Inheritance patterns

Inheritance Patterns

- The inheritance patterns trace the transmission of genetically encoded traits, conditions or diseases to offspring.
- There are several modes of inheritance:
- **Single Gene or Mendelian**
- **Multifactorial**
- **Mitochondrial**

Single Gene Inheritance

- Genetic conditions caused by a mutation in a single gene follow predictable patterns of inheritance within families.
- Single gene inheritance is also referred to as Mendelian inheritance as that follow transmission patterns he observed in his research on peas.

Monogenic disorders

- Precise and well-established risks can be given regarding its occurrence in other family members
- DNA analysis is possible in some cases

Monogenic diseases

- Typicaly in childhood- not exclusively!
- Less then10% manifest after puberty,

  1% after reproductive age
- Incidence of monogenic disorders- 0,36%

Mendelian inheritance-types

There are four types of Mendelian inheritance patterns:

Autosomal dominant

Autosomal recessive

X-linked recessive

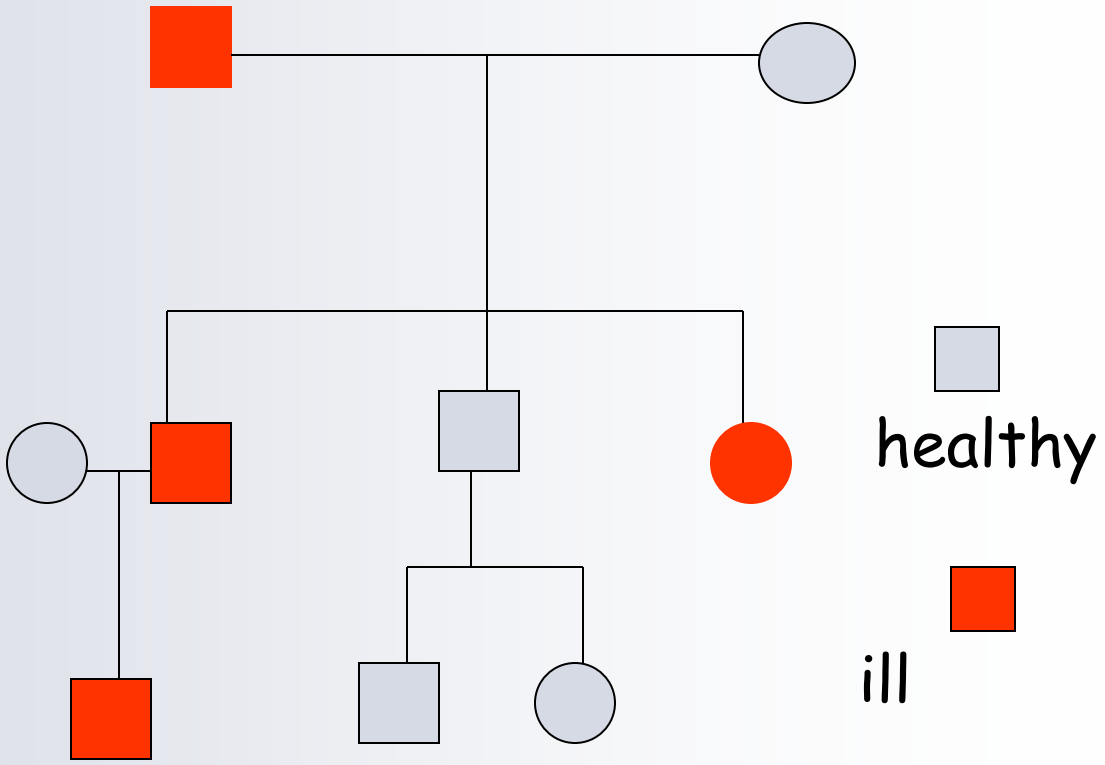
X-linked dominant

Autosomal Dominant

- the gene responsible for the phenotype is located on one of autosomes
- The sexes are involved equally
- Conditions are manifest in heterozygotes
- Affected individual's 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.

Pedigree AD inheritance

- the risk 50%



AD - diseases

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

Neurofibromatosis

- member of the *neurocutaneous syndromes* (*phakomatoses*)
- **NF type I-** from nerve tissue grows benign tumors (neurofibromas)

NF1 gene-neurofibromin(17q11.2)

Café au lait spots,Neurofibromas, plexiform Neurofibromas axillary and inguinary freckling, Iris Hamartomas(Lisch nodules),MR 10-30%, skeletal symptoms

- **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

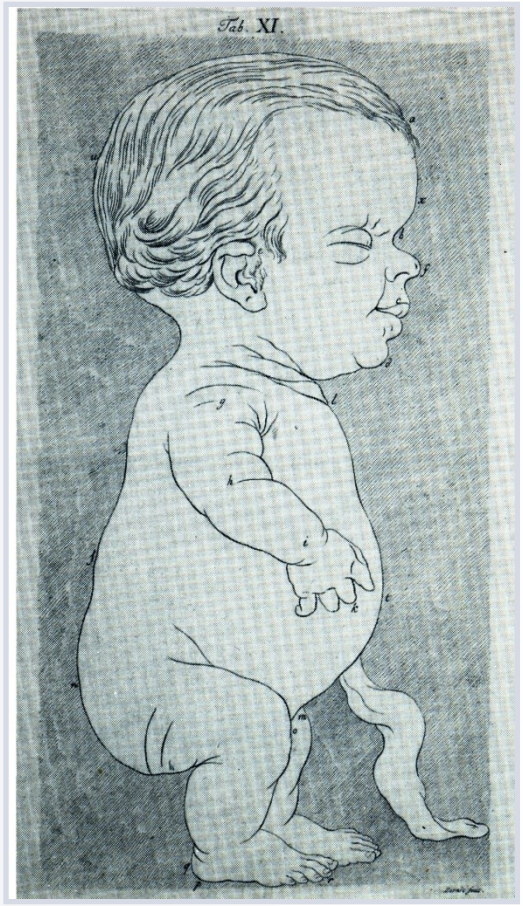
- trinucleotide repeat expansion (CTG)n in the dystrophia myotonica-protein kinase gene (DMPK) 19q13.32
- Myotonia (delayed muscle relaxation after contraction), cataract,atrial arrythmias, hypogonadism, testicular atrophy
- congenital form(over 2000 repeats)-hypotonia, poor feeding,severe mental retardation, 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
80% 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.
- The diagnosis of HD rests on positive family history, 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

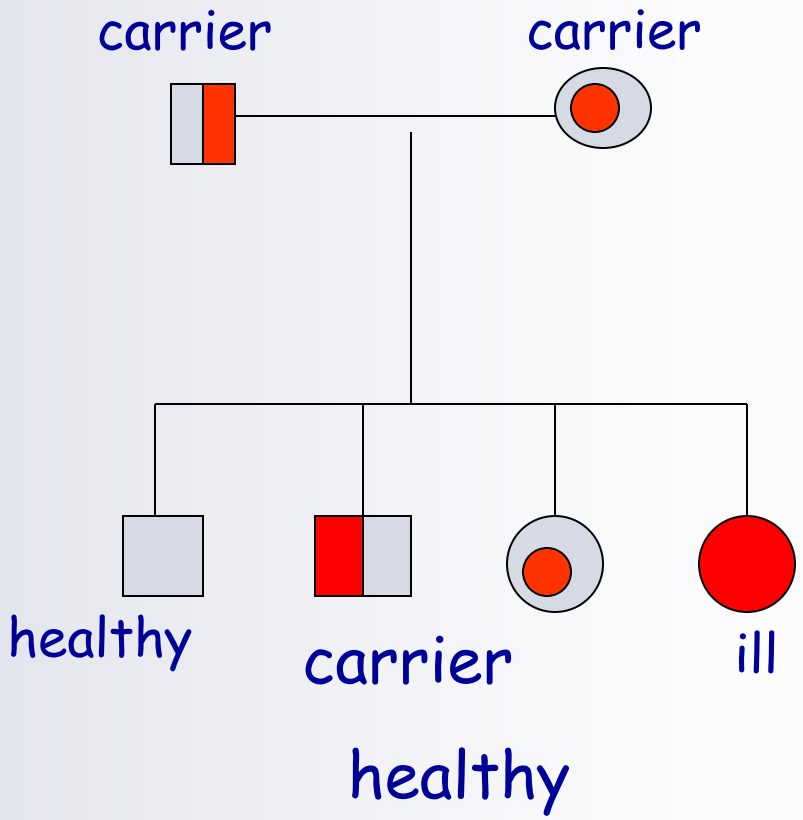
- Predictive testing in asymptomatic adults at 50% risk is possible but requires careful thought
- including pretest and post-test genetic counseling
- Asymptomatic at-risk individuals younger than age 18 years should not have predictive testing.
- prenatal testing by molecular genetic testing is possible 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 manifest 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%



Consanguinity

- Consanguineous marriage is the union of individuals having a common ancestor. It is categorized as 1^{st}, 2^{nd} and 3^{rd} 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

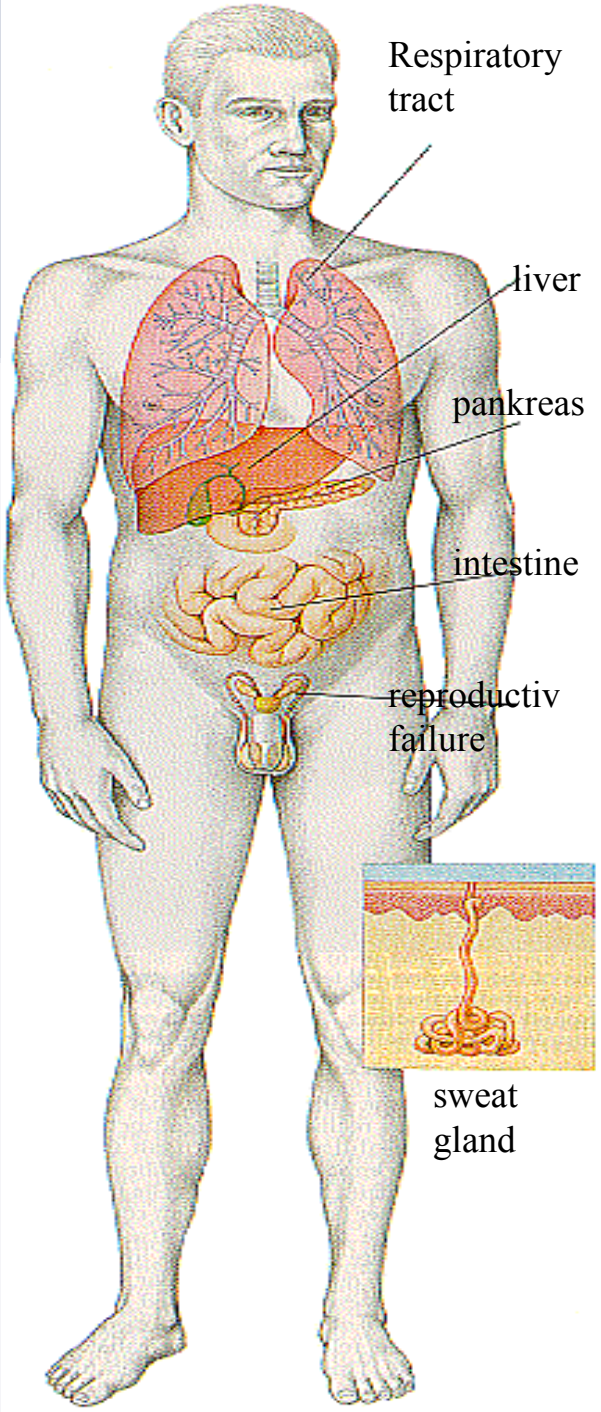
- Localized on chromosome 7q
- CFTR gene
- Frequency of Cystic Fibrosis in the Czech Republic: about 1/3000
- Frequency of heterozygots in the Czech Republic about 1/25-1/29
- About 1900 mutations in CFTR gene were identified

CF-ethnical differences

	frequence of CF	frequence of heterozygotes
Caucasians	1/3000	1/25
Hispanics	1/9000	1/46
Amer. Africans	1/15000	1/60
Asians	1/32000	1/90

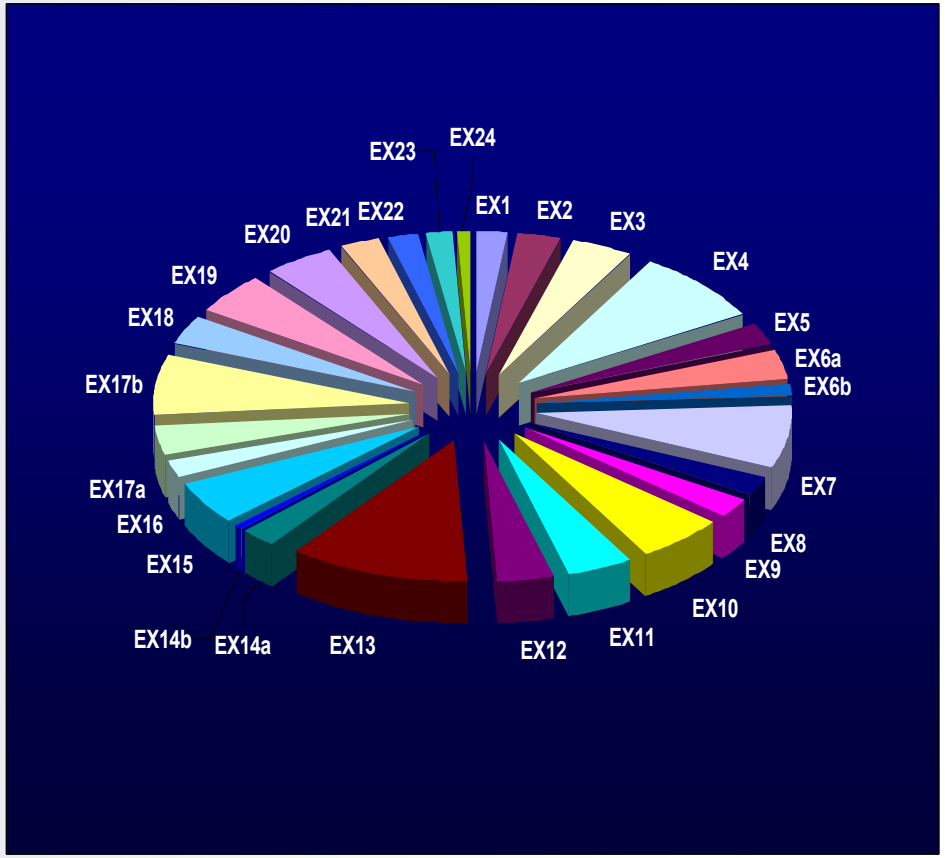
Cystic fibrosis

- 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(CYP21 deficiency, 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 only have one copy of the X chromosome.
- Females are not affected as severaly as males or are not affected
- 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 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

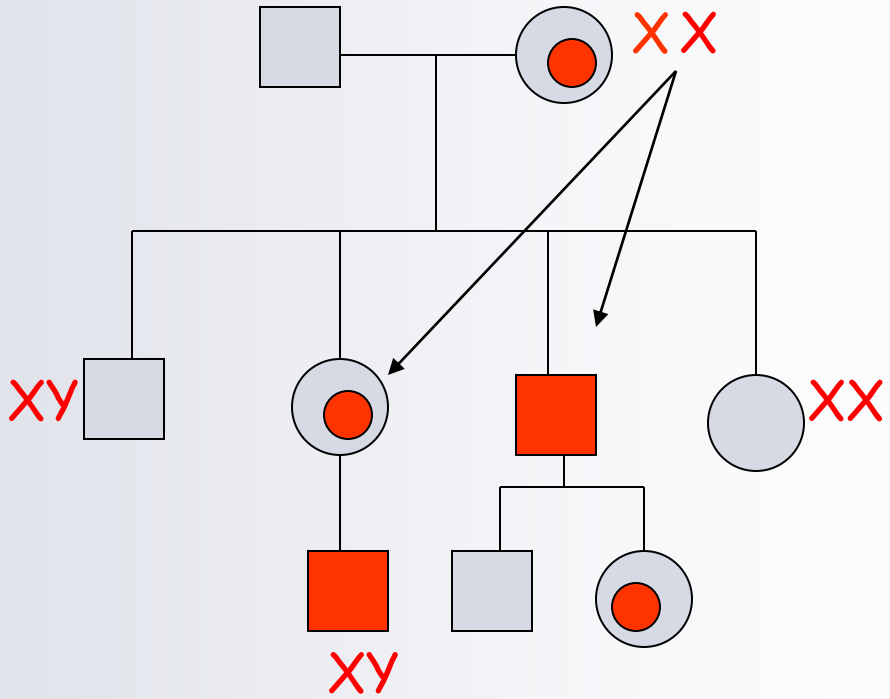
- Risk for daughters of a carrier mother- 50% for carrier

- Risk for sons of carrier mother

- 50% for disease

Pedigree

X- recesive inheritance



XR - diseases

- Hemophilia A and B
- Duchenne and Becker muscular dystrophy

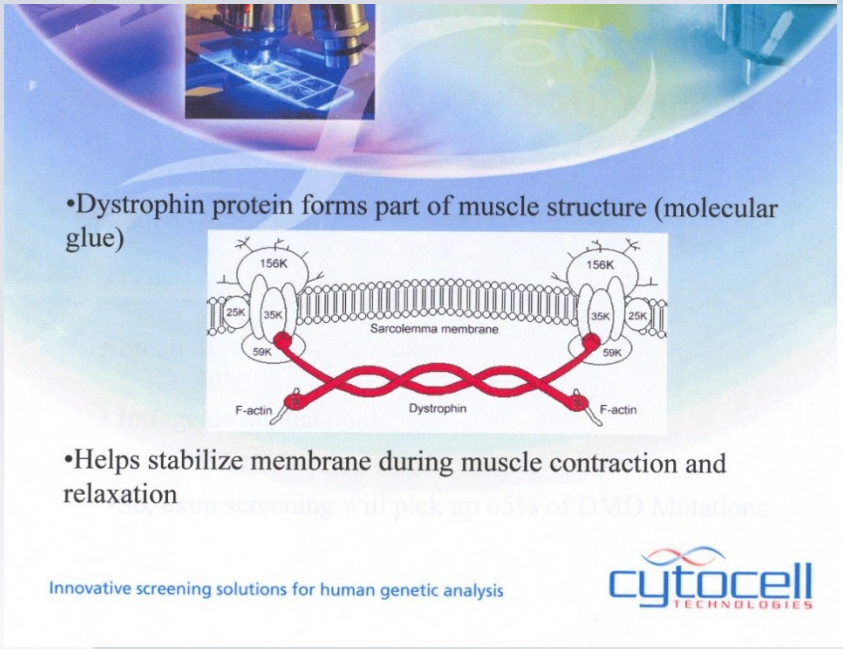
Hemophilia

- 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 a spectrum of muscle disease caused by mutations in *DMD gene*, which encodes the protein dystrophin-Xp21.2
- Duchenne muscular dystrophy (DMD) usually presents in early childhood by delays in sitting and standing independently. Proximal weakness causes a waddling gait and difficulty climbing. DMD is rapidly progressive, with affected children being wheelchair dependent by age 12 years. Cardiomyopathy occurs in individuals with DMD after age 18 years. 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 DCM 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

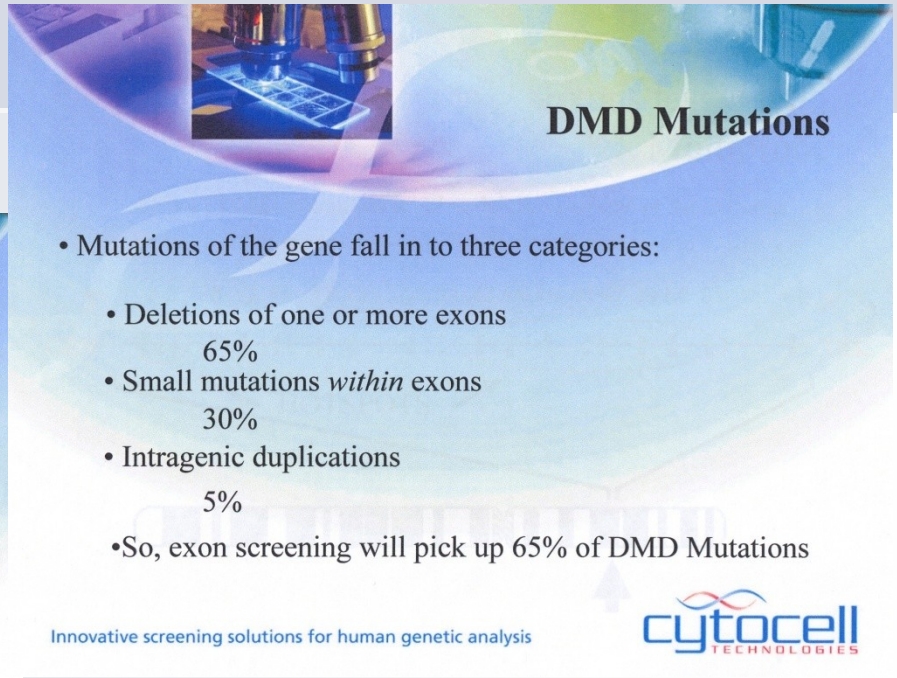


•Dystrophin protein forms part of muscle structure (molecular glue)

•Helps stabilize membrane during muscle contraction and relaxation

Innovative screening solutions for human genetic analysis

cytocell TECHNOLOGIES



DMD Mutations

- Mutations of the gene fall in to three categories:
  - Deletions of one or more exons
    65%
  - Small mutations *within* exons
    30%
  - Intragenic duplications
    5%
- So, exon screening will pick up 65% of DMD Mutations

Innovative screening solutions for human genetic analysis

cytocell TECHNOLOGIES

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 seen only in the heterozygous females, the affected(hemizygous) males being undetected or appearing as an excess of spontaneous abortion

- Incontinentia pigmenti
- Vitamin D resistant rickets
- Rett syndrome

Fragile X syndrome

- most common form of inherited mental retardation - developmental delay, variable levels of mental retardation, and behavioral and emotional difficulties.

  - characteristic physical traits-macrocephaly,coarse facies ,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.

Genetic risks in cancer

Cancer- genetic connection

- **80% sporadic cancers**
- **10% common cancers**
- **5-10% - familial tumour syndromes following mendelian**

Hereditary tumour syndromes

- 2 or more cases of occurrence in the family
- Particularly young age at onset
- Combination of certain types of cancer(breast and ovarian cancer, uterine and colorectal ca)
- Any evidence of one of the rare tumour syndromes
- 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
- Incidence in later 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)

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
- 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

Neurofibromatosis

- Gene NF1,NF2
- Secondary prevention: neurology, dermatology, ophtalmology, orthopedy, ORL, CT,NMR,US…

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

Problemes

- 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

Syndromes of chromosomal instability

- Specific mendelian disorders showing a generalized tendency to malignancy especially in early life
- Follow autosomal recesive inheritance-most
- Inborn errors of DNA repair
- Immune deficiencies

Syndromes predisposing to malignancy-examples

- Xeroderma pigmentosum AR
- Fanconi pancytopenia AR
- Ataxia teleangiectasia AR
- Bloom syndrome AR
- Cockayne syndrome AR
- Nijmegen syndrome AR
- Werner syndrome AR
- Wiskot-Aldrich syndrome XR

Mitochondrial inheritance

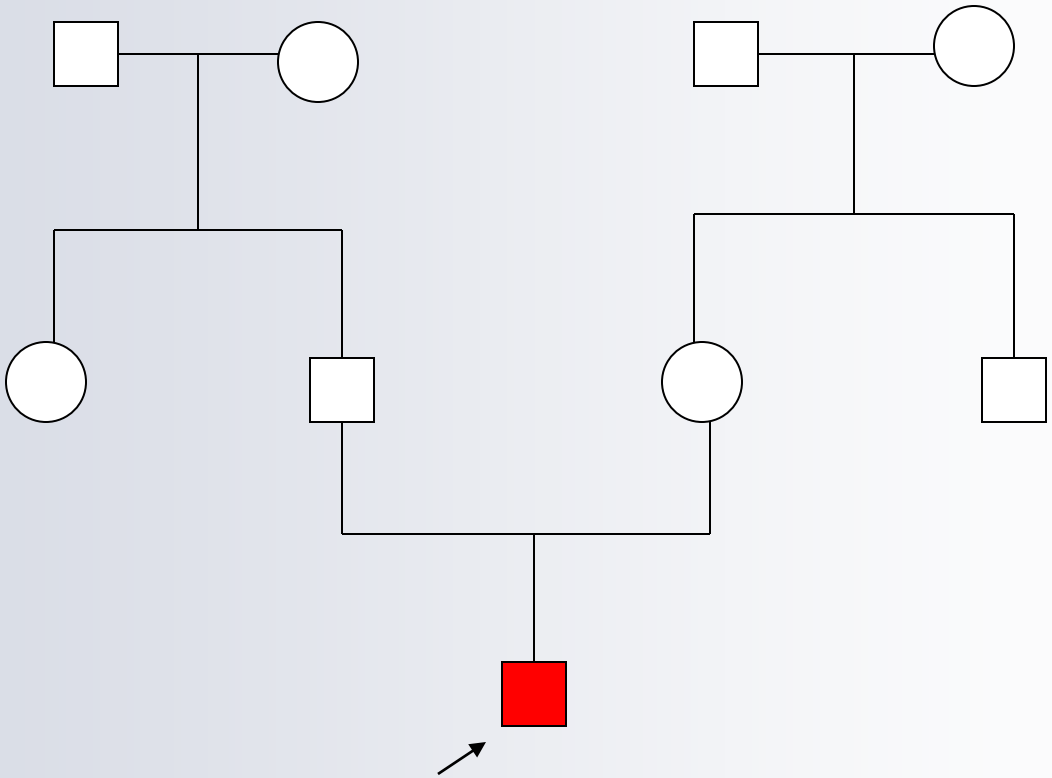
- Mitochondrias are organelles found in the cytoplasm of cells and they have multiple copies of a circular chromosome- mitochondrial DNA
- Because only egg cells contribute mitochondria to the developing embryo, only mothers can pass on mitochondrial conditions to their children- maternal inheritance
- 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, liver, and kidneys.

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

Pedigree- usual situation



Molecular genetic testing

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

Diseases with a single causative mutation

- Huntington disease
- Myotonic dystrophy
- Fragile X syndrome

- **DNA analysis can confirm or exclude disease**

DNA diagnosis difficult

- Large genes
- Private-unique mutations
- disease with multiple genes responsible

Multifaktorial –polygenic inheritance

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**
- 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 kindship

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

Common congenital defects

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 first-degree relatives	50
Sib of isolated case	2-3
Second-degree relatives	1–2
Offspring-affected father	2-3
Offspring—affected mother	5
Two affected sibs	10

Cleft lip and palate

- Population incidence 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

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 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. day after conception – 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-rays

- 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 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 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..)

Hydantoin

- 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 dysmorfism, cleft lip and/or palate, small mandible, ears anomalies, hydrocephaly, growth and mental retardation, miscarriages

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, antropozoonosis, chlamydia..)**

- abbreviation **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
- severe, life-threatening infection of the mother at the same time threatens the life of the fetus
- infection of the membranes can cause premature labor or miscarriage otherwise healthy fetus
- Some developmental disorders can cause 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 domage, 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

  Untreated - short stature, oligophrenia, hearing loss, disruption hips (duck walk)
  Hyperthyreosis - rather risk SA

Genetic consulting

- Primary prevention (pre-conception advice, based on the history of an optimal procedure)
- Secondary prevention (adjust therapy during pregnancy, to ensure specific prenatal. diagnosis)

  Extreme solutions – genetic indication of interruption of pregnancy

Medical termination of pregnancy

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