1. The types of the inheritance

2. Hereditary tumor syndromes

The Inheritance

- the transmission of genetically encoded traits, conditions or diseases to offspring

- The types of the inheritance

Single Gene or Mendelian

Mitochondrial

Multifactorial

Single Gene Inheritance

- Genetic condition is caused by a mutation in a single- major gene
- It follows predictable pattern of inheritance within families.
- These trasmission patterns observed J.G.Mendel i his research- Mendelian inheritance.

Laws of Mendel

- The law of the unit of the inhertitance –the inherited traits are determined by the genes. The allele is one form of the gene
- The law of the dominance – the alleles are in each individual in the pair, but the effect of one allele can be overlaped by a dominant effect of the second allele
- The law of the segregation – the alleles divide during gametogenesis. Pairs of the allele reunite during fertilization
- The law of free combination – the alleles of different genes combine each other independently

Monogenic diseases

- About 8000 diseases
- Manifestation - typicaly in childhood- not exclusively!
- Less then 10% manifest after puberty,
  1% after reproductive age
- Incidence of monogenic disorders- 0,36%

Mendelian inheritance-types

Autosomal dominant

Autosomal recessive

X-linked recessive

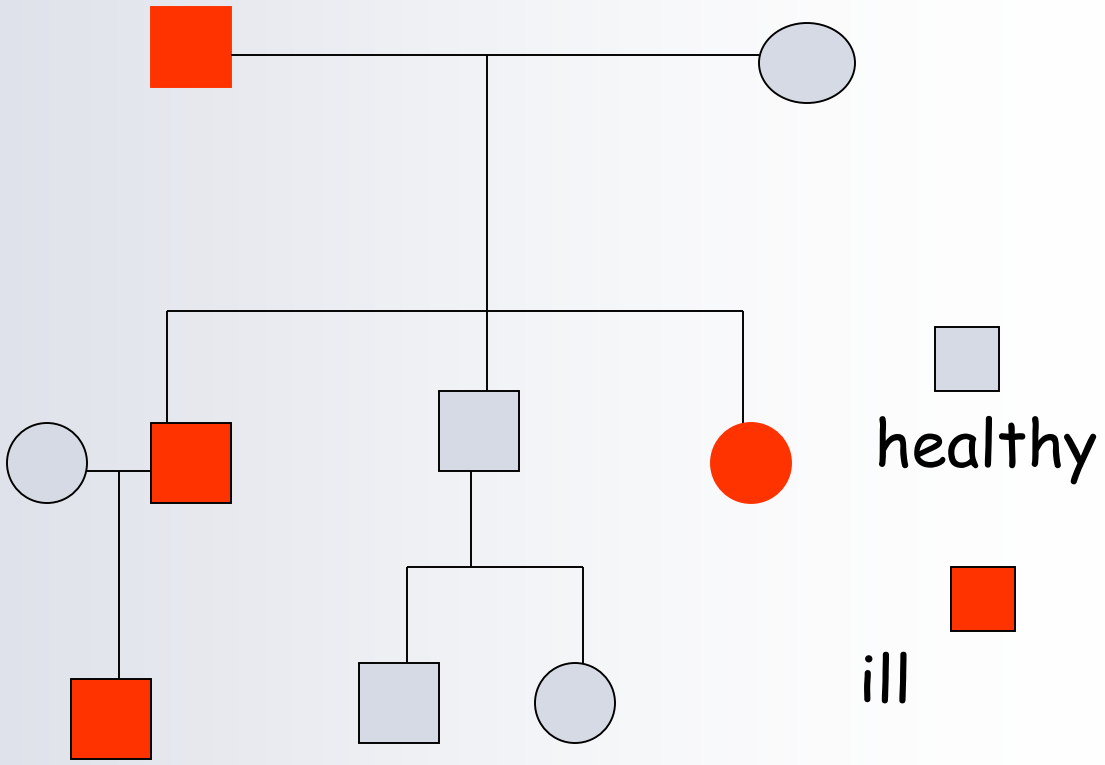
X-linked dominant

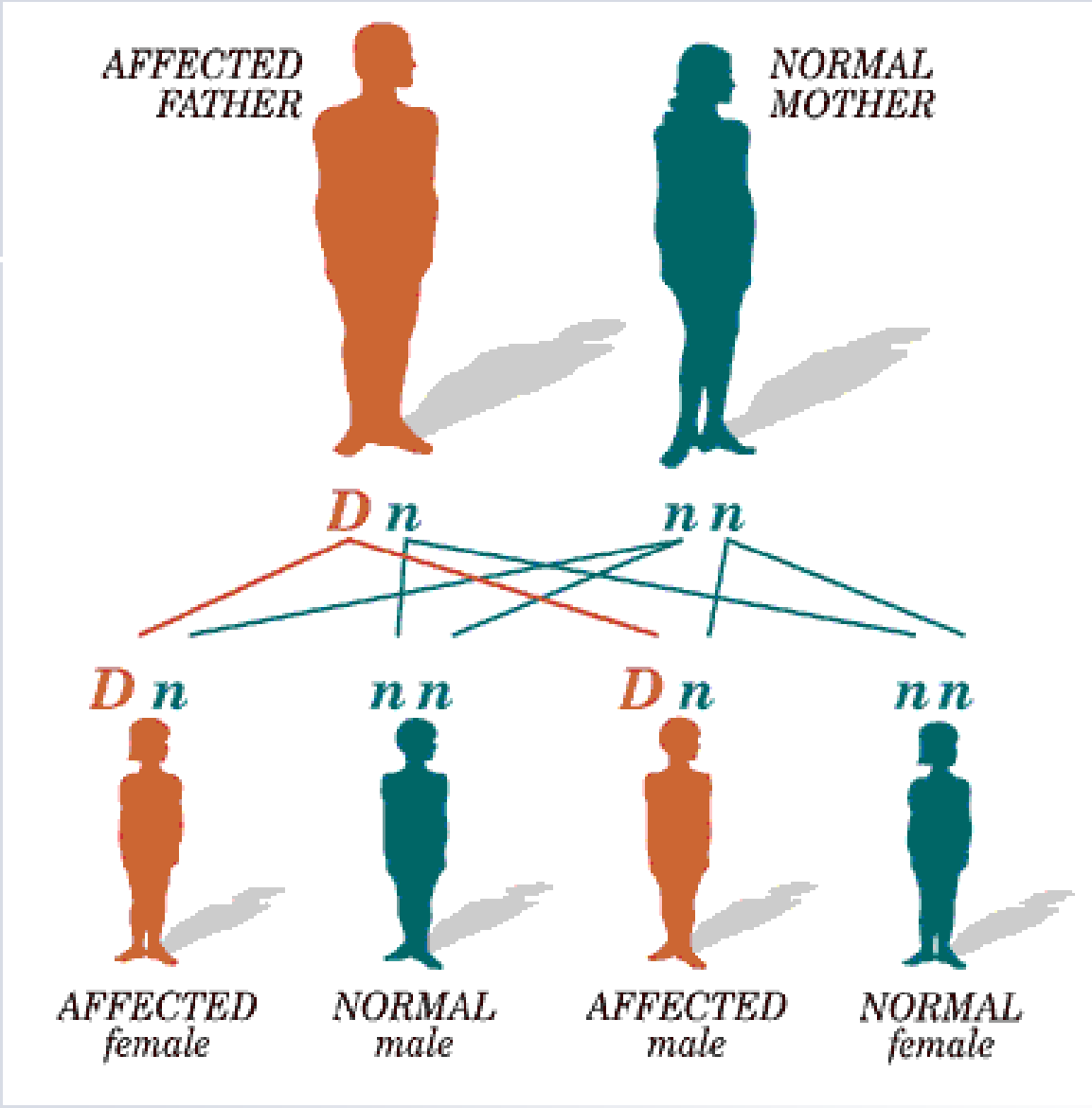
Autosomal Dominant

- the gene is located on one of autosomes
- the sexes are affected equally
- the condition manifests in heterozygotes
- affected individuals have one normal copy of the gene and one mutant copy of the gene
- each offspring has a 50% chance on inheriting the mutant allele.

AD inheritance

- the risk 50%




AFFECTED
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male
NORMAL
female

AD - diseases

- Neurofibromatosis types I and II
- Achondroplasia
- Myotonic dystrophy
- Huntington disease

Neurofibromatoses

- members of the *neurocutaneous syndromes* (*phakomatoses)*
- **NF type I**

Café au lait spots, neurofibromas, plexiform neurofibromas
axillary and inguinary freckling, hamartomas of iris(Lisch nodules),MR 10-30%, skeletal symptoms

NF1 gene-neurofibromin(17q11.2)

- **NF type II- central type-**bilat.acoustic neurinomas (tumors of the vestibulocochlear nerve)-hearing loss, meningiomas, ependymomas,gliomas,astrocytomas, juvenile cortical cataract retinal hamartoma ,no Lisch nodules

NF2 gene- merlin (22q12.2)

- **Neoplasias**
- **Variation in expression**
- **50% new mutations**.

Myotonic dystrophy I

- trinucleotide repeat expansion (CTG)n in the dystrophia myotonica-protein kinase gene (DMPK) 19q13.32
- Myotonia (delayed muscle relaxation after contraction), cataract,atrial arrythmias, hypogonadism, testicular atrophy
- congenital form(over 2000 repeats)-hypotonia, poor feeding,severe mental retardation, prenatal polyhydramnios, reduced fetal movement

- **Myotonic dystrophy type 2** (**DM2**), also called **proximal myotonic myopathy** (**PROMM**)-rarer than DM1 and generally manifests with milder signs and symptoms.
- Specific defect -repeat of the CCTG tetranucleotide in the *ZNF9* gene (3q21.3).

Achondroplasia

Autosomal dominant with complete penetrance
90% cases new mutations
100% of the mutations are G380R in FGFR3
Paternal age effect

Short-limb dwarfism identifiable at birth
Mean male adult height, 131 cm
mean female height, 124 cm
Frontal bossing ,megalencephaly
midface hypoplasia,low nasal bridge

Huntington disease

- a progressive disorder of motor, cognitive, and psychiatric disturbances.
- the mean age of onset is 35 to 50 years and the median survival time is 15 to 18 years after onset.
- characteristic clinical findings-Hyperreflexia ,Chorea ,Dementia Bradykinesia ,Rigidity, psychiatric:depression,psychotic symptoms, outbursts of aggression;
- expansion of 36 or more CAG trinucleotide repeats in *HTT* (the huntingtin gene 4p16.3).
- *Treatment of manifestations:* neuroleptics ,anti-parkinsonian agents , psychotropic drugs or some antiepileptic drugs . Supportive care with attention to nursing needs, dietary intake, special equipment, and eligibility for state benefits.

HD- genetic counseling

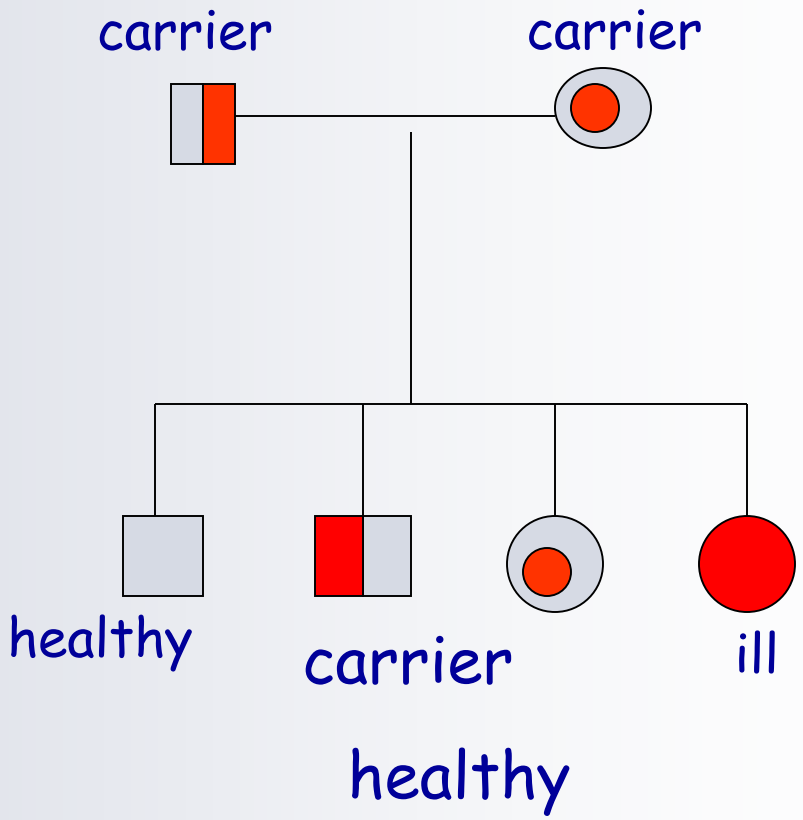
- Predictive testing in asymptomatic adults at 50% risk is possible but requires careful thought
- including pretest and post-test genetic counseling
- Asymptomatic at-risk individuals younger than age 18 years should not have predictive testing.
- prenatal testing by molecular genetic testing is possible for pregnancies at 50% risk. Prenatal testing for pregnancies at 25% risk cannot be performed because genetic status of the at-risk parent can reveal. Linkage analysis can be used for preimplantation genetic diagnosis
- Families may benefit from referral to a local HD support group for educational materials and psychological support.

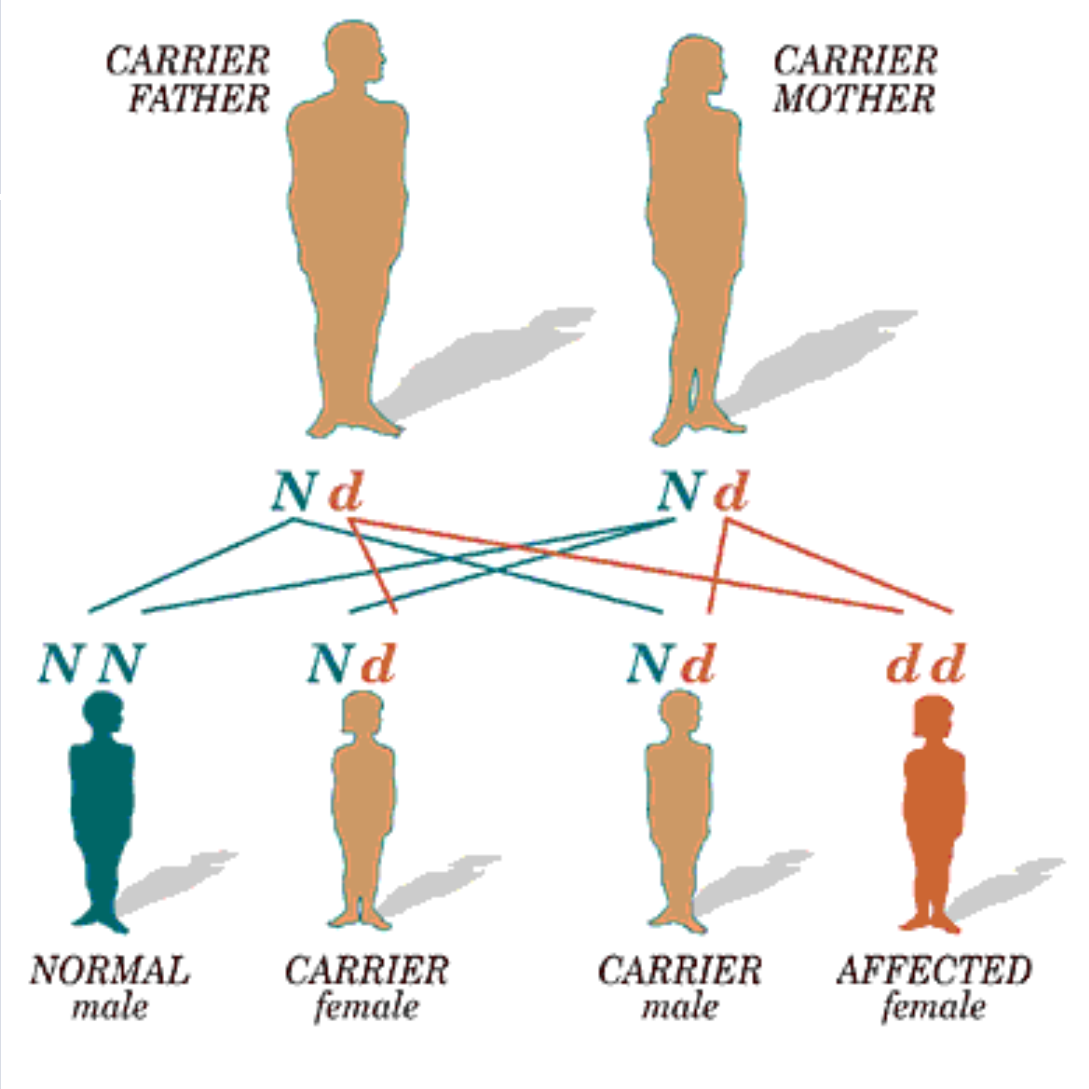
Autosomal Recesive

- Recessive conditions are clinically manifested only when an individual has two copies of the mutant allele.
- Females and males are affected equally
- When two carriers mate, each child has a 25% chance of being homozygous wild-type (unaffected); a 25% chance of being homozygous mutant (affected); or a 50% chance of being heterozygous (unaffected carrier).

Pedegree - AR inheritance

- The risk for next child 25%




CARRIER
FATHER
CARRIER
MOTHER
N d
N d
N N
N d
N d
d d
NORMAL
male
CARRIER
female
CARRIER
male
AFFECTED
female

Consanguinity

- Consanguineous marriage is the union of individuals having a common ancestor. It is categorized as 1st, 2nd and 3rd degree
- Consanguineous marriages increase the risk of manifestation autosomal recesive diseases in offsprings
- genetic consanguinity is expressed

  with the coefficient of relationship- is defined as the fraction of homozygous due to the consanguinity under discussion

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

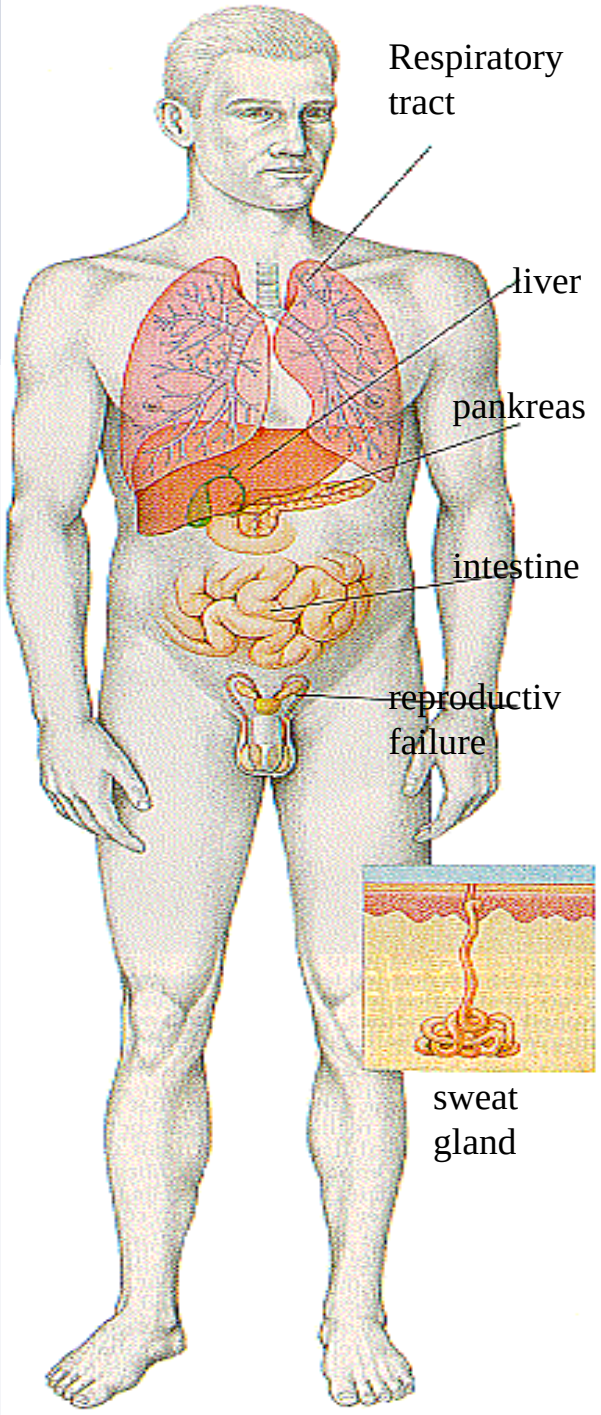
- Localized on chromosome 7q
- CFTR gene
- Frequency of Cystic Fibrosis in the Czech Republic: about 1/4000
- Frequency of heterozygots in the Czech Republic about 1/25-1/29
- About 2000 mutations in CFTR gene were identified

CF-ethnical differences

	frequence of CF	frequence of heterozygotes
Caucasians	1/ 4000-6000	1/27
Hispanics	1/9000	1/46
Amer. Africans	1/15000	1/60
Asians	1/32000	1/90

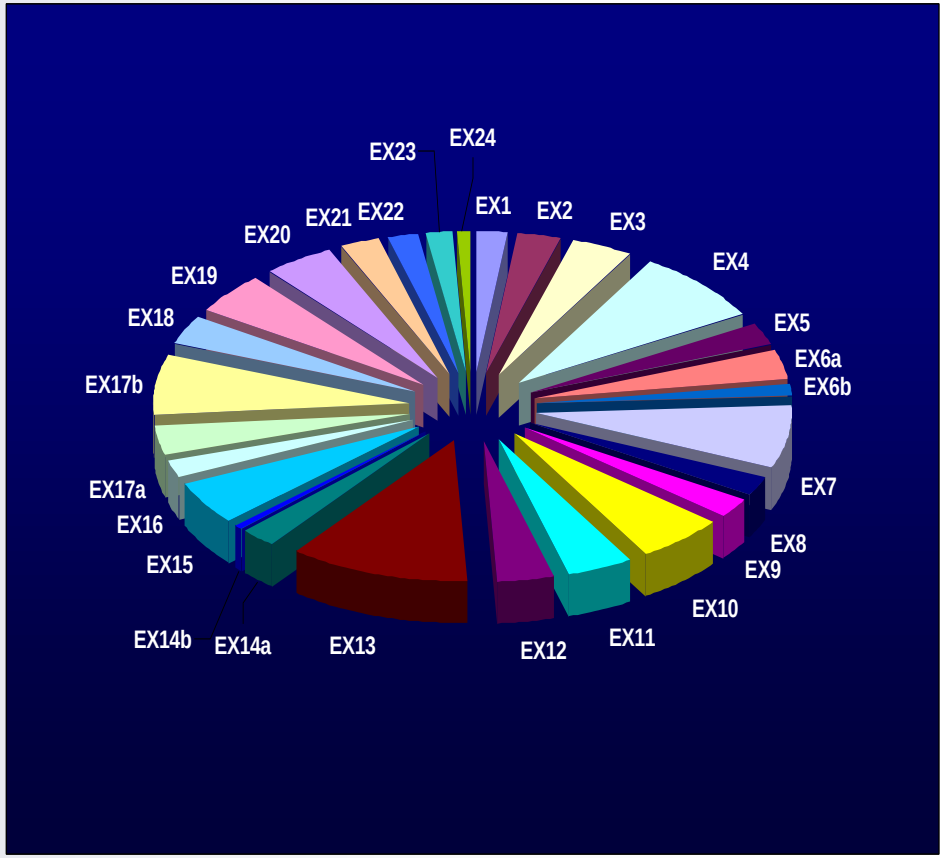
Cystic fibrosis

- Chronic bronchopulmonary infection Bronchiectasis ,Asthma ,Pseudomonas colonization
- Pancreatic insufficiency in 80%, Biliary cirrhosis, Meconium ileus in neonates (10-15%) Distal intestinal obstruction syndrome Rectal prolapse
- Male infertility (98%) due to congenital bilateral absence of the vas deferens (CBAVD) ,Female decreased fertility due to thickened cervical secretions and chronic lung disease
- Laboratory Abnormalities - High sweat sodium and chloride
  Hyponatremic dehydratation, rarely Hypercalciuria
  Abnormal nasal potential differences
  High newborn serum levels of immunoreactive trypsinogen



The reason for CFTR gene analysis

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



CFTR gene - distrubitions of 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

Congenital adrenal hyperplasia- CAH

- Group of congenital enzymatic defects of adrenal steroidogenesis
- most frequent- 21-hydroxylase deficiency(CYP21A2, 6p21)

CAH-symptoms

- Due to inadequate mineralocorticoids:

  vomiting due to salt-wasting leading to dehydratation and death
- Due to excess androgens:

  virilization ,ambiguous genitalia, in some females, such that it can be initially difficult to determine sex, early pubic hair and rapid growth in childhood,

  precociosus puberty or failure of puberty,infertility due to anovulation,enlarged clitoris and shallow vagina

Phenylketonuria-PKU

- Phenylalanine hydroxylase (PAH) deficiency results in intolerance to the dietary intake of the essential amino acid phenylalanine and produces a spectrum of disorders including phenylketonuria (PKU), non-PKU hyperphenylalaninemia (non-PKU HPA), and variant PKU.
- PAH gene 12q24
- Symptomes:intellectual disability and other serious health problems -seizures, delayed development, behavioral problems, psychiatric disorders are also common, lighter skin and hair,eczemas
- Treatment elimination diet
- **Diagnosis/testing.** PAH deficiency can be diagnosed by newborn screening

Spinal muscular atrophy-SMA

- Spinal muscular atrophy (SMA) is characterized by progressive muscle weakness resulting from degeneration and loss of the anterior horn cells (lower motor neurons) in the spinal cord and the brain stem nuclei. Onset ranges from before birth to adolescence or young adulthood. Poor weight gain, sleep difficulties, pneumonia, scoliosis, and joint contractures are common complications.
- **SMN1 gene(5q12.2-q13.3)-** About 95%-98% of individuals with SMA are homozygous for a deletion
- Clinical subtypes:

  severe infantile acute SMA (Werdnig-Hoffman disease)

  infantile chronic SMA

  juvenile SMA,(Kugelberg-Welander disease)

  adult-onset SMA.

X-linked recesive

- traits are fully evident in males because they have only one copy of the X chromosome.
- Females are not affected or have only microsymptoms
- An affected male cannot transmit the trait to his sons, because the trait is on X-chromosome, and the father must necessarily transmit his Y-chromosome to a son
- All 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

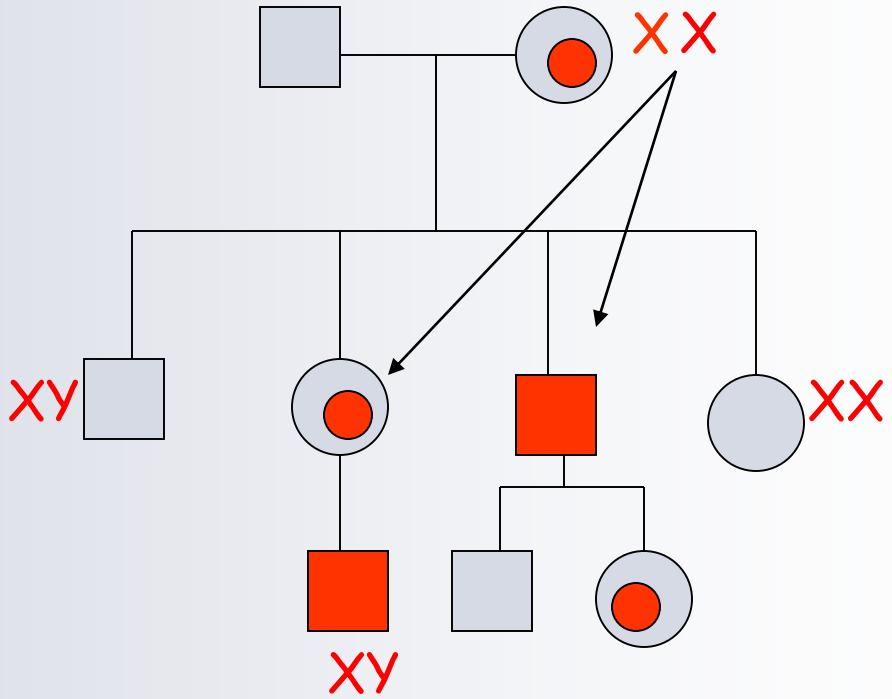
- Risk for daughters of a carrier mother- 50% for carrier

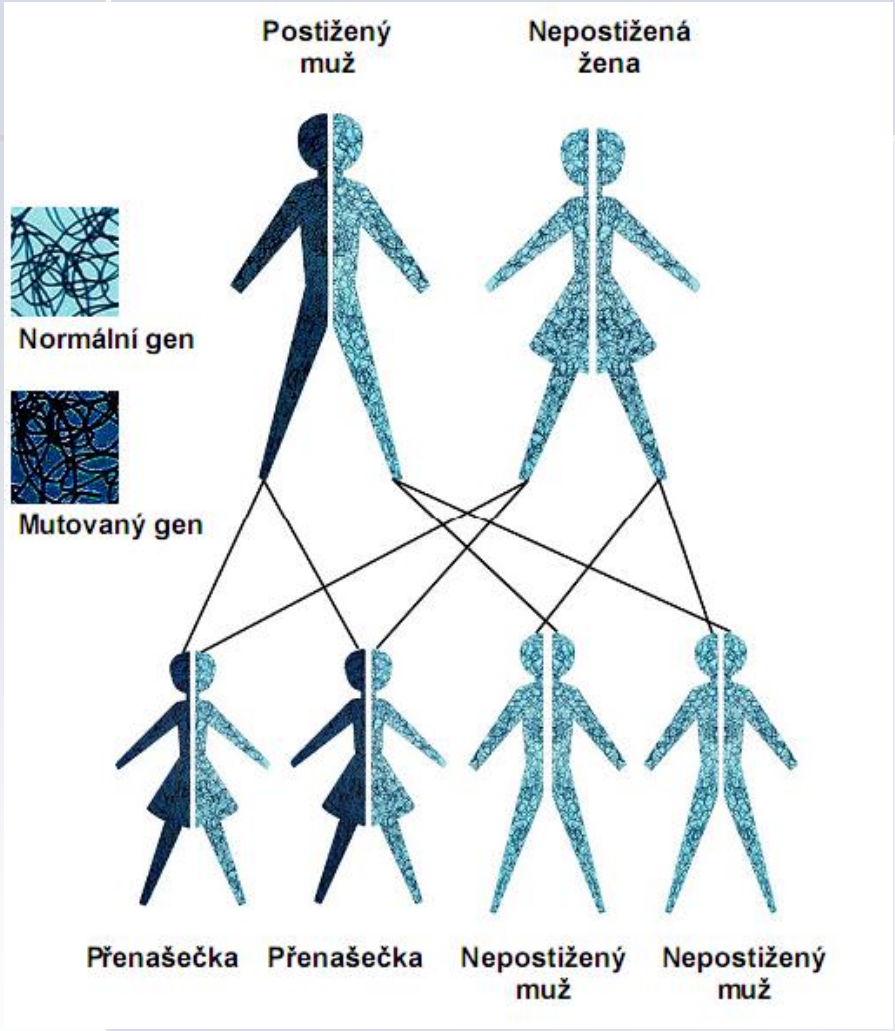
- Risk for sons of carrier mother

- 50% for disease

Pedigree

X- recesive inheritance




Postižený muž
Nepostižená žena
Normální gen
Mutovaný gen
Přenašečka
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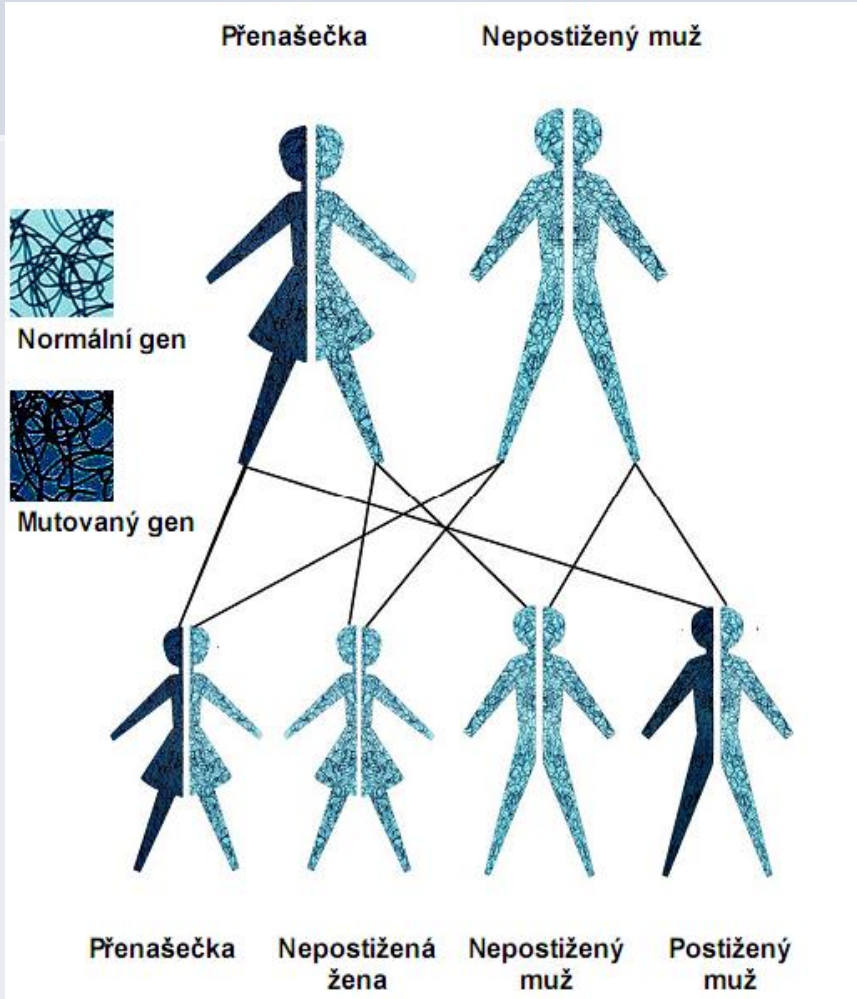
Přenašečka
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Postižený muž

XR - diseases

- Hemophilia A and B
- Duchenne and Becker muscular dystrophy

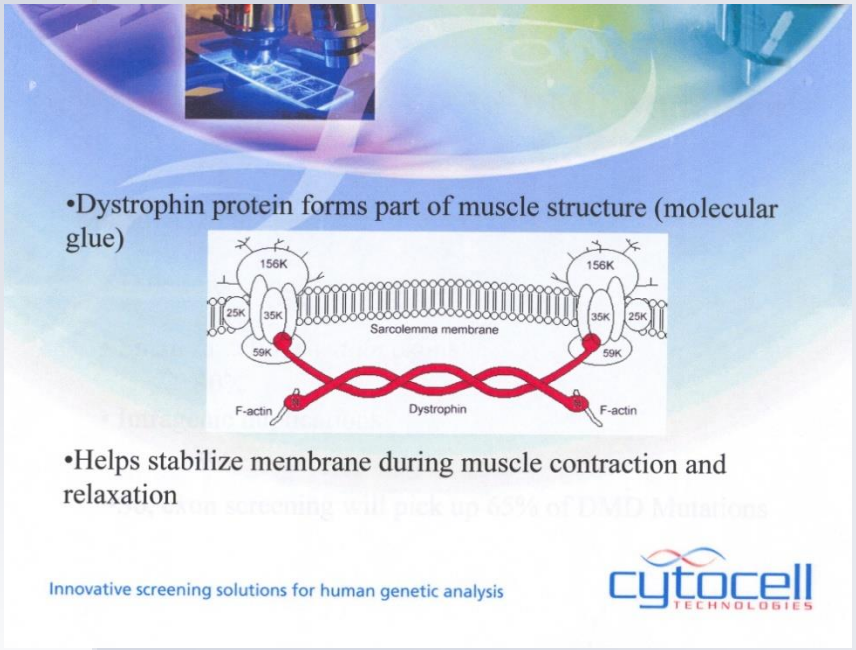
Hemophilia

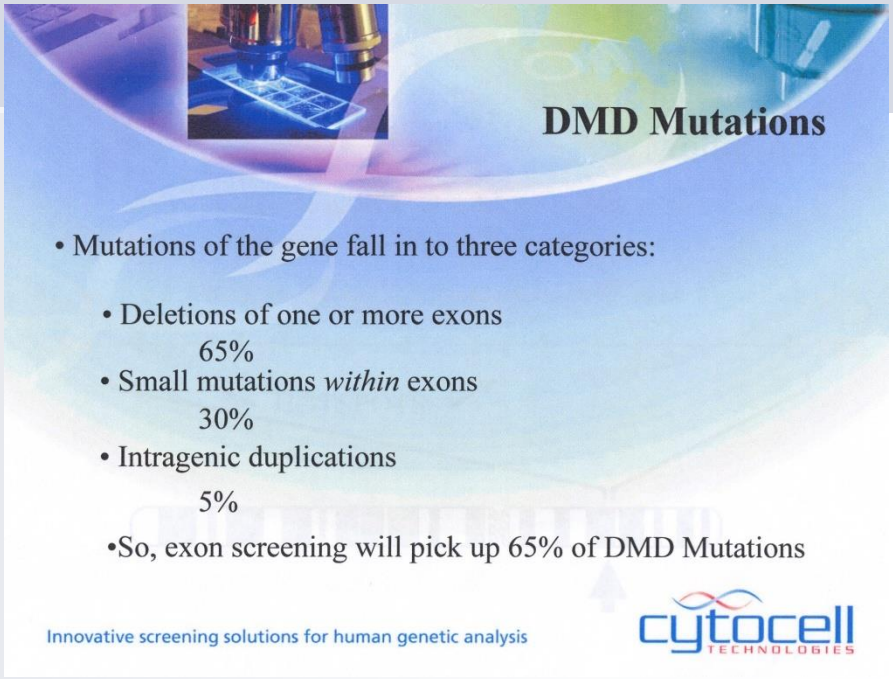
- Hemophilia A (clotting factor VIII deficiency,F8,Xq28)- 80% cases
- Hemophilia B(factor IX deficiency, F9, Xq27)-20% cases
- Characteristic symptoms vary with severity. In general symptoms are internal or external bleeding episodes
- Complication:deep muscle bleeding,haemarthrosis,intracranial hemorrhage,adverse reaction to clotting factor treatment,transfusion transmitted infection

Dystrophinopathies

- The dystrophinopathies include two alelic forms of muscular dystrophy , caused by mutations in *DMD gene*, which encodes the protein dystrophin-Xp21.2
- Duchenne muscular dystrophy (DMD) is rapidly progressive form, usually manifests in early childhood by problems with sitting and standing independently. Proximal weakness causes a waddling gait and difficulty with climbing. Affected boys are being wheelchair dependent by age 12 years. Cardiomyopathy occurs in individuals with DMD after age 18 years. Only few survive beyond the third decade, with respiratory complications and cardiomyopathy being common causes of death.
- Becker muscular dystrophy (BMD) is characterized by later-onset skeletal muscle weakness; individuals move independently into their 20s. Despite the milder skeletal muscle involvement, heart failure from DCMP is a common cause of morbidity and the most common cause of death in BMD. Mean age of death is in the mid-50s.

Duchenn/Becker muscular dystrophy



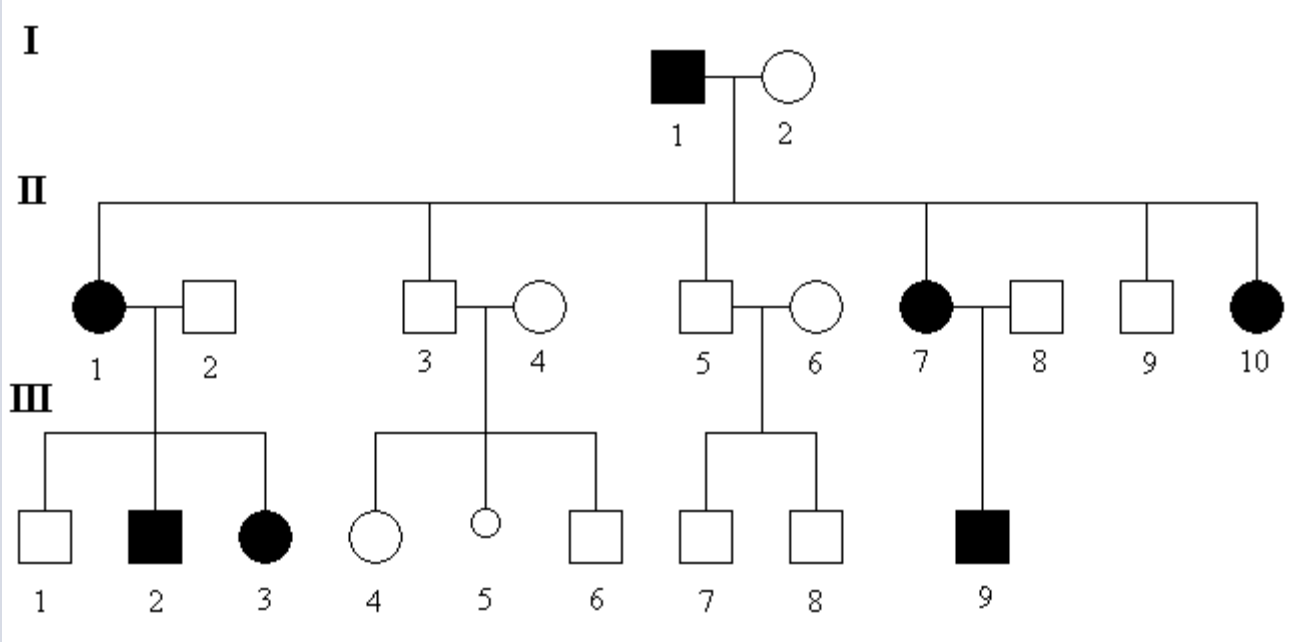


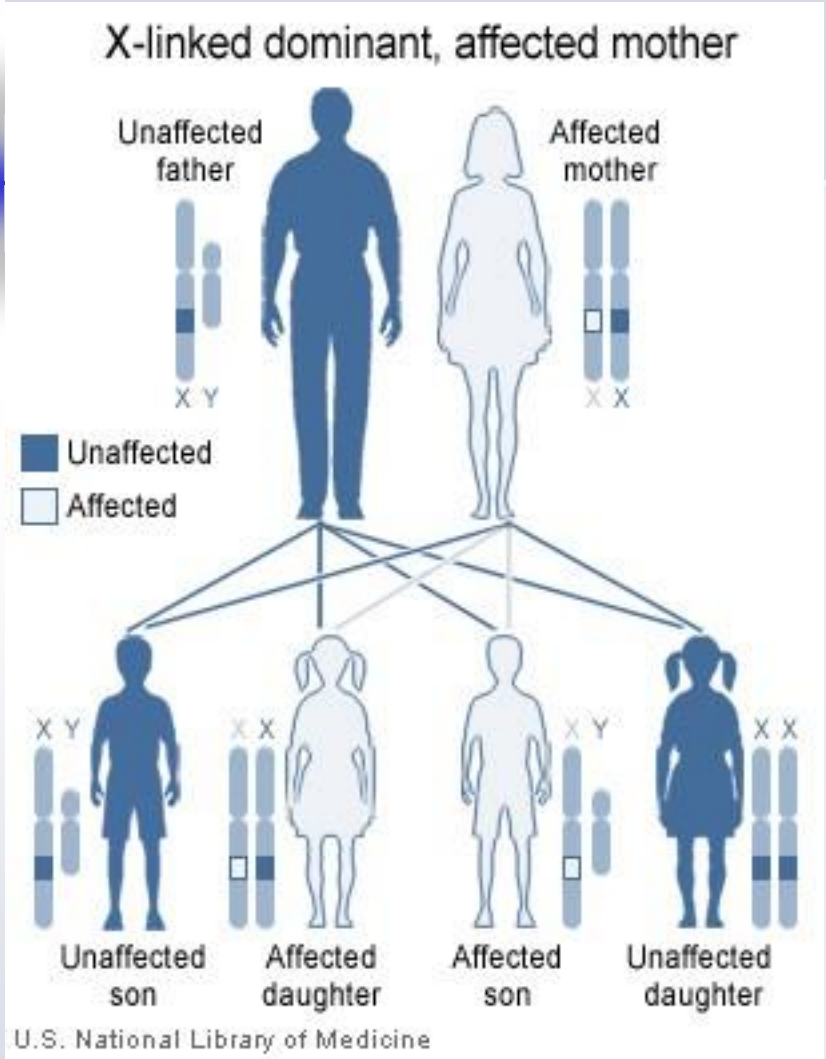
X linked-dominant

- The pattern may at first glance be mistaken for AD inheritance, but if offspring of affected males are considered,all sons are unafected,all daughters are affected
- Sometimes the disorder is visible only in the heterozygous females, the affected(hemizygous) males being undetected or appearing as an excess of spontaneous abortion

- Fragile X syndrome
- Rett syndrome

Pedigree- X-linked dominant




X-linked dominant, affected mother
Unaffected father
Affected mother
X Y
X X
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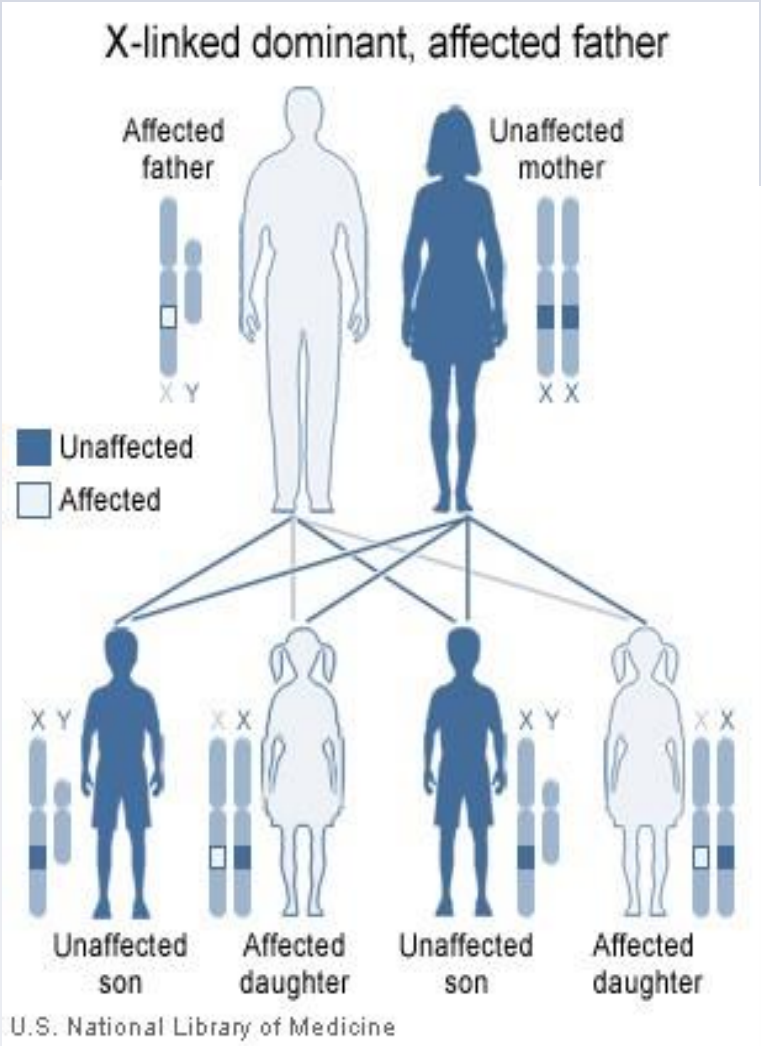
X X
Unaffected son
Affected daughter
Affected son
Unaffected daughter
U.S. National Library of Medicine


X-linked dominant, affected father
Affected father
Unaffected mother
X Y
X X
Unaffected
Affected
X Y
X X
X Y
X X
Unaffected son
Affected daughter
Unaffected son
Affected daughter
U.S. National Library of Medicine

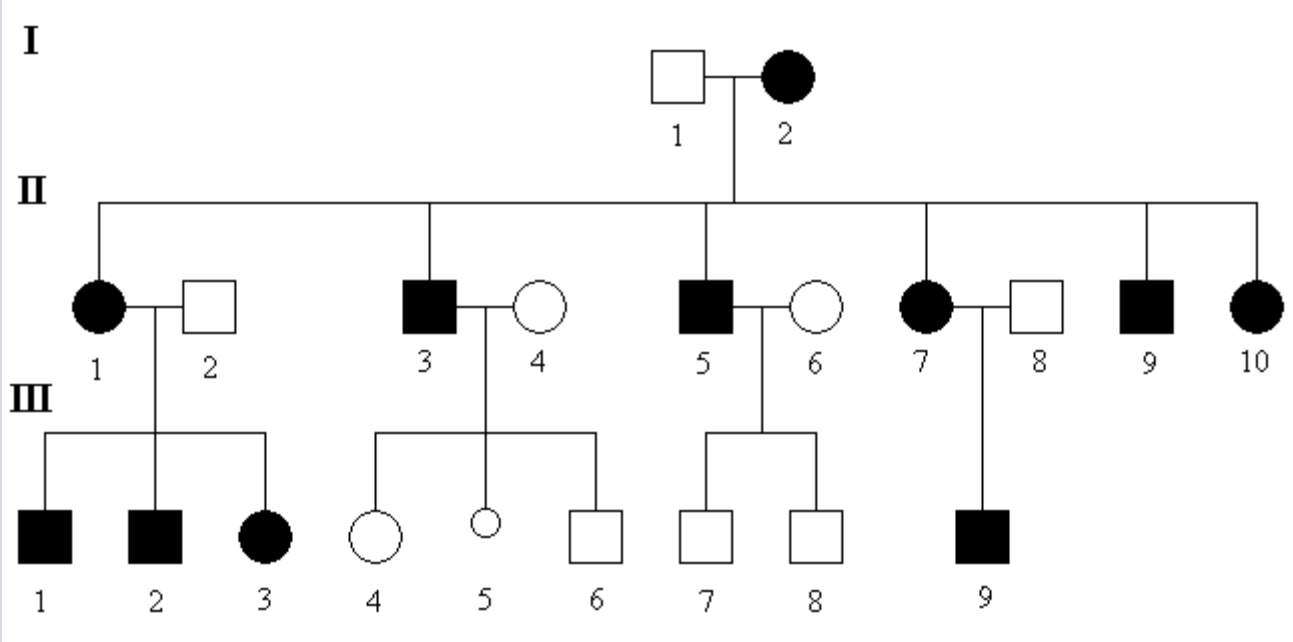
Fragile X syndrome

- most common form of inherited mental retardation - developmental delay, variable levels of mental retardation, and behavioral and emotional difficulties.
- characteristic somatic traits-macrocephaly,coarse facial features, large forehead,long face,prominent jaw ,large ears. macroorchidism-postpubertal
- Generally, males are affected with moderate mental retardation and females with mild mental retardation.
- FMR1 gene- FRAXA (Xq27.3)
- a trinucleotide (CGG)n repeat expansion of greater than 200 repeats.

Mitochondrial inheritance

- Mitochondrias are organelles found in the cytoplasm of cells and they have multiple copies of a circular chromosome- mitochondrial DNA
- Because only egg cells carry mitochondria to the developing embryo, only mothers can pass on mitochondrial conditions to their children- maternal inheritance
- The primary function of mitochondria is conversion of molecule into usable energy. Thus many diseases transmitted by mitochondrial inheritance affect organs with high-energy use such as the CNS,heart, skeletal muscle, sensory organs, liver, and kidneys.

Maternal inheritance



Mitochondrial diseases

- Mitochondrial myopathy,encephalopathy ,lactic acidosis and stroke-like episodes **MELAS**
- Leber hereditary optic neuropathy- **LHON**
- Myoclonic epilepsy associeted with ragged-red fibers- **MERRF**
- Neuropathy, ataxia and retinitis pigmentosa **NARP**

Multifaktorial –polygenic inheritance

Charakterization

- disease with multifactorial inheritance includes non mendelian types of inheritance

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

Charakterization

- in the pathogenesis of the disease play an important role non-genetic factors
- disease is more common among close relatives and in distant relatives is becoming less frequent
- risk of recurrence can be determined empirically

Empirical risk

- The risk of recurrence of the disease observed in similar families and relatives of the same degree of affinity

Monogenic x multifactorial inheritance

Monogenic

- In early age
- No enviromental influence
- Typicaly inheritance patterns sometimes according the gender
- High penetrance
- Low frequency

Multifactorial

- In later age
- Combination genetic and enviromental factors
- No typical patterns of inheritance
- Incomplete penetrance
- High frequency

Examples

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

Congenital heart defects

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

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 CLP 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

Genetic risks in cancer

Cancer- genetic connection

The second most common cause of death

Every third person has risk of tumour

- **80% sporadic cancers**
- **10% common cancers - familial**
- **10% - hereditary tumour syndromes following mendelian inheritance**

Hereditary tumour syndromes

- 2 or more cases of occurrence in the family
- Particularly young age of onset
- Combination of certain types of cancer(breast and ovarian cancer, uterine and colorectal ca)
- Any evidence of more then one of the rare tumour in family
- Bilateral occurrence in paired organs
- Multiple cancers in a single individual
- Strong family history of a single form of cancer
- Mendelian inheritance, usually AD

Common cancers

- 2 or more cases of occurrence in the family
- Onset- later in life(older age)
- unclear inheritance (random occurrence, environmental factors, genetic factors - genes with low penetrance, polygenic inheritance)

Familial tumour syndromes with folloving AD inheritance- examples

- **Breast cancer (BRCA 1,2)**
- **Lynch syndrome (HNPCC) (MMR genes, MLH1, MSH2, PMS1, PMS2, MLH6)**
- **FAP (APC gene)**
- **Li Fraumeni syndrome - P53 gene**
- **Von Hippel Lindau syndrome (VHL gene)**
- **MEN 1 a 2 (Ret oncogene)**
- **Retinoblastoma- (Rb gene)**
- **Neurofibromatosis 1,2 - gene NF1,2**
- **Wilms´ tumour (WT1gene)**
- **Cowden disease (PTEN)**

The target of genetic testing

- Is in the family genetic predisposition?
- To identify persons at risk
- To ensure molecular genetic testing as possible
- Predictive testing of relatives at risk
- To ensure primary and secondary prevention in cooperation with oncologists and other specialists

Conditions of genetic testing

- The examination is indicated by a clinical geneticist- genetic counseling, always informed consent
- The genetic test is voluntary, from testing the patient may withdraw or refuse to know the result at any time
- protocol procedures
- Optimal is the beginning of an examination with a sick person in the family
- if the mutation is not found in the patient, it does not mean that hereditary form in the family is excluded
- Appropriate is also psychological support

Methods of genetic testing

- Testing of individual risk genes -Sanger Sequence testing, screening methods (HRM-high-resolution analysis of melting curves, high resolution liquid chromatography, …)
- MLPA (Multiple Ligase Conditional Amplification) to detect intragene deletions/duplications
- NGS, Panel Screening (ThruSight Cancer panel, CZECANCA, BRONCO)
- Whole-exome sequencing - so far only research.

NGS

- Fast diagnosis involving a larger spectrum of causal genes
- The analysis of the results is complex, but difficult, necessary to filtrate insignificant variants, verificate potentially pathogenic variants
- Verification of pathogenic mutation by an independent method (Sanger. sequencing)
- It captures point mutations, but does not capture larger deletions / duplications - MLPA
- Difficult examination of genes containing pseudogens

Primary prevention

- Reduce pollutants- no smoking, alcohol…
- diet with reduced fat, meat, spicy dishes, sausages
- enough fiber, at least 4 to 5 portions of fruit and vegetables a day
- stress prevention
- prevention of sunburn
- adequate physical activity

Secondary prevention

- Specific procedures for monitoring or preventive treatments given at different syndromes with regard to the amount of risk and patient age

Hereditary Breast and Ovarian Cancer Syndrome

- BRCA1, BRCA2
- Other: TP53, MLH1, MSH2, MSH6, STK11, CDH1, PTEN, CDKN2A,ATM,CHEK2,PALB2, BRIP1
- High risks of breast and ovarian ca
- Other:carcinoma of the uterus, prostate, stomach,colorectal, pancreas
- Secondary prevention: selfmonitoring, UZ, mammography,NMR,tumor markers, occult blood test, colonoscopy, gastroscopy, mastectomy and ovariectomy

HNPCC-Lynch syndrome

- MMR genes, MLH1, MSH2, PMS1, PMS2, MLH6)
- High risk of colorectal ca
- Other: ca of uterine, stomach, liver, kidneys, brain tu
- Secondary prevention: colonoscopy, gastroduodenoscopy, gynecology(vaginal US), abdominal US, tu markers, urological ex., MMG,

FAP

- APC gene
- Multiple adenomatous polyps
- Age: 7-35
- High risk of colorectal ca, other: meduloblastoma, thyreoid ca,hepatoblastoma, ca of pancreas, stomach
- Secondary prevention: colonoscopy, gastroscopy, protecticve bowel resection

Von Hippel-Lindau syndrome

- Gene VHL
- Retinal hemangioblastomas, hemangioblastomas of CNS, multiple renal, pancreatic or hepatal cysts, pheochromocytoma,
- Secondary prevention: ophtalmology,neurology,endocrinology, CT,NMR,US

Li-Fraumeni syndrome

- geneTP53
- breast cancer, soft tissue sarcoma, osteosarcoma, brain tumors, adrenal tumors, leukemia,melanoma, gastric, pancreatic, colorectal ca, etc.
- Difficult prevention

Presymptomatic testing

- Specific
- Protocol procedures
- Up to 18 years (exception-FAP, MEN, VHL, Rb,WT, NF-where can offer prevention in children)
- completely voluntary
- Genetic consultation before testing-meaning informed consent, follow-up information
- Genetic consultation after notification of the result of test-resulting risks, prevention (surveillance, surgery, chemoprevention)
- Transmission contact to specialist –doctors providing preventive monitoring, including a psychologist

Problems

- **Ethical:** we can not eliminate tumor formation
  difficult prevention in some syndromes
- **Psychological:** high risks lifetime
  high risks for children
  division of family members on healthy x ill
- **Social:** risk of discrimination such as commercial insurers, employers

Preconception counseling

- Birth control
- Monitoring of spontaneous chromosomal aberrations
- cryopreservation of gametes
- monitoring risk pregnancies
- Prenatal diagnosis,
- IVF-PGD

Molecular genetic testing

- **Detection of mutations**
- **Search asymptomatic carriers**
- **Prenatal diagnosis, PGD**
- **Predictive testing of diseases with onset in adulthood**
- **Onkogenetic -diagnosis, predictive testing**
- **Paternity and relationship testing**

Teratogens

Teratogens

- teratogen is a substance whose by 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 (infectious agents...)
- Metabolic imbalance (disease of mother)

The effect of teratogens depends on :

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

Critical period

- **14.-18. day after conception –applies the rule „all or nothing "**
- **18.-90. day – organogenesis**
- **The most sensitive period for the emergence of developmental defects**
- between 5. to 7. week of pregnancy is the most sensitive period for individual organs

Critical periods

- 3th to 6th week - CNS, heart
  4th to 7th week - limbs and eyes
  6th to 8th week - teeth
  late 6th - to 12th week – palate
  7th-12th week - external genitalia
  4th to 12th week - ears

X-ray

- mutagenic effect
  teratogenic effects
- growth retardation, major congenital malformations ,fetal death

  border dose - 0.6 Gy
  teratogenic dose - 2.0 Gy
  conventional X-ray examination. dose of 0.01 Gy
- calculation of radiation doses-Institute of Nuclear safety

Drugs

- Distribution of medicines in practice into categories
- A
- B
- C
- D
- X
- Food and Drug Administration, 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 have shown adverse effect, but in controlled studies in women it have not been confirmed

product appears to be relatively safe

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

The product should be administered with caution and only in cases where the benefit for the woman of its 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
- Thyreostatic drugs
- Androgens
- Penicilamin
- Enelapril, Captopril
- Antituberkulotics-Streptomycin

Thalidomide

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

Hydantoins

- are used to treat a wide range of seizures types.
- Atypicaly face, growth retardation, mild mental retardation, behavioral problems, hypoplastic nails and fingers

Aminopterin a Methotrexat

- folic acid antagonist
  facial dysmorphias, cleft lip and/or palate, small mandible, ears anomalies, hydrocephaly, growth and mental retardation, miscarriages

Warfarin

- coumarin antikoagulans
- facial dysmorphias – 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, antropozoonosis, chlamydia..)

- TORCH

Consequences of Infections

- direct infection of the fetus and its consequences
- infection of the placenta-failure of the exchange of oxygen and nutrients
- prolonged high fever mother may affect fetal development, even without direct infection
- infection of the membranes can cause premature labor or miscarriage otherwise healthy fetus
- Some developmental disorders can be caused by infection treatment

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 damage, mental retardation
- Eye defects

- Prenatal dg. - serology, DNA-PCR

Metabolic dysbalance

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

Fetal alcohol syndrom

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

- Abuse of 60g pure alcohol / day (longterm)
- Combine with malnutrition, folic acid deficiency, inadequate health care...

Maternal Phenylketonuria

- Low birth weith
- hypertonia
- mikrocefaly, mental retardation
- Cong. heart defects
- hyperaktivity

Diabetes mellitus

- risk of congenital malformations to the fetus 2-3x higher
  CNS - anencephaly, microcephaly
  cardiovascular and genitourinary anomalies
  skelet - caudal regression syndrome
  face - cleft palate, eye involvement
  Prevention - preconception compensation

Hypothyreosis

- coarse facial features, macroglossia, inverted nose
  brachycephalia
  dry skin, sleepiness, constipation
  delayed bone maturation, short stature, oligophrenia, hearing loss, disruption hips (duck walk)

- Hyperthyreosis - rather risk SA

Genetic consulting

- Primary prevention (pre-conception advice, which proposes an optimal procedure)
- Secondary prevention (to adjust therapy during pregnancy, to ensure specific prenatal. diagnosis)

  Extreme solutions – possibility of medical termination of pregnancy

Medical termination of pregnancy

- until the end of 24th. week of pregnancy in Czech Republic- of law
- (determined by the Act and the Decree of the Ministry of Health in CR)
- It indicates only a clinical geneticist!
- Respecting the decisions of pregnancy