Clinical Genetics

Renata Gaillyová

Clinical genetics

- Dept. of medical genetics
- Genetic diseases
- Rare diseases
- Patients on the departement of clinical genetics
- Genetic counselling
- Genetic prevention
- Chromosome abnormalities
- AD,AR,XR inheritance, disorders
- Multifactorial inheritance
- Teratogenes, Environmental hazards
- Prenatal diagnosis
- Neonatal screening
- Reproductive genetics

Dept. of Medical genetics

- Genetic ambulance

genetic counselling

- Laboratory part
- Cytogenetic laboratories

Prenatal cytogenetics

Postnatal cytogenetics

Oncocytogenetics

Molecular – cytogenetics

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

Medical Genetics

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

Genetics diseases

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

- Monogen diseases
- about 0,36%

(study in 1 000 000 newborns)

- most then 90% of monogen diseases occur in childhood

- Multifactorial (polygenic or complex) disorders
- Occur in about 80% in the population

Rare diseases

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

What are the major issues affecting people with rare diseases?

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

EURORDIS
RARE DISEASES EUROPE

Rare diseases

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

What is a Rare Disease?

- **A disease or disorder is defined as rare in Europe when it affects fewer than 1 in 2000.**
- A disease or disorder is defined as rare in the USA when it affects fewer than 200,000 Americans at any given time.
- One rare disease may affect only a handful of patients in the EU (European Union), and another may touch as many as 245,000. In the EU, as many as 30 million people may be affected by one of over **6000 existing rare diseases.**

What is a Rare Disease?

- **80% of rare diseases have identified genetic origins whilst others are the result of infections (bacterial or viral), allergies and environmental causes, or are degenerative and proliferative.**
- **50% of rare diseases affect children.**
- **Over 6000 rare diseases are characterised by a broad diversity of disorders and symptoms that vary not only from disease to disease but also from patient to patient suffering from the same disease.**
- **Orpha.net**

Rare Disease

- **Relatively common symptoms can hide underlying rare diseases leading to misdiagnosis and delaying treatment. Quintessentially disabling, the patients quality of life is affected by the lack or loss of autonomy due to the chronic, progressive, degenerative, and frequently life-threatening aspects of the disease.**
- **The fact that there are often no existing effective cures adds to the high level of pain and suffering endured by patients and their families.**

Rare Disease

- The lack of scientific knowledge and quality information on the disease often results in a delay in diagnosis. Also the need for appropriate quality health care engenders inequalities and difficulties in access to treatment and care. This often results in heavy social and financial burdens on patients.

Rare Disease Day

- takes place on **the last day of February each year.** The main objective of Rare Disease Day is to **raise awareness** amongst the general public and decision-makers about **rare diseases and their impact on patients' lives**.
- The campaign targets primarily the general public and also seeks to raise awareness amongst policy makers, public authorities, industry representatives, researchers, health professionals and anyone who has a genuine interest in rare diseases.

Czech Association for Rare Diseases

- **The Czech Association for Rare Diseases (ČAVO) was founded in March 2012.**
- **ČAVO's mission is to bring together the organizations serving people with rare diseases as well as individuals, to represent their interests and to strengthen awareness of rare disease issues among experts in health care, leaders of state and international institutions and the public.**

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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

Children

- Congenital malformations

Children

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

Children

- Suspition on congenital chromosom aberations (children with congenital malformations, abnormal face, atipical visage, pre- or postnatal growth retardation, premature birth)

Children

- early or delayed puberty
- Malformations of the external or internal genitalia
- Low or high figure

Children or adults

- 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)

Children and adulds

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

Adults

- Donors of gametes

(preventive tests)

Adults

- Related partners

(increased risk for hereditary disease with AR inheritance)

adults

- Infertility
- Repeated spontaneous abortions

Pregnant women

- With unfavorable family history

Pregnant women

- with adverse pregnancy history (chronic diseases with established therapies, acute disease in early pregnancy - temperature, drugs, X-rays, CT, vaccinations, toxoplasmosis, rubella, ...)

Pregnant women

- Prenatal biochemical screening

(Pathological results)

Pregnant women

- Ultrasound prenatal screening – pathological results
- Congenital malformations in the fetus
- Risk of chromosomal abnormality in the fetus

Genetic counselling

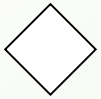
- Anamnesis
- Family history
- Pedigree analysis
- Examination of the patient
- Laboratory analysis
- Other examinations - neurology, psychology, hematology, CT, MRI …

Three-generation pedigree

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

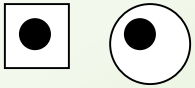
man

woman

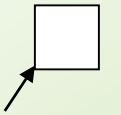


Unknown gender

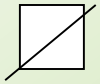
diseased



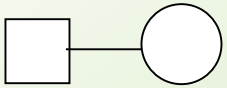
carrier



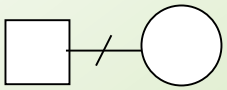
proband



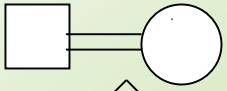
dead person



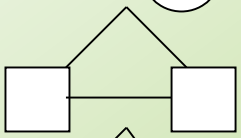
marriage



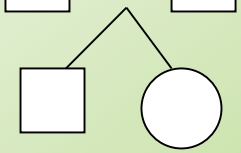
divorce



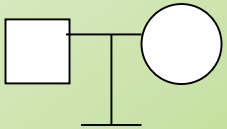
konsanguinity



monozyg. twins



dizygot. twins



childless

miscarriage

Clinical examination

Usually the child is like their parents.

Next steps

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

The result of genetic counselling

- Specify exact diagnosis (if possible)

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

Patient

Cell

Chromosome

DNA

Patient

Primary genetic prevention

- **Before pregnancy**
- Folic acid (cca 0,8 mg/day, 3+3 months)
- Vaccination (rubella)
- Genetic counselling
- Contraception, family can opt for adoption or donor of gamets (oocytes, sperm)
- Pregnancy planning
- Rediction of environmental hazards (drugs, radiation, chemicals…)

Reproduction of the optimal age

- In women increases the risk of accidental congenital chromosomal aberrations in the offspring

- In men may increase the risk of de novo mutations in some monogenic diseases (Neurofibromatosis I, Achondroplasia..)

Prevention of spontaneous and induced mutations

- Healthy Lifestyle

- The restriction of harmful substances - drugs, environmental hazards

Vacctination, infection prevention

- Prevention of rubella embryopathie

  Prevention of congenital toxoplasmosis

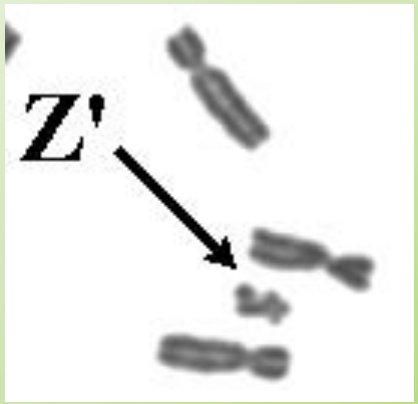
- Testing for infectious disease risk in mothers (CMV, varicella-zoster virus, ...)

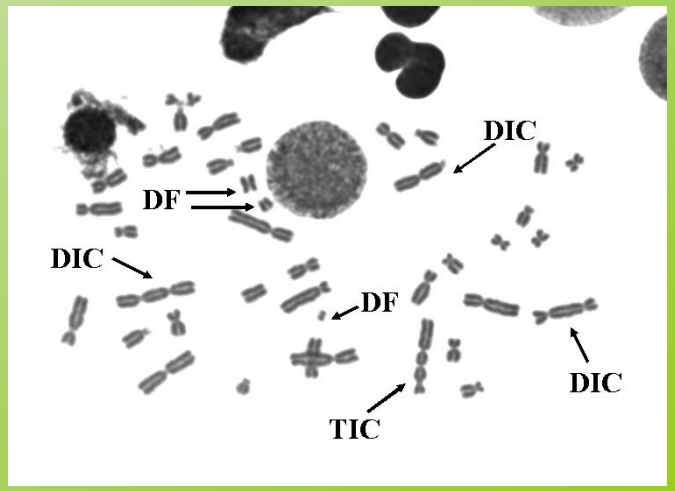
Vitamin prevention of neural tube defects, anterior abdominal wall defects, clefts

- Folic acid at a dose of 0.8 mg daily (twice the dose in non-pregnant) for 3-6 months prior to conception and till the end of 12. week of pregnancy

Examination of acquired chromosomal aberrations

- Preventive examinations of persons exposed to environmetal risks at work or persons with risk of long-term therapy (immunosuppressants, cytostatics, ...)
- The possibility of vitamin therapy to improve repair of DNA (3-6 months)





Contraception, sterilization

- Contraception - temporarily prevents conception in the limited impact of risk (treatment)

- Sterilization - the long-term inhibition of pregnancy in a high risk of disease in the offspring (Hereditary disease)

Adoption

- Alternative family care as an option at high genetic risk families

Donation

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

Secondary genetic prevention

- Prenatal diagnosis
- Prenatal screening
- Prenatal tests
- Genetic counselling
- Termination of pregnancy (the law in Czech Republic- end of 24. week of gestation)
- Postnatal screening
- Newborn screening

Chromosome abnormalities

0,6-0,7% live born

Congenital chromosome abnormalities

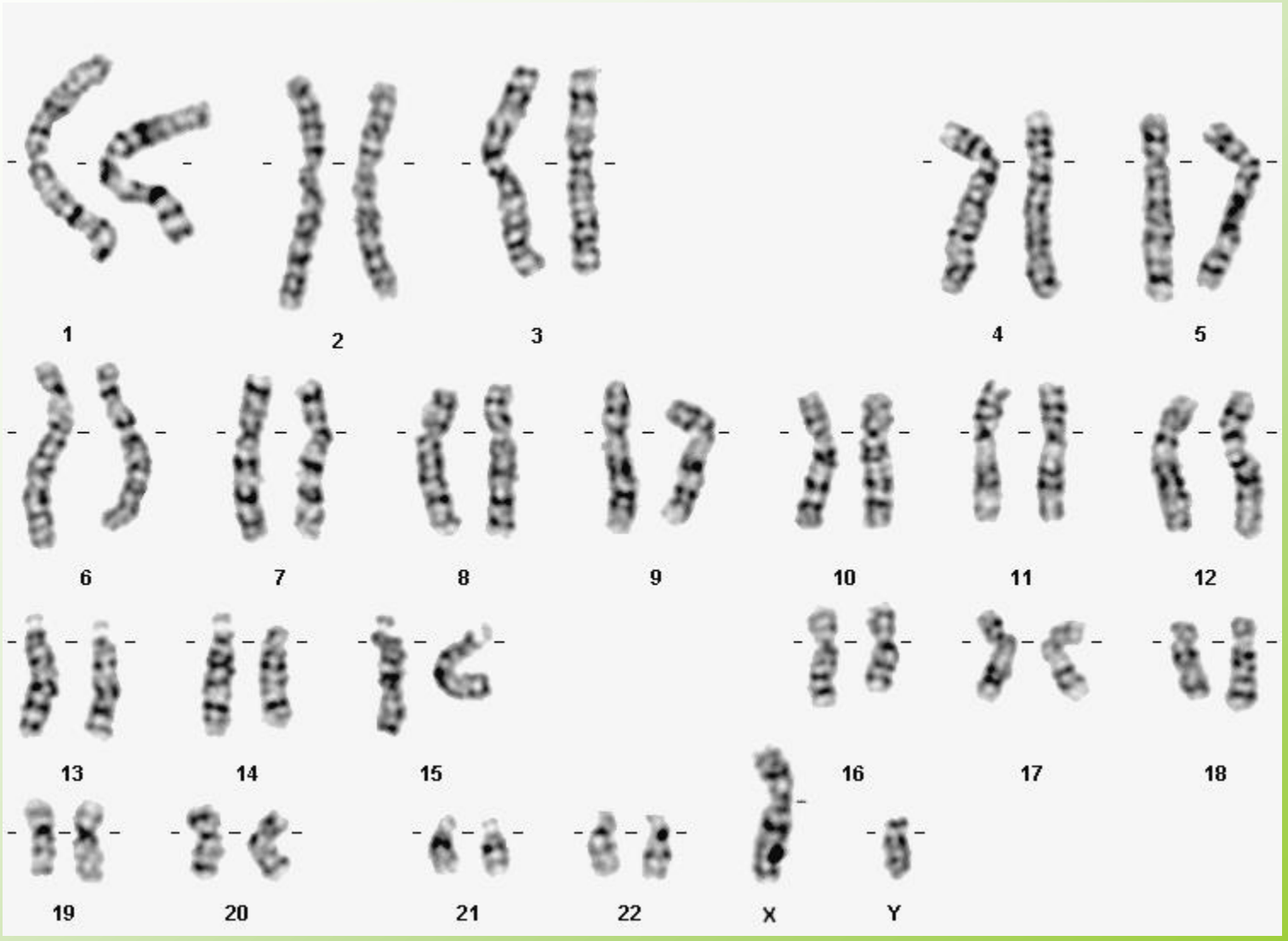
- Autosomes
- Gonosomes

- Numerous
- Structural

- Balanced
- Unbalanced

Populations frequency

Trisomy 21	1,5 per 1000 live births
Trisomy 18	0,12
Trisomy 13	0,07
Klinefelter syndrome	1,5
Turner syndrome	0,4
XYY syndrome	1,5
XXX syndrome	0,65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X
Y

Chromosome abnormalities in spont. abortions

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

Maternal age and chromosome abnormalities in AMC (per 1000)

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

Down syndrome

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

Down syndrome- prenatal diagnosis

- I. trimester screening – combined screening
- 10.-14. week of gestation
- Ultrasound
- Nuchal translucency - NT (⇧)
- (Absence of nose bone)
- Blood
- PAPP-A (⇩)
- free-beta hCG (⇧)
- Fals positive results less then 5%
- Reveals about 95% of fetuses with Down syndrome
- 1/100 – positiv – genetic counselling and karyotiping
- 1/100-1/1000 – US and genetic counselling
- 1/1000 – negativ - US

Down syndrome- prenatal diagnosis

- II. trimester screening – biochemical screening
- 16. -18. week of gestation
- AFP – alpha-fetoprotein (⇩)
- total hCG - chorionic gonadotropin (⇧)
- uE3 - unconjugated estriol (⇩)

- Fals positive results about 5%

- Reveals about 70% of fetuses with Down syndrome

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

Down syndrome- prenatal diagnosis

- Ultrasound

- 10.-14. week
- NT
- NB

- 20. week
- US- congenital heart disease and other malformations

Down syndrome- prenatal diagnosis

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

Edwards syndrome

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

Patau syndrome

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

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

Turner syndrom 45,X

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

Klinefelter syndrome

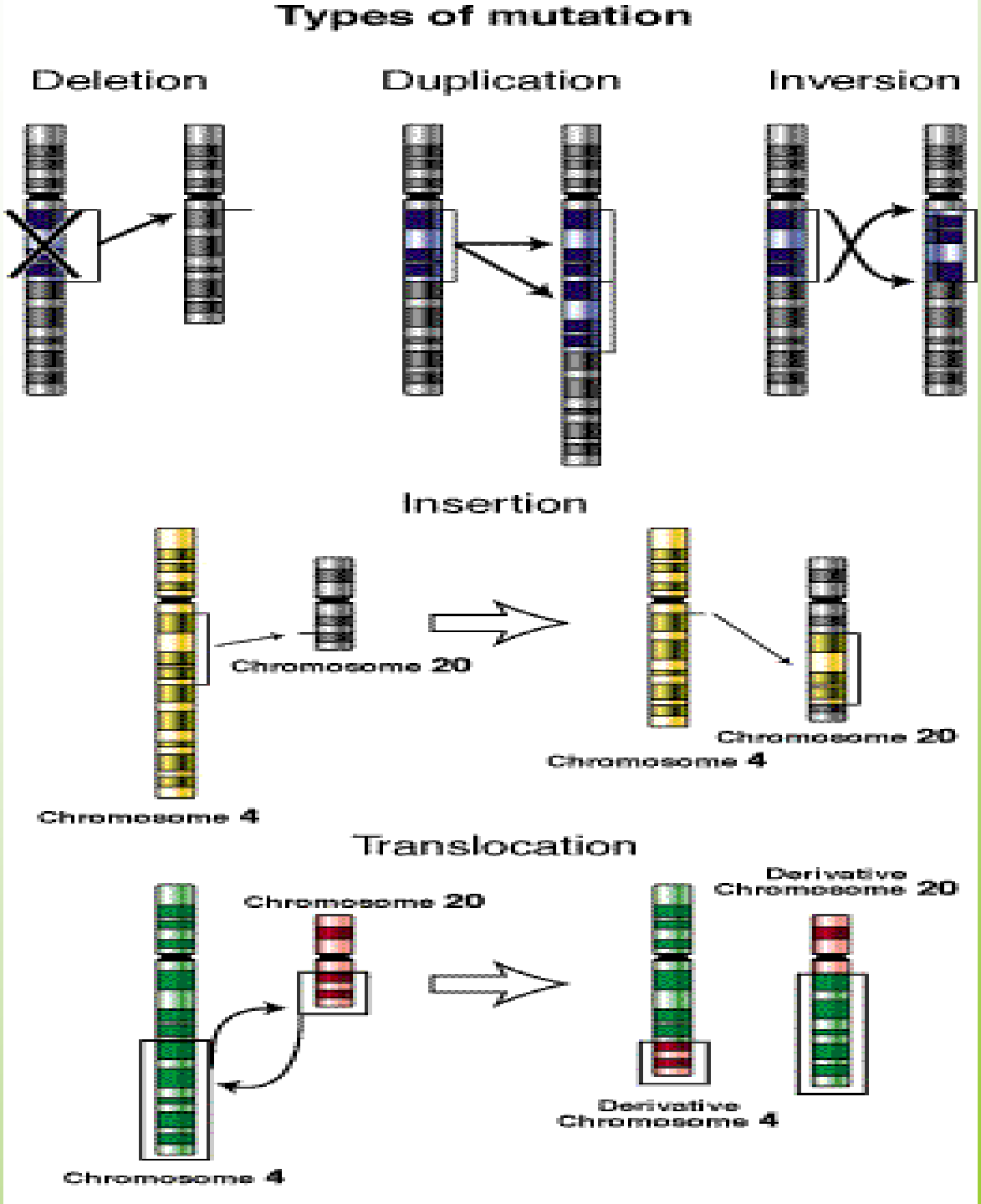
- 47,XXY
- relatively frequent 1/600-1000 liveborn males
- tall stature
- hypogonadism, gynekomastia
- sterility, infertility

Others gonoseme abnormalities

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

Structural 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 ...

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

Other structural chromosomal aberrations

Mikrocytogenetic
Molekular cytogenetic

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

Microdeletions

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

Williams - Beuren syndrom

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

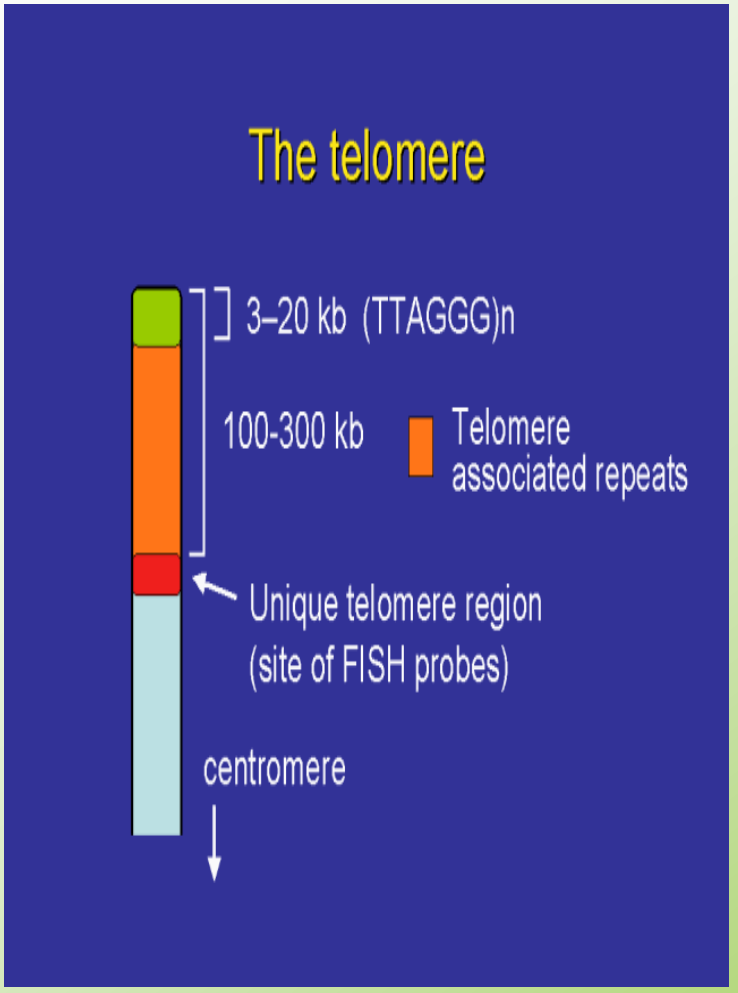
Prader-Willi syndrom

- 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)

Mendelian inheritance

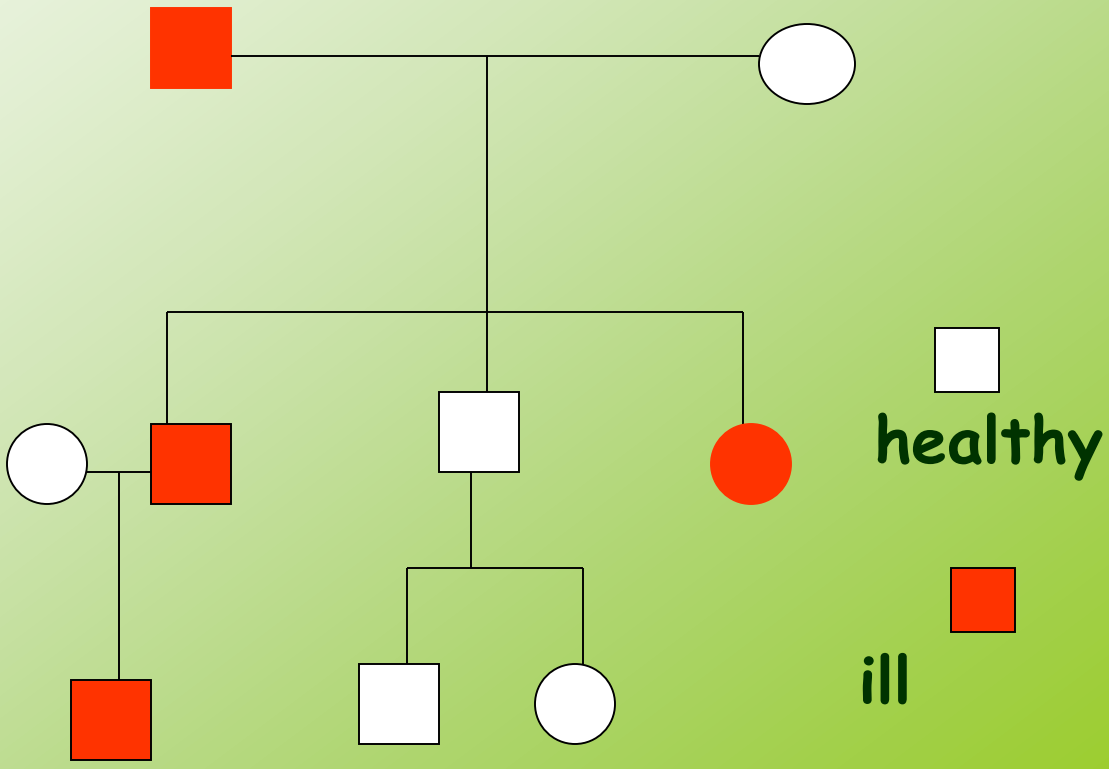
Monogenic diseases

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
- Achondroplasia
- Huntington disease
- Marfan syndrome
- Myotonic dystrophy 1 and 2
- Long QT syndrome

Neurofibromatosis I

- the frequency of the disease about 1/3000
- localization 17q11.2
- inheritance - autosomal dominanant with nearly 100 % penetrance and variable expressivity
- approximately 50 % of cases are new mutations (paternal origin)
- progressive disease
- mutations in tumor supresor gene – risk of oncologic disease

Huntington disease

is an inherited neurodegenerative brain disease

that affects individuals of both sexes

Symptoms usually begin between the 20th to 45th year , often after it has been disposition for a disease transmitted to the next generation, usually manifested by involuntary movements, abnormal gait and speech-impaired, patients are gradually reflected in the loss of cognitive ability, mood and behavior - senile dementia, psychiatric symptomatology

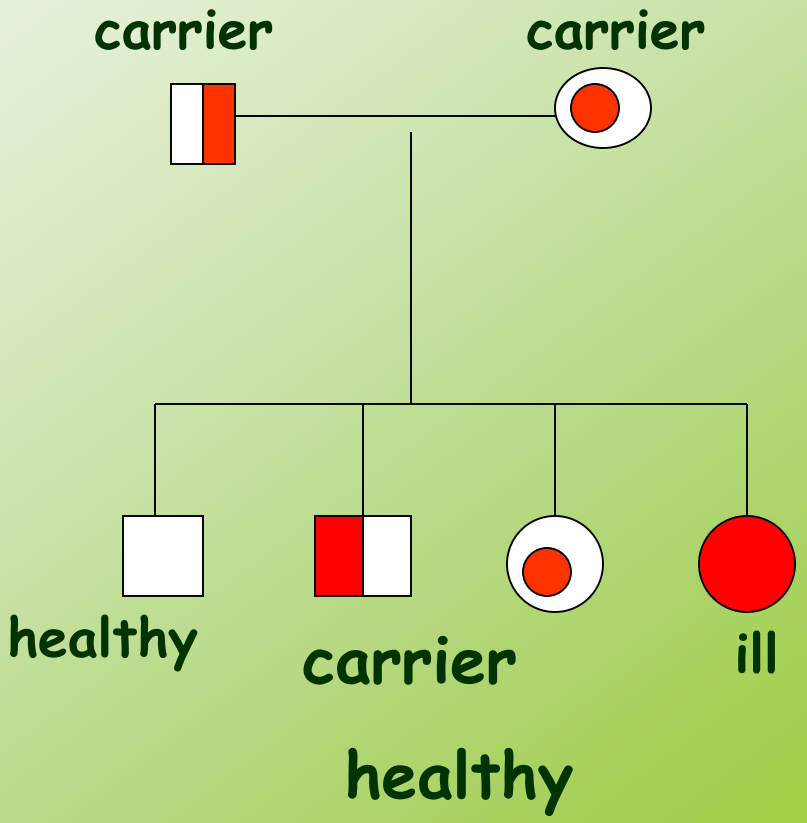
- **Achondroplasia (ACH)**
- 2 mutations in FGFR3 gene
- New mutations
- Paternal origin on new mutations
- older fathers

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- 1/30)

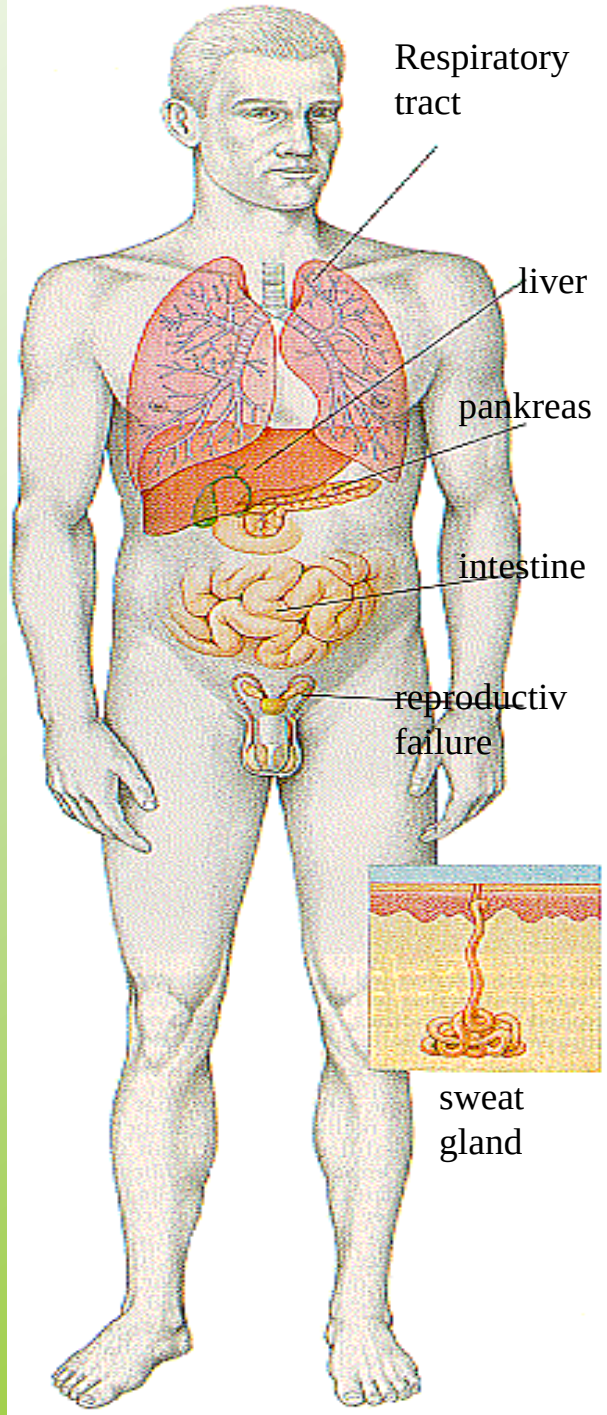
- Phenylketounria (1/40)

- Congenital adrenal hyperplasia (1/40)

- Spinal muscular atrophy (1/60-80)

Cystic fibrosis

- disease affecting multiple organs
- more then 2000 patological sequence variants (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

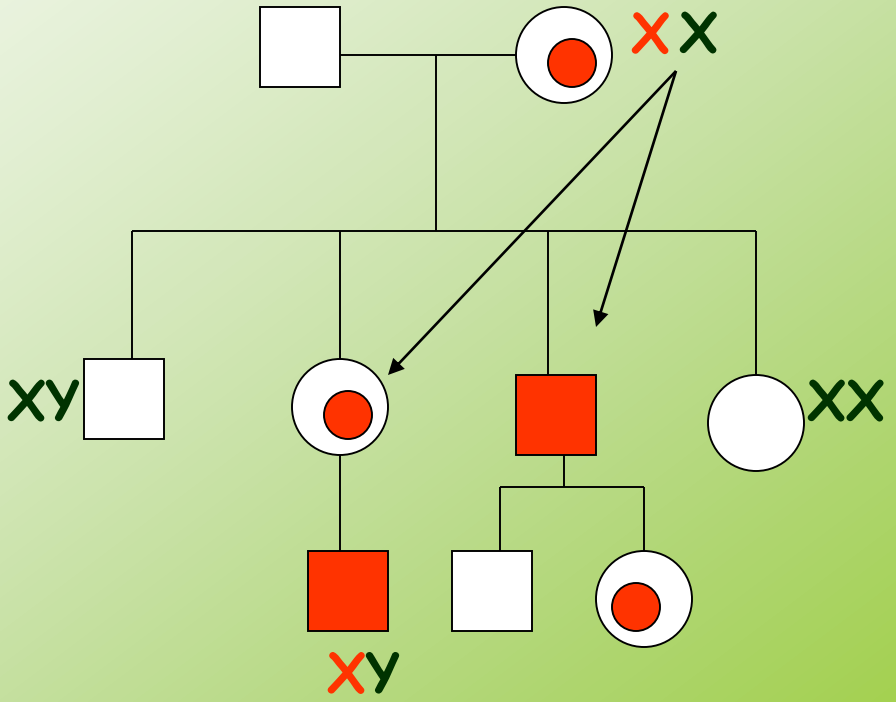
- Females are not affected as severaly as males or are not affected
- An affected male cannot transmit the train to his sons, becose the trait is on X-chromosome, and the father must necessarily transmit his Y-chromosome to a son
- All of the daughters of an affected male must be carriers, because the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

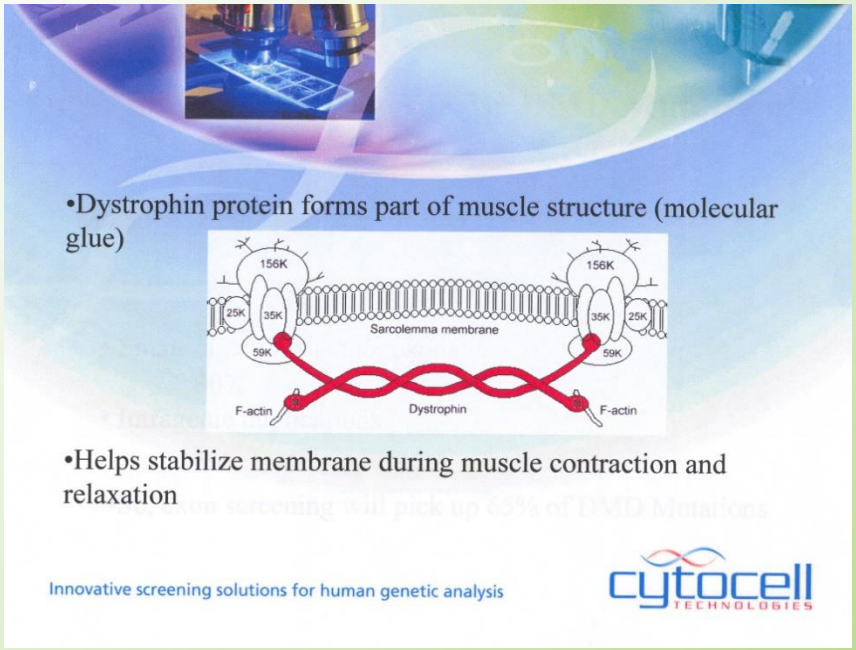
X- recesive inheritance

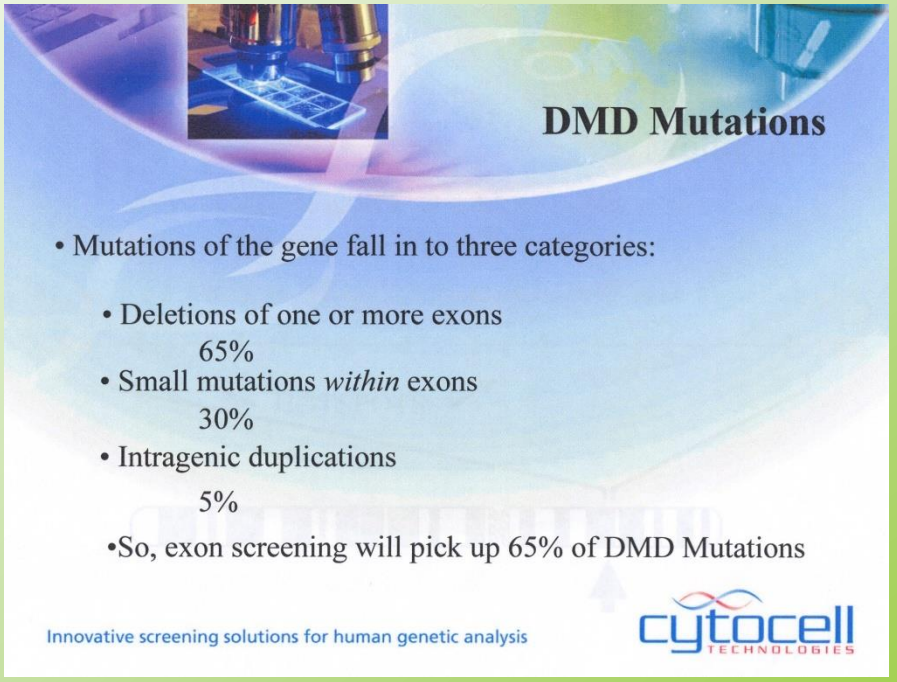


XR - diseases

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

Duchenn/Becker muscular dystrophy





Hemofilia A

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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

Multifaktorial –polygenic inheritance
Dieseases with complex heritability

Teratogens

Charakteristic

- 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

Charakteristic

- 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

- Congenital 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% combine with 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 (CLP) 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%	

CLP - Diff. Dg.

- Patau syndrome, 47,XX,+13
- EEC syndrome
- Van der Woude syndrome
- Sequence Pierre Robin

Neural tube defects

- Multifactorial inheritance (risk for I. degree relatives about 2 - 4%)
- Maternal serum screening – elevated level of AFP
- Prenatal diagnosis by ultrasonography
- Raised AFP levels in amniotic fluid
- Primary prevention in pregnancies - folic acid
- Risk in the population - 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 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, ears anomalies, hydrocephaly, 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
- hydrocephaly 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
- hypertonia
- mikrocephaly, mental retardation
- Cong. heart defects
- hyperaktivity

- newborn screening
- (frequency 1/10 000 newborns
- inheritance - AR)
- initiation of treatment within three weeks to prevent mental retardation in the child

Reproductive Genetics

Preconceptional testing
Genetic counselling and analysis
in couples with reproductive disorders
Prenatal diagnosis
Preimplantation genetic diagnosis
Examination of potential donor gametes

Secondary prevention of genetic

- The procedures in pregnancy - prenatal diagnosis and early postnatal diagnosis

Prenatal diagnosis

- Non invasive methods- screening
- Screening

- Invasive methods
- CVS – after the 10. week of gestation
- AMC – 15.-18. week of gestation
- Cordocentesis – after the 20. week of gestation

Prenatal diagnosis results

- CVS – karyotype – about 5 days
- AMC – karyotype – about 14-21 days

- DNA analysis (monogen diseases)
- About 5-15 days
- DNA from amniocytes after cultivation - exclusion contamination by maternal tissues

Prenatal analysis of most frewquent aneuploidias
QF PCR

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

Prenatal screening (CR)

- Ultrasound (12. - 2 0. - 33. week)
- Ultrasound 20.week – cong. defect
- Ultrasound 20-22. week – cong. heart defect
- 10-14. week of gestation
- Free beta hCG, PAPP-A, US-NT,NB..
- 16.-18.week of gestation
- AFP, hCG, uE3

NIPT - non-invazive prenatal testing

examination of fetal DNA in maternal plasma

- aneuploidy (21, 13, 18, X/Y and others – microdetetions…)
- Rh in the fetus
- SRY in the fetus – in X linked diseases in the family
- Some mongenic diseases in the fetus (achondroplasie)

Indications for prenatal examination / genetic counselling

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

Preimplatation Genetic Diagnostics

Preimplatation Genetic Diagnostics

- IVF – assisted reproduction

- Preimplantation genetic screening
- aneuploidy - array-CGH, chip technology
- (FISH -13,18,21,X,Y, 15,16,22)

- Preimplantation Genetic Diagnostics
- Structural chromososmal aberations
- (parents are carries of balanced rearangement)
- Monogenic diseases (known in family history)

PG Diagnostic
X
PG Screening

- PGD - high genetic risk

- PGS - (most common) aneuploidies

Genetic counselling in infertility

Infertility

- Is the infertility one aspect of a genetic disorder that might be transmitted?
- Will correction if infertility give an increased risk of malformations in the offspring?

- Genetic testing before use of metods of asisted reproduction.

Infertility

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

Infertility

- A search for possible lethal mendelian causes (consanguinity- risk for AR diseases, X-linked dominant disorders lethal in male, myotonic dystrophy which gives heavy fetal loss in the offspring of mildly affected women)
- Inherited trombophilias in women with recurrent abortions (factor V Leiden, factor II - G20210A, hyperhomocystinaemia ? (MTHFR - C677T)

Factor V - Leiden

- frequency in the white European population of about 5 - 9%
- AD inheritance
- increased risk of thromboembolism in homozygots for FVL 50-100x, in heterozygots 5-10x

- increased risk of fetal loss after the 10. week of gestation

Sterility in male

- Klinefelter syndrome and other chromosomal aberations

- AZF (azoospermia factor) deletions of the DAZ gene Yq (deleted in azoospermia)
- Infertile man – 4-5%
- Men with azoospermia – about 15%

- CFTR mutations and polymorphisms
- Other genes

Postnatal care and neonatal screening

- Early diagnosis

  Dispensary

  Specialized Care

Prenatal and perinatal managment of prenagncies with malformation or genetic disease in the fetus

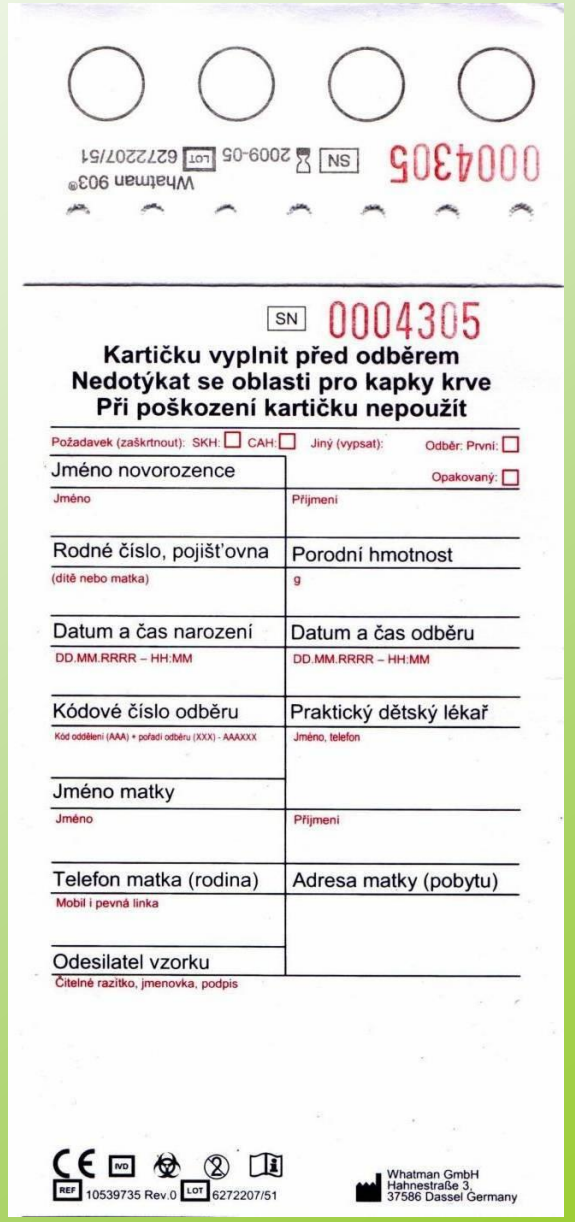
- Consultation with experts, who will continue to take care of the pregnant woman - ultrasound specialist, gynecologist, obstetrician, psychological support ..

  Consultions with specialists, who will care after the birth of newborns with disabilities

  The planned delivery of specialized care workplace - kardiocentrum, pediatric surgery, cardiology…

Newborn screening

Sampler card



0004305 NS 2009-05 LOT 6272207/51
Whatman 903®

SN 0004305

Kartičku vyplnit před odběrem
Nedotýkat se oblasti pro kapky krve
Při poškození kartičku nepoužít

Požadavek (zaškrtnout): SKH: ☐ CAH: ☐ Jiný (vypsat): Odběr: První: ☐ Opakovaný: ☐

Jméno novorozence	
Jméno	Příjmení
Rodné číslo, pojišťovna	Porodní hmotnost
(dítě nebo matka)	g
Datum a čas narození	Datum a čas odběru
DD.MM.RRRR – HH:MM	DD.MM.RRRR – HH:MM
Kódové číslo odběru	Praktický dětský lékař
Kód oddělení (AAA) + pořadí odběru (XXX) - AAAXXX	Jméno, telefon
Jméno matky	
Jméno	Příjmení
Telefon matka (rodina)	Adresa matky (pobytu)
Mobil i pevná linka	
Odesilatel vzorku	

Čitelné razítko, jmenovka, podpis

REF 10539735 Rev.0 LOT 6272207/51

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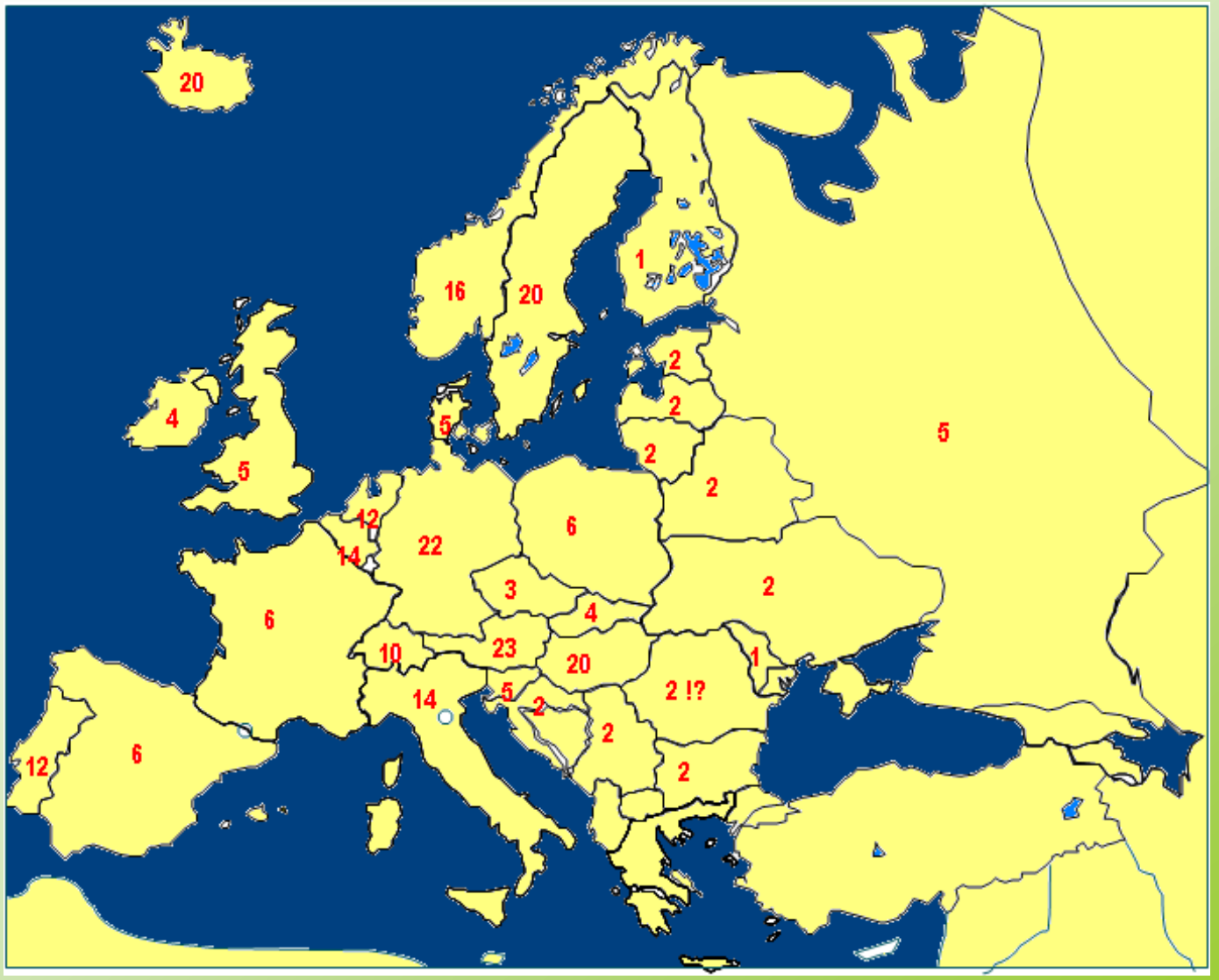
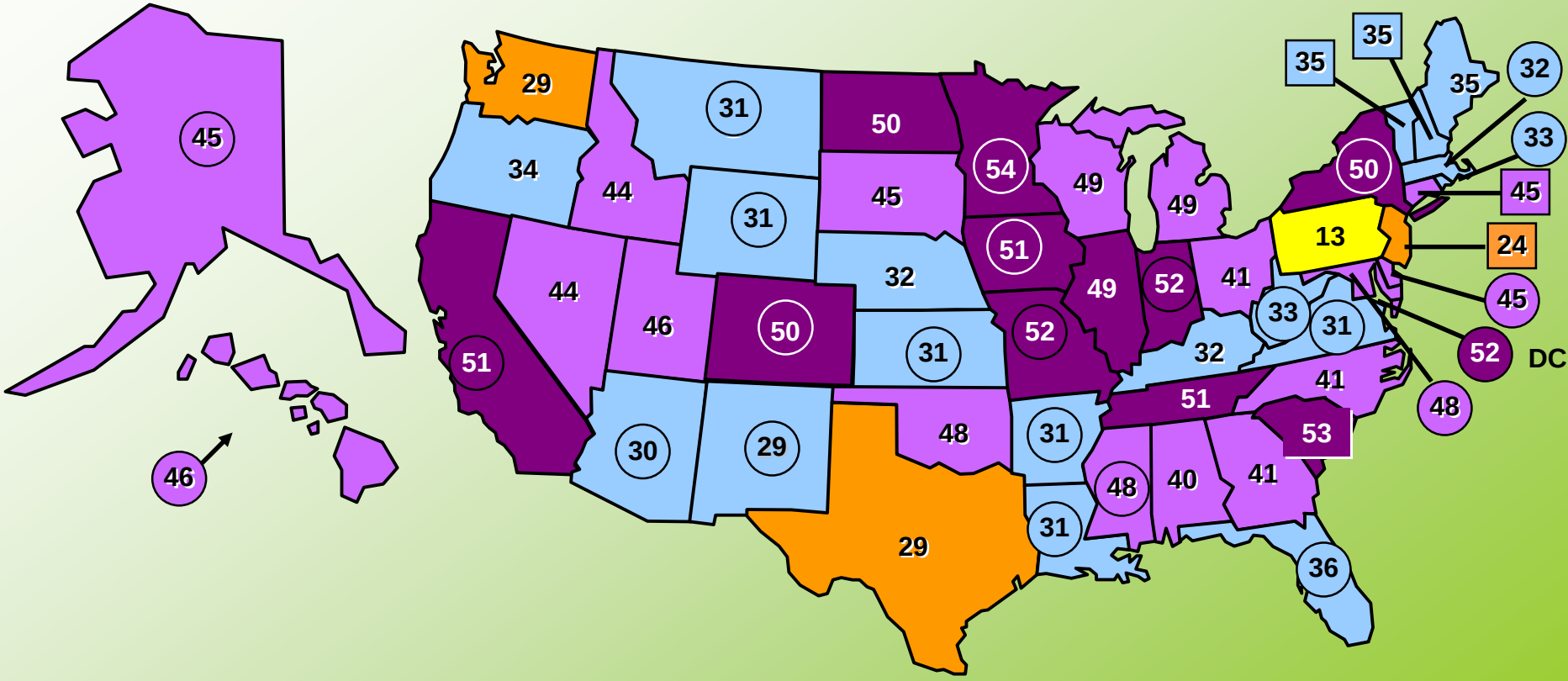
37586 Dassel Germany

NS Evrope-2009



NS USA-2009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Screened diseases in CR from 10/2009

- Kongenital hypothyreosis
- Kongenital adrenal hyperplasia – CAH

Screened diseases in CR from 10/2009

- **Inborn errors of metabolism**
- Fenylketonuria (PKU, HPA)
- Leucinosis
- MCAD
- LCHAD
- VLCAD
- Def.karnitinpalmitoyltransferasis I a II
- Def.karnitinacylkarnitintranslocasis
- Glutaric aciduria
- Izovaleric acidurie

Screened diseases in CR from 6/2016

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

Screened diseases in CR from 10/2009

- Cystic fibrosis

- cumulative risk of all 13 screened diseases in CR - 1/1200