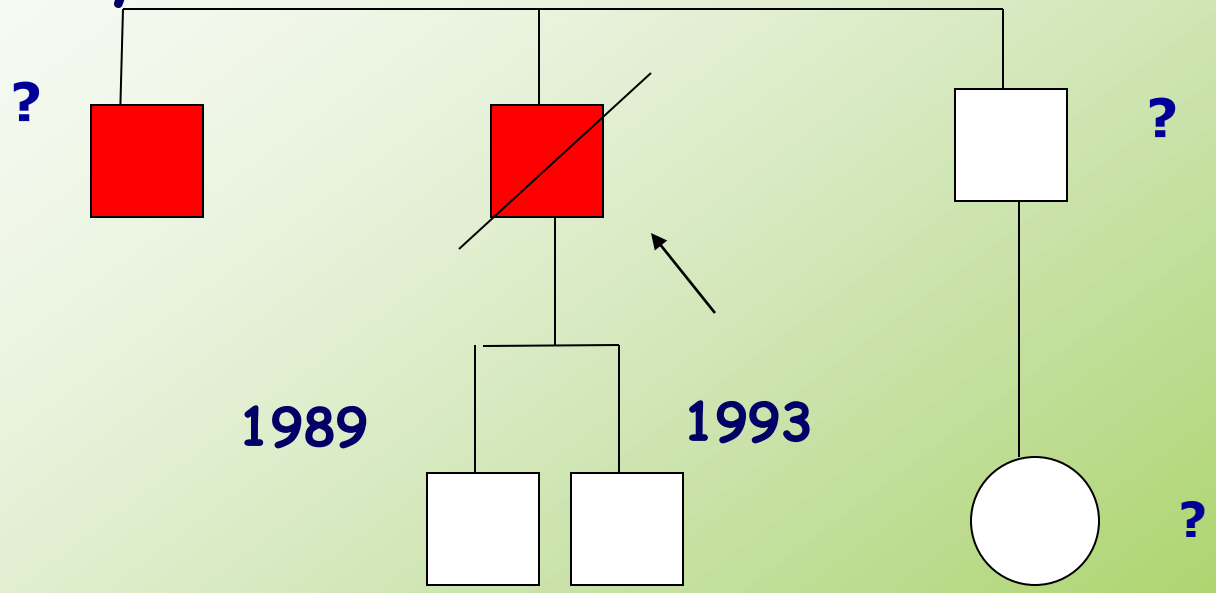
Genetic testing in Hereditary cancer syndromes

- 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