Genetic diseases
Genetics in dentistry

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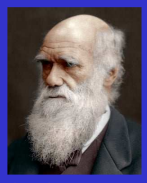
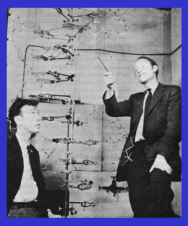
History of genetics

- The first theories of heredity – Aristoteles, Hypokrates, Epikuros
- 1859 – Charles Darwin – „On the Origins of Species"
- 1866 – Johann Gregor Mendel – scientist, Augustinian friar and abbot of St. Thomas' Abbey in Brno – „father of genetics" – Mendelian laws of inheritance
- 1944 - Oswald Awery - isolated DNA as the material of which genes and chromosomes are made.
- 1953 - James Watson and Francis Crick - structural model of DNA - in 1962 Nobel price.
- Francis Crick – „Central dogma"
  DNA → RNA → protein
- From 1990 – Human Genome Project
- 2003 – the first official information about complete mapping of human genome, but still „filling of gaps"
- 2022 - the complete sequence of a human Y chromosome


Charles Darwin


Johann Gregor Mendel


James Watson and Francis Crick

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Genetic code

- genetic information is written in the structure of DNA in the form of a genetic code
- genetic code – nucleotide triplet
- 1 triplet (1 codon) determines an inclusion of one amino acid to protein chain

Central dogma of molecular biology (F. Crick 1958)

How genetic information is expressed

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Genetic information

Redundancy (degeneration) of genetic code

6	CGA CGC CGG CGT AGA AGG	Arg	
	CTA CTC CTG CTT TTA TTG	Leu	
	TCA TCC TCG TCT AGC AGT	Ser	
4	ACA ACC ACG ACT	Thr	
	CCA CCC CCG CCT	Pro	
	GCA GCC GCG GCT	Ala	
	GGA GGC GGG GGT	Gly	
	GTA GTC GTG GTT	Val	
3	ATA ATC ATT	Ile	
2	AAA AAG	Lyz	
	AAC AAT	Asn	
	GAC GAT	Asp	
	CAA CAG	Gln	
	TAC TAT	Tyr	
	CAC CAT	His	
	TGC TGT	Cys	
	GAA GAG	Glu	
	TTC TTT	Phe	
	TAA TAG TGA	Stop	
1	ATG	Met Start	
	TGG	Trp	

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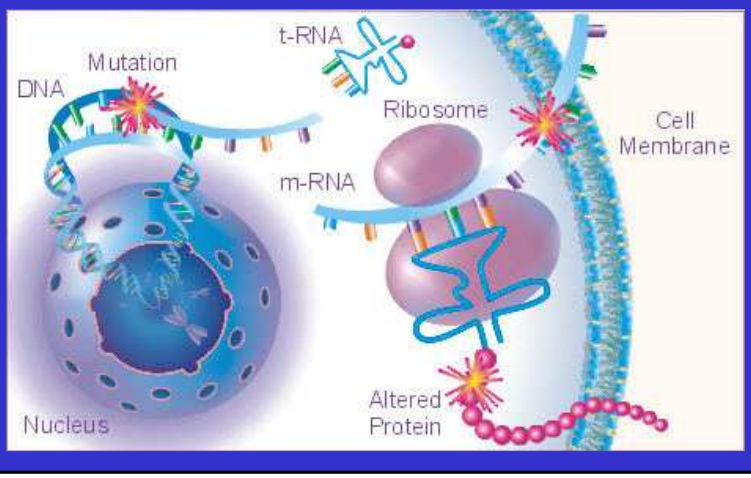
Mutations



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Mutations - definition

- Changes in DNA structure, changes in nucleotide sequence

Mutations - classification

- Etiology
  - **spontaneous** – mistakes in replication, DNA repare mechanisms
  - **induced** - mutagens (physical, chemical, biological)
- Localisation
  - **gametic**
  - **somatic**
- Extenth
  - **single gene mutations (point mutations)**
  - **structural chromosomal aberrations**
  - **numeric chromosomal aberrations**

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- Effect on gene function
  - **Loss-of-function** – inactivation - reduction or loss of function
  - **Gain-of-function** - activation - increase in activity or loss of regulation
- Impact on health
  - **Mutations with a neutral effect on the state of health** - neither negative nor positive effect on the state of health and the function of the organism
    - silent mutations - not visible in the phenotype
    - genetic polymorphism - changes in the structure of DNA that lead to an increase in the variability of the phenotypic expression of a given trait in the population
  - **Mutations with a negative effect on health** - cause disease or death of the organism
  - **Mutations with a positive effect on the state of health** - they favor their carriers from a certain point of view
    - carriers of the sickle cell mutation (heterozygotes) are resistant to malaria
    - a specific mutation in the CCR5 gene (C-C chemokine receptor type 5) leads to resistance to HIV infection
    - persistence of lactase activity

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Single gene mutations

Cassification according to changes in nucleotide sequence

Substitutions

Transition

Thr	Val
ACA	GTA
GCA	GCA
Ala	Ala

Transversion

Ile	Gly
ATT	GGA
ATA	TGA
Ile	Stop

Deletion

Thr	Val	His
ACAGTACAC		
Thr	Tyr	?
ACATACAC		

Inzertion

Ile	Gly
ATTGGA	
Ile	Arg	?
ATTCGGA	

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Single gene mutations

Cassification according to amino acids sequence

- silent mutation
  - samesense mutation

Ile
ATT
ATA
Ile

- missense mutation

Glu
GAG
GTG
Val

- nonsense mutation

Gly
GGA
TGA
Stop

- frame shift mutation

Thr Val His
ACAGTACAC
Thr Tyr ?
ACATACAC

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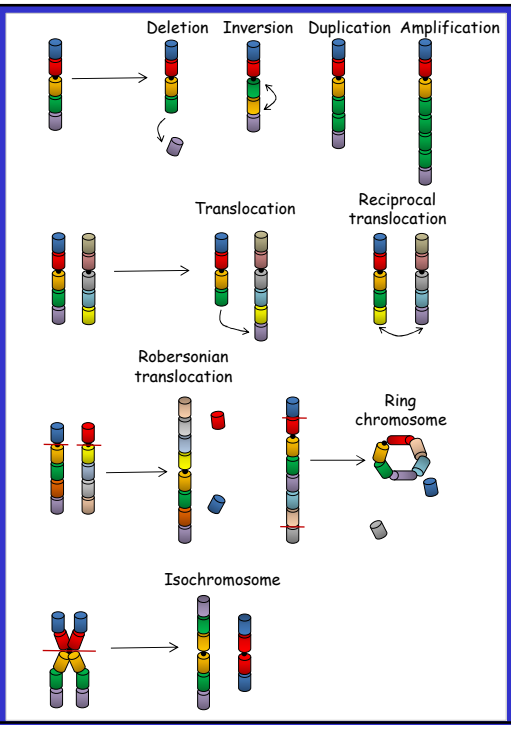
Chromosomal mutations

Structural chromosomal aberrations



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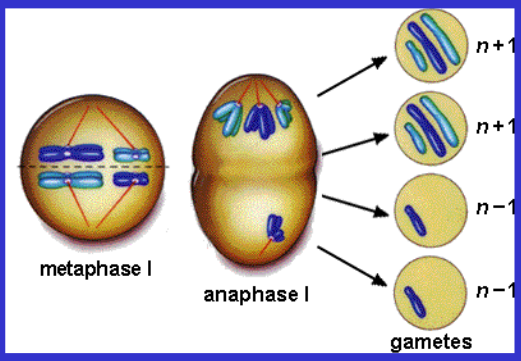
Abnormalities in number of chromosomes

- polyploidy – more then diploid number of chromosomes (diplod number - 46, 69 – triploidy, 92 - tetraploidy)
- aneuploidy – abnormal number of chromosomes (normal - 46, aneuploidy – 47 or 45 – trisomy, monosomy)

Nondisjunction

The failure of homologous chromosomes or sister chromatids to separate properly during cell division



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- Genetic disorder – a disorder caused by mutatin
- Hereditary disease – a disorder inherited from one or both parents
- Congenital disease – a condition present at birth regardless of its cause
- Familial disease – a disease with an increased incidence in the family

Genetic disorders

- Monogenic (single genes) diseases
- Chromosomal diseases
- Polygenic (multifactorial) diseases

New groups
- Genetic alterations of somatic cells (neoplasms)
- Mitochondrial disorders
- Dynamic mutations (trinucleotide repeat disorders)

Latest groups
- Disorders of gene expression (epigenetic diseases)

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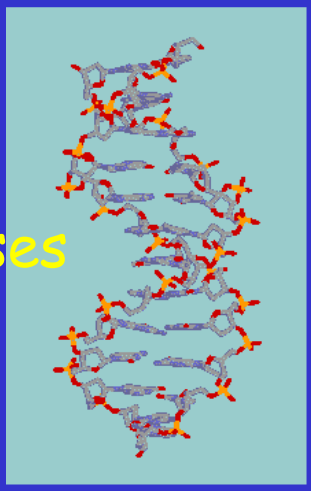
Monogenic diseases



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Monogenic diseases

characterisation

- 0,6 – 0,8 % of population
- cause – inherited single gene mutation

clasifications

- autosomal
- sex-linked
- dominant
- recessive

AD, AR, XD, XR

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Affected proteins

Function	Example of disease (protein)	Inheritance
Enzyme	Phenylketonuria (phenylalanine hydroxylase) Galactosemia (galactose-1-tranpherase) Acute Intermittent Porphyria (porphobilinogen deaminase)	AR AR AD
Transporter	Cystic fibrosis (Cl^- channel) Talasemia (hemoglobin) Sickle cell anemia (Hb)	AR AR AR
Structure	Osteogenesis imperfecta (collagen I) Duchenne dystrophy (dystrophin)	AR, AD XR
Plasma proteins	Immunodeficiency (complement) Hemophilia A (coagulation factor VIII)	AR, AD XR
Cell signalization	Cancers (transcription factors, signal molecules, signal receptors...)	AD
Growth and differentiation	Retinoblastoma (Rb-gene product) Breast cancer (BRCA-gene product)	AR AR
Other	.....	.....

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Autosomal dominant diseases

localisation of pathological gene	autosome
clinical manifestation	clinical signs expressed in heterozygotes and also in homozygotes in some AD diseases homozygote may have more serious symptoms
product of gene	mainly proteins with morphological and structural function, transporters, receptors
diseases	Familial hypercholesterolemia Familial combined hyperlipidaemia Marfan syndrome Achondroplasia Acute intermitent porfyria

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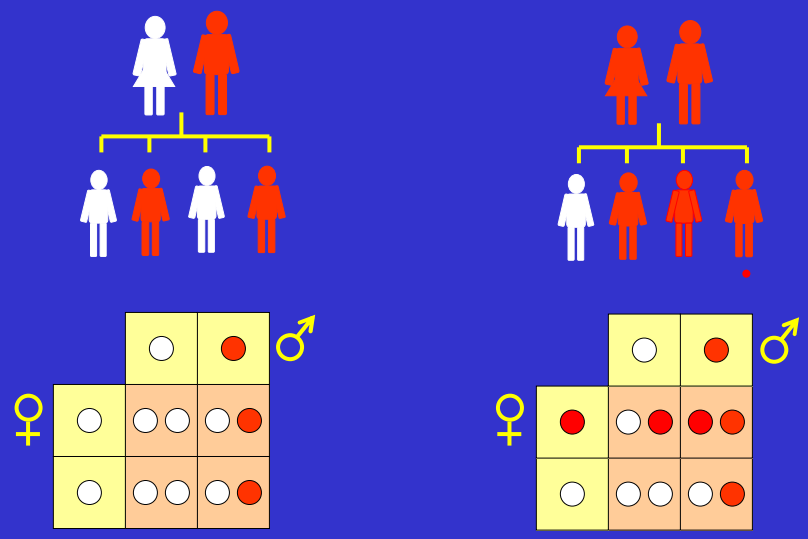
Autosomal dominant diseases



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Dominance
complete, incomplete, codominance

- Dominance – relationship between two alleles of one gene
  - Complete dominance - dominant allele completely masks effect of recessive allele in phenotype, homozygote and heterozygote have the same phenotype
  - Incomplete dominance - Homozygote and heterozygote have differences in phenotype – clinical signs of homozygote are much intensive than in heterozygote (familial hypercholesterolemia)
  - Codominance – can be seen effects of both alleles in phenotype (ABO blood groups)

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Expressivity, penetrance

- Expressivity – qualitative variations of phenotype between people with the same genotype (porphyria)
  - Variable expressivity – different intensity of phenotype in people with the same genotype – from 10 people with the same mutation all 10 have clinical signs but intensity is different
- Penetrance – quantitative variations of phenotype between people with the same genotype (porphyria)
  - Complete penetrance – 100 % - all people with mutation have clinical signs
  - Incomplete penetrance – e.g. 60 % - from 10 people with the same mutation only 6 have clinical signs, 4 are without clinical signs

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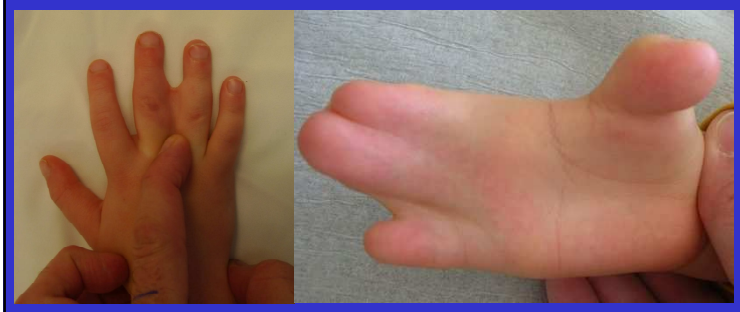
Variabile expresivity
Syndactyly



Incomplete penetrance

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Marfan syndrome

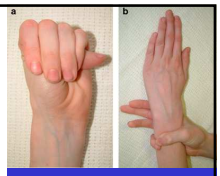
- a genetic connective tissue disorder

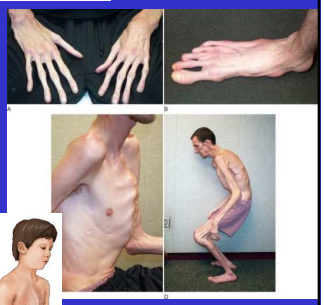
Cause

- AD inherited mutation in the *FBN1* gene on chromosome 15, which encodes fibrillin-1, a glycoprotein component of the extracellular matrix.

Clinical signs

- Tall, long limbs, long fingers – arachnodactyly
- Increased joints flexibility
- Scoliosis, lordosis
- Lens dislocation – fibrillin is one protein of apparatus that fix sclera in position
- Valvular disorders, aneurysm, varices





Abraham Lincoln, Nicolo Paganini, Michael Phelps
Ussama Bin Ladin

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Familial hypercholesterolaemia

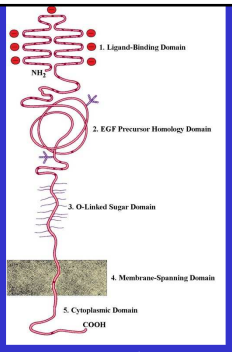
- AD inherited mutation of LDL receptor gene

Symptoms

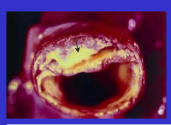
- high plasma cholesterol concentration (LDL)
- rapid development of coronary artery disease

- heterozygots
  - myocardial infarction before the age of 40 in men and before the age of 60 in women
  - half LDL receptor activity and double LDL concentration

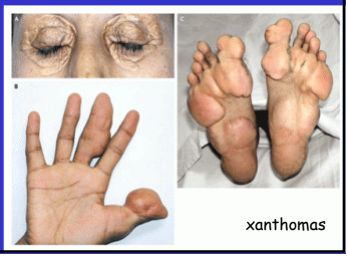
- homozygots
  - very high LDL concentration (total chol. up to 25 mmol/l)
  - atherosclerosis, myocardial infarction (2.-3. decenium), xantomas



LDL receptor



atheroslerosis



xanthomas

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Achondroplasia

- Bone growth disorder manifested by disproportionate short stature with short limbs.The most frequent cause of dwarfism.

Cause

- AD inherited mutation in fibroblast growth factor receptor 3 (FGFR3) gene
- More than 80% - neomutation

Clinical signs

- Disproportionate dwarfism, short limbs, normal trunk, big head
- Deformations – bowleg, knee
- Kyphosis, lordosis – disorders of ventilation
- Short fingers and toes with trident hands
- Large head with prominent forehead frontal bossing, small midface with a flattened nasal bridge
- Normal inteligence

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Autosomal recessive diseases

localisation of pathological gene	autosome
clinical manifestation	clinical signs expressed only in homozygotes, heterozygots are obviously clinical healthy carriers
product of gene	primarily enzymes (enzymopathies)
diseases	majority of enzymopathies Sickle cells anaemia Cystic fibrosis Xeroderma pigmentosum

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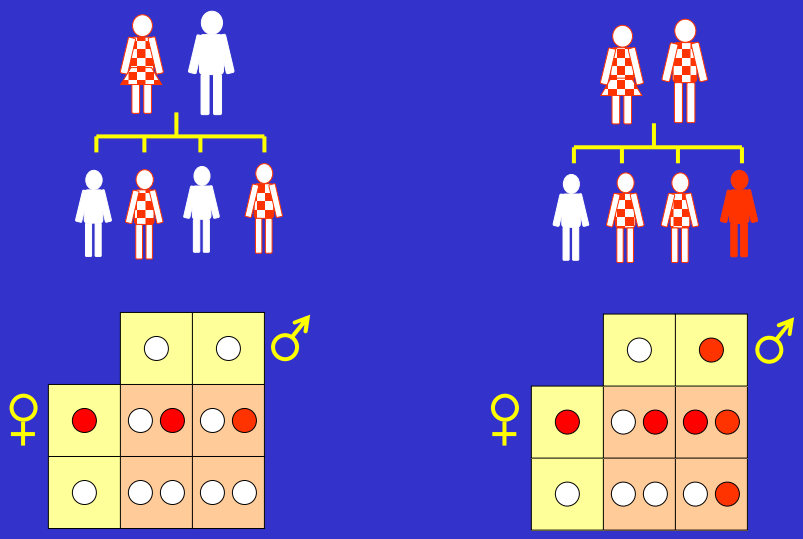
Autosomal recessive diseases



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Phenylketonuria

(hyperphenylalaninemia, Oligophrenia phenylpyruvica)

- Inborn disorder of metabolism

Cause

- Phenylalanine hydroxylase deficiency
- disorder of amino acid phenylalanine metabolism
- phenylalanine + 3 phenylalanine derivates (phenylpyruvic acid, phenyllactic acid, phenylacetic acid)

Clinical signs

- newborn babies - no symptoms
- age 3 - 6 months - vomiting, irritability, eczema-like rash
- by 1 year of age - brain damage - mental retardation
  - hyperkinesis, tremor
- melanin → blond hair, blue eyes
  → photosensitivity - erythema

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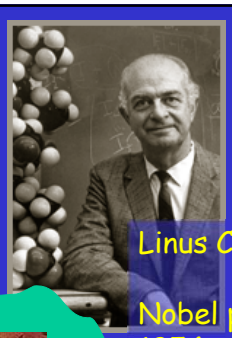
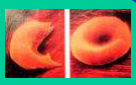
Sickle cell anaemia



Linus Carl Pauling

Nobel prices
1954 - chemistry
1962 - peace



Haemoglobin beta (HBB) gene
on 11th chromosome

Met	Val	His	Leu	Thr	Pro	Glu	Glu	
ATG	GTG	CAC	CTG	ACT	CCT	GAG	GAG	HbA
-1	1	2	3	4	5	6	7	
ATG	GTG	CAC	CTG	ACT	CCT	GTG	GAG	HbS
Met	Val	His	Leu	Thr	Pro	Val	Glu	

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Sickle cell anaemia

Signs and symptoms
- Deformation of red blood cells, loss of elasticity
- Occlusion of vessels
- Hemolysis
- Pain
- Anemia
- Stroke

Heterozygotes
- Carriers, resistant to malaria
- Clinically – AR – without clinical signs
- Hematology – codominant – in blood can be found HbA and HbS

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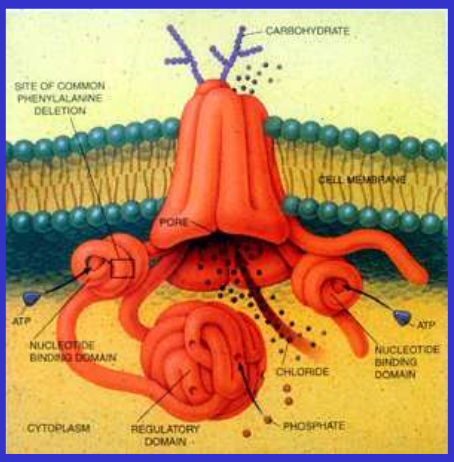
Cystic fibrosis

Cause

Deletion of F508 gene for CFTR (cystic fibrosis transmembrane conductance regulator) - chloride channel

Deletion of 3 nucleotides - phenylalanine is missing from the protein molecule



Ion transport disorder → water transport disorder → thick secretions

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Signs and symptoms

Lungs

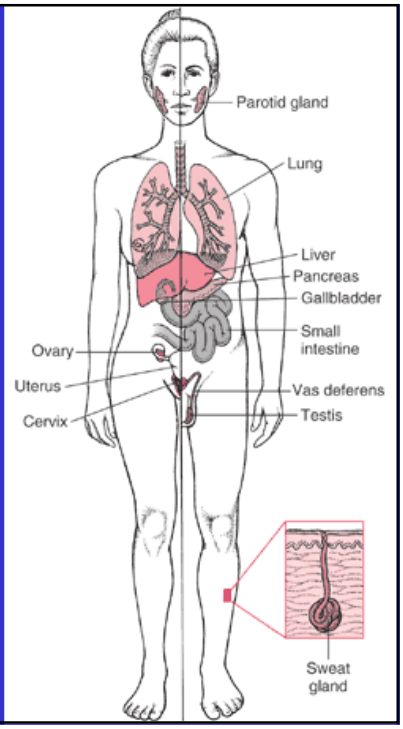
- persistent cough, frequent inflammations
- wheezing, shallow breathing
- frequent lung and respiratory infections
- asthma and sinus infections progressing to lung damage

GIT

- low absorption of nutrients from the diet
- great appetite with minimal weight gain
- slow growth
- greasy, thick stools
- chronic inflammation of the pancreas
- intestinal obstruction in newborns

Other

- significantly salty sweat - often the first sign in young children
- infertility – mainly men



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X-linked dominant diseases

localisation of pathological gene	X chromosome
clinical manifestation	men and women
diseases	Vit. D resistent rachitis Rett syndrome

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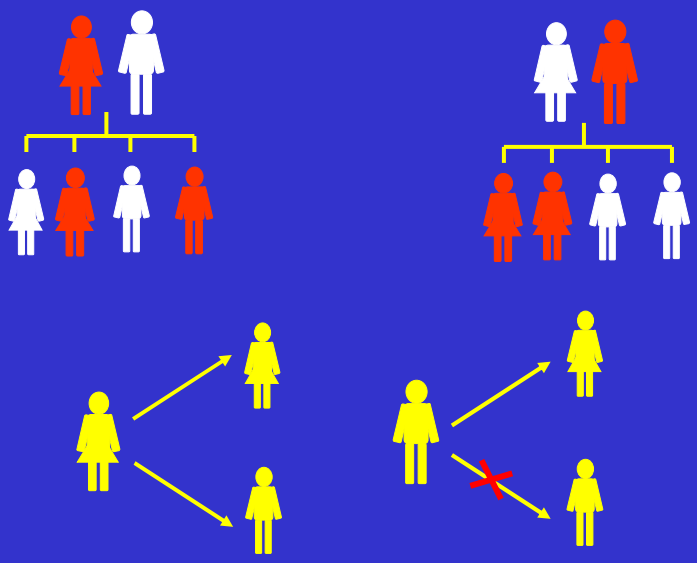
X-linked dominant diseases



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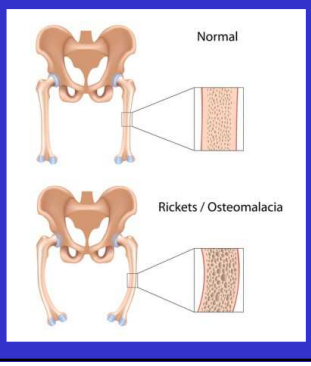
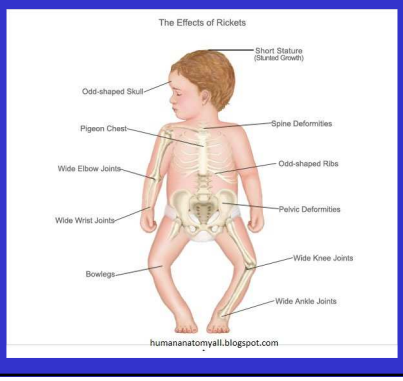
X-linked vitamin D-resistant rickets

- **XD** mutation in the PHEX gene on X chromosome
- The PHEX protein regulates fibroblast growth factor 23 (FGF-23) that inhibits the kidneys' ability to reabsorb phosphate into the bloodstream.
- Overactivity of FGF-23 reduces vitamin D 1a-hydroxylation and phosphate reabsorption by the kidneys, leading to hypophosphatemia and hypophosphatemic rickets.





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X-linked recessive diseases

localisation of pathological gene	X chromosome
clinical manifestation	men
diseases	Hemophilia A, hemophilia B Duchenne muscular dystrophia Becker muscular dystrophia Lesh-Nyhan syndrome Ocular albinism (type I and II) Color blindness

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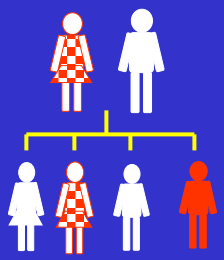
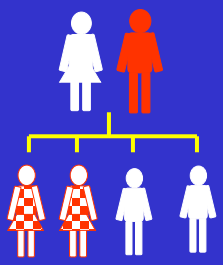
X-linked recessive diseases





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Hemophilia A

- XR inherited mutation of clotting factor VIII

Signs and symptoms

- Severe, intensive, prolonged bleeding often without injury
  - Superficial – skin, tooth extraction…
  - Joints, muscles, brain, inner organs… - pain, inflammation, degeneration…

Queen Victoria - the best known carrer of hemophilia, her daughters passed mutation to Germany, Spain and Russia royal families

The best known patient with hemophilia A – russian tsarevich Alexei

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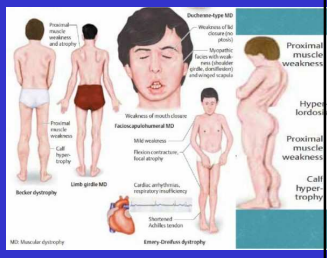
Duchenne muscular dystrophy

Causes:

- XR mutation of DMD gene (Xp21) that codes the protein dystrophin – structural component of muscles - no protein production



Signs and symptoms

- progressive muscle weakness – pelvis, calves, arms, neck (age 5-6 years)
- awkward manner of walking, running (on forefoot)
- frequent falls
- fatigue
- lumbar lordosis, scoliosis
- muscle contractures
- pseudohypertrophy of tongue and calf muscles
- higher risk of learning dificulties (because of muscular fatigue)

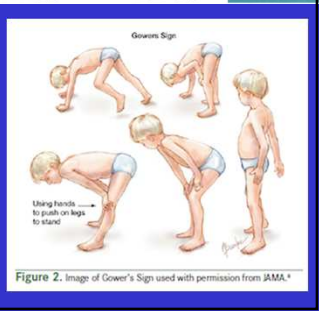


Figure 2. Image of Gower's Sign used with permission from JAMA.[4]

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Genetics in dentistry
Monogenic diseases

Marfan´s syndrome

(AD genetic connective tissue disorder)

- high-arched soft palate
- crowding of the teeth

Ehlers-Danlos syndrome

(AD genetic connective tissue disorder)

- severe periodontal disease
- extreme laxity of joints and skin
- easy bruisability

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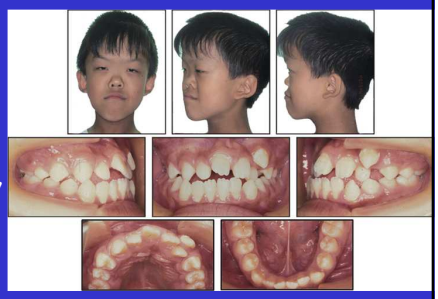
Genetics in dentistry
Monogenic diseases

Achondroplasia

(AD skeletal dysplasia, dwarfism)

- characteristic craniofacial features, relative macrocephaly, depressed nasal bridge, maxillary hypoplasia, macroglossia, gingivitis...



Lesch-Nyhan syndrome

(AR purine metabolism disorder

- self-induced mutilation ot the teeth, tongue, and lips

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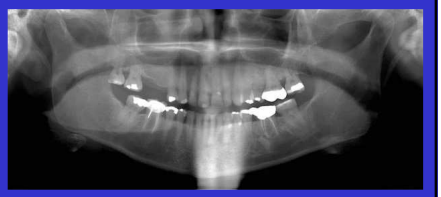
Genetics in dentistry
Monogenic diseases

Gaucher´s syndrome

(AR, sphingolipid metabolism disorder)

- radioluscent lesons in the jaw
- loosing of teeth



Osler-Weber-Rendu sy.

(AD, blood vessel disorder)

- teleangiectasia of the tongue, oral cavity and nasal mucosa

Osteogenesis imperfecta

(britle bone disease, AD collagen metabolism disorder)

- opalescent freely movable teeth

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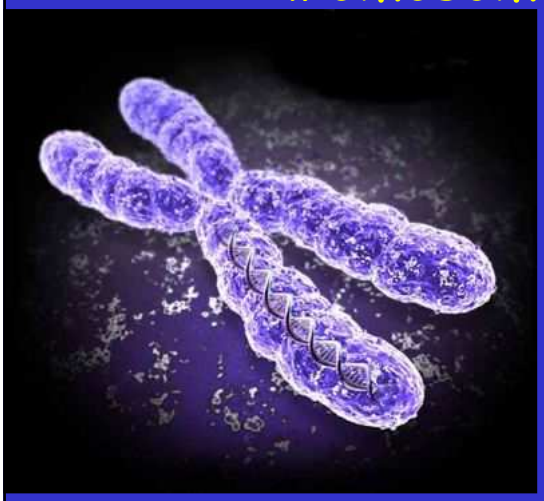
Chromosomal aberrations



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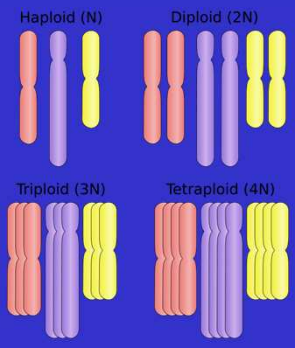
Numerical aberrations of chromosomes



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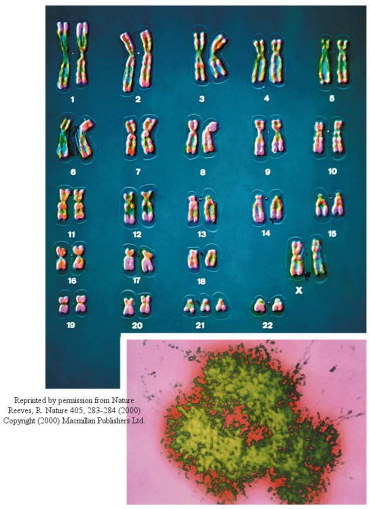
Autosomal aneuploidy

Down syndrome

Free trisomy: 47,XY+21; 47,XX+21
Mosaic: 46/47,XY/XY+21
Translocation: 46XY,t(14q21q)



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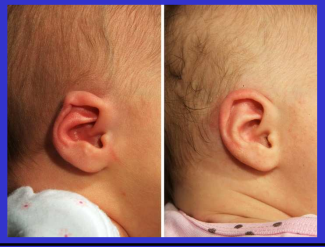
Symptoms

- Mental reatrdation - IQ 50
- Motor impairment
- Hypotonia
- Leukemia
- Congenital heart diseases
- Hypothyroidism

- Flat face
- Epicantus
- Hand deformation – short fingers, abnormal lines on hand
- Deformities of toes
- Heperglossia
- Flattened nose
- Small ears
- …



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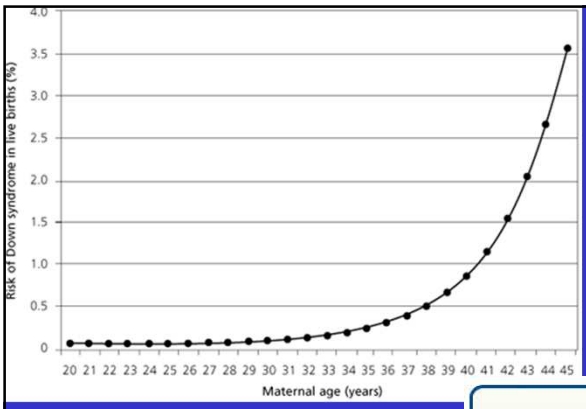

Maternal age and risk of Down syndrome

Maternal age	Risk of Down syndrome at birth
20	1 in 1,527
25	1 in 1,352
30	1 in 895
32	1 in 659
34	1 in 446
36	1 in 280
38	1 in 167
40	1 in 97
42	1 in 55

Source: Fetal Medicine Foundation

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Patau syndrome

trisomy of chromosome 13

- Intelectual and motor dissability
- Microcephaly
- Polydactyly
- Cyclopia
- Heart deffects
- ....

Edwards syndrome

trisomy of chromosome 18

- Intelectual and motor dissability
- Microcephaly
- Cleft palate
- Contractures of joints
- Heart deffects
- ....

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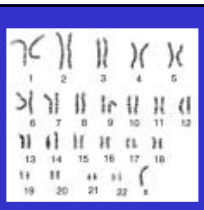
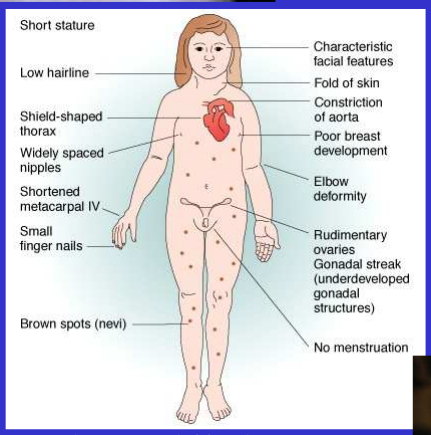
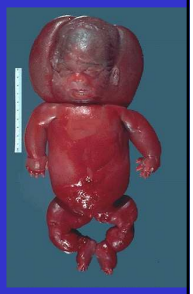


Sex chromosome aneuploidy

Turner syndrome
45, X0





- low stature
- infertility
- normal inteligence, sometimes learning difficulties
- different developmental malformations

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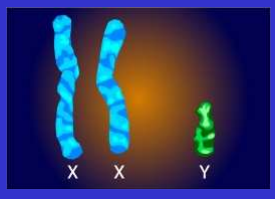
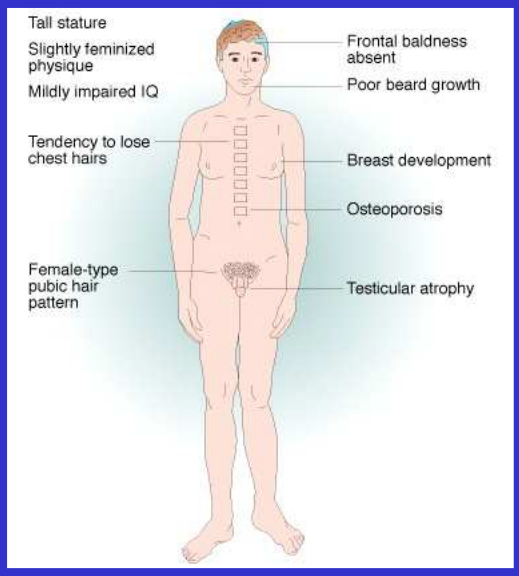
Klinefelter syndrome 47,XXY





- tall stature
- feminisation
- infertility
- mild mantal retardation

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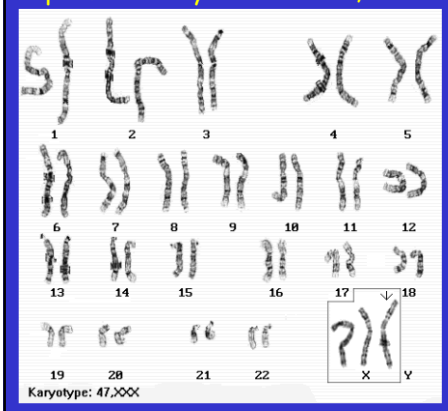
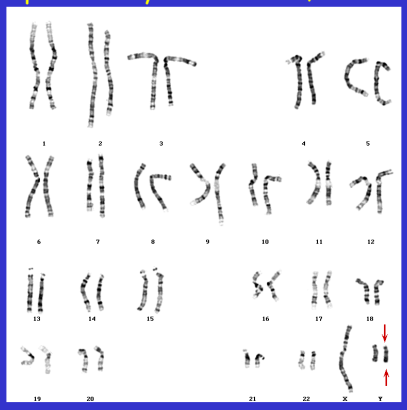
Superfemale syndrome 47,XXX



Superfemale
- normal appearance
- tall stature
- normal fertility
- mild mental problems – learning problems
- hypotonia

Supermale syndrome 47,XYY



Supermale
- normal appearance
- tall stature
- normal fertility
- normal intelligence, sometimes mild learning problems
- aggression ??? (not proved)

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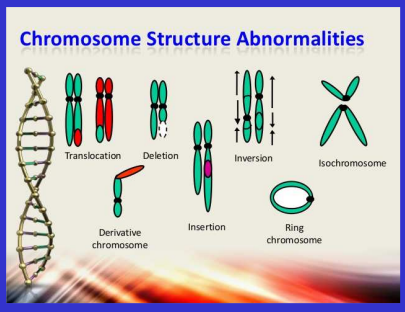
Structure aberrations of chromosomes



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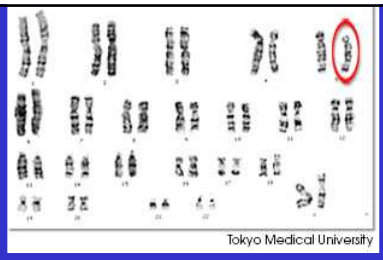
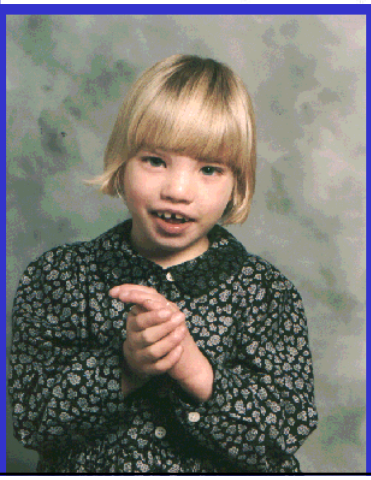
Cri du chat

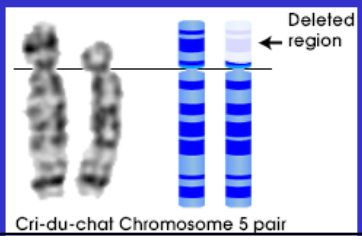
Deletion of the short arm of 5th chromosome

Signs and symptoms

- characteristic cry similar to kitten meowing due to problems with the larynx and nervous system.
- mental retardation
- feeding problems because of difficulty in swallowing and sucking
- hypotonia
- Small head, wide eyes, epicantus, other typical face features
- other developmental problems – heart, kidneys...







Cri-du-chat Chromosome 5 pair

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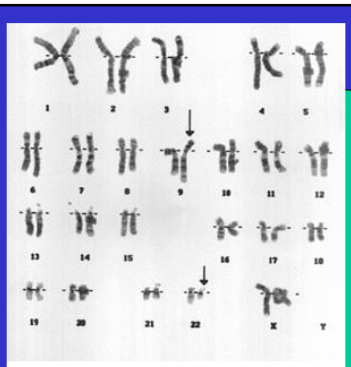
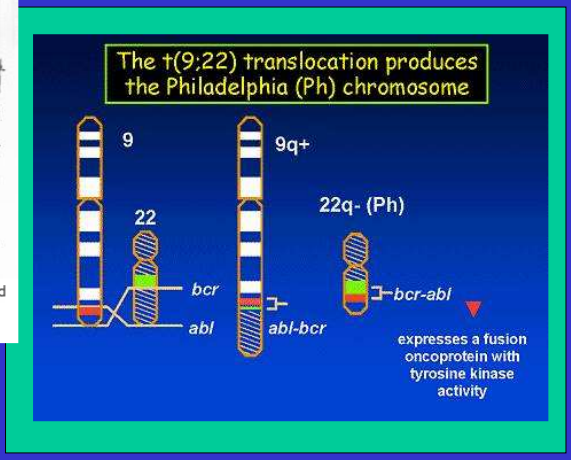
Philadelphia chromosome


The abnormality seen by Nowell & Hungerford on chromosome 22, Now known as the Philadelphia Chromosome.




Slide 75

chronic myeloid leukemia

translocation between 9th and 22nd chromosomes

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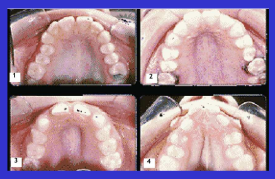
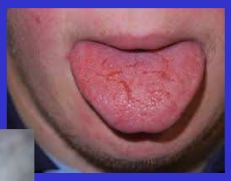
Genetics in dentistry
Chromosomal diseases

Turner syndrome
(45,X0)
- high palatal vault



Down syndrome
(trisomy 21)
- macroglosia with hypertophic papillae
- cleft or high-arched palate



Cri-du-Chat syndrome
(partial chromosome 5 monosomy)
- mandibular microretrognathia, high palate, enamel hypoplasia, generalized chronic periodontitis, delayed tooth eruption

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Non Mendelian inheritance

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Dynamic mutations
Trinucleotide repeat disorders

- genes with physiological repetitive triplet sequences of various lenghts

Cause
- abnormal trinucleotide repeat expansions - more triplet repetitions – increased severity of disease
- anticipation – increased number of repetitions from generation to generation

Diseases
- Fragile X chromosome
- Huntington chorea
- Friedreich ataxia
- Myotonic dystrophy

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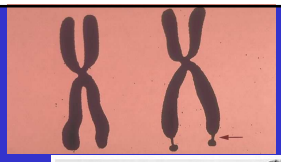
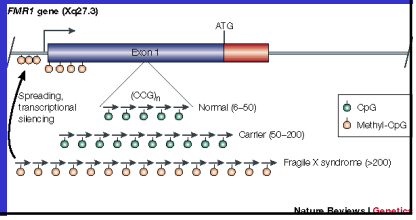
Fragile X chromosome
(Martin-Bell syndrome)



- Mental retardation(IQ 60 – 20)
- Face signs – prolonged face, protruding ears
- Autism, stereotyic movement, speech
- Makroorchidism
- Prolapse of mitral valve

- Fragile area on long arm of X chromosome
- CGG repetitions in fragile X mental retardation 1 (FMR1) gene
- 6 – 53 (the most frequently 29)
  - norm
- 54 – 200
  - „premutation"
- 200 – 4000
  - full mutation



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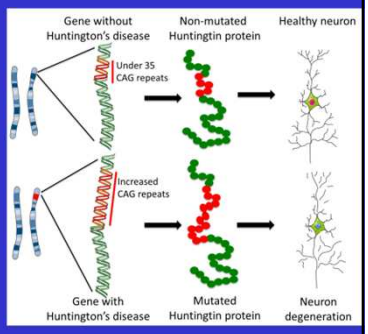
Huntington´s disease
(Huntington´s chorea)

- Inherited neurodegenerative disease



Cause
- AD inherited mutation of gene HTT, that codes protein huntingtin – function ?
- The HTT gene (on chromosome 4) contains a sequence of CAG (repeated multiple times) of variable length (healthy people < 27, affected people > 35)
- CAG codes amino acid glutamine → proteine contains polyglutamine tract (polyQ)

Clinical signs
- Initially slight changes in personality and motor skills (restlessness, incomplete movement…)
- Later typical chorea - uncontrolled movements
- Loss of cognitive abilities - thinking, memory
- Mental changes - depression, anxiety
- Personality changes - gambling, alcoholism, hypersexuality
- Other changes - glucose intolerance, heart failure, muscle atrophy…

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Imprinting

- Classical Mendelian inheritance: expression of both alleles of one gene (one inherited from mother and one from father) is simultaneous
  - both alleles are expressed
  - majority of human genes

- Genomic imprinting – different expression of alleles from father and from mother
  - parent-of-origin-specific expression
  - gene expression occurs from only one allele (only from father or only from mother)
  - 1% (3% ?????) of human genes

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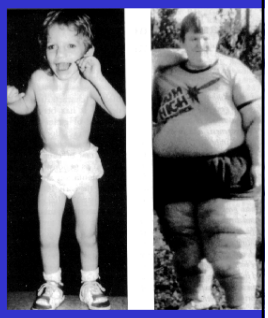
Imprinting

- Prader-Willi and Angelman synfromes
- Two different diseases caused by the same deletion – deletion of 15th chromosome

- PWS – deletion of CH15 inherited from father
- AS - deletion of CH15 inherited from mother

- PWS: Hypotonia, mental retardation (milder), hyperphagia, weight gain, hypogonadism
- AS: Happy pupett sy., mental and motor retardation, seizures, spasms, insomnia, epilepsy



Prader-Willi syndrome

Angelman syndrome

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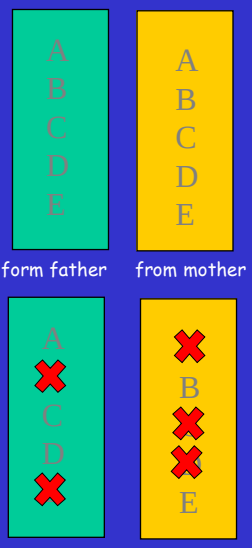
Different expression of alleles from father and from mother



Majority of genes
Both sets of genes (from father and from mother) can be expressed.
We have 2 active sets of genes - 2xABCDE

Impritning
From pair of alles only one gene is active (e.g. from father) and the second one (from mother) is blocked.
Genes are blocked by hypermethylation.
This situation is normal for small group of genes – physiological reduction of genetic information.
Active is only one set of genes - 1xABCDE

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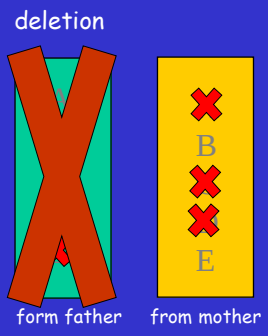

Deletion (loss) of the only active allele causes disease.

Deletion on picture shows total loss and absolute missing of genes A, C, D.

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Mitochondrial inheritance

- mtDNA – evolutionary different from nuclear DNA - bacteria
- Maternal inheritance - degradation of sperm mtDNA in the male genital tract or in the fertilized egg.

Structure

- circular, covalently closed, double-stranded DNA
- 100 - 10 000 copies of mtDNA in somatic cell
  cca 200 000 in human egg, cca 5 in sperm
- 37 genes: 13 for proteins (for terminal oxidation pathway), 22 for transfer RNA, 2 for ribosomal RNA

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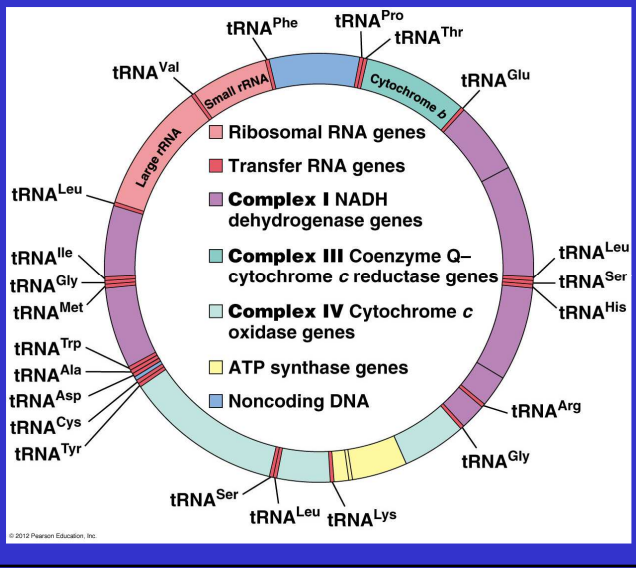
Mitochondrial DNA



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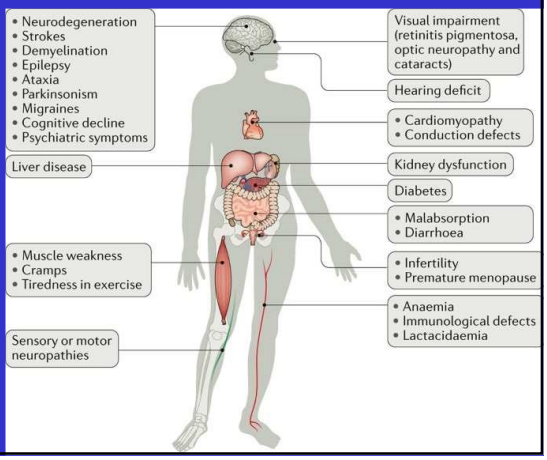
Mitochondrial diseases

- KSS – Kearns-Sayre sy.
- LHON – Leber hereditary optic neuropathy
- MERFF – Myoclonic epilepsy, ragged red fibers
- MELAS – Myopathy, encephalopathy, lactic acidosis, apoplexia

- Symptoms are caused mainly by missing of energy in energy-demanding tissues – nervous system, muscles, heart, senses
- Accumulation of mutations in mtDNA – aging?



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Genetics in dentistry
Non Mendelian diseases

Fragile X syndrome

- Large and ling face
- Prominent forehead and jaw
- High-arched palate
- Macroglossia, microdontia, supernumerary teeth, and abnormal occlusion (eg, open or cross-bite)

Angelman syndrome

- Smooth philtrum, thin upper lip, prominent lower lip
- Wide mouth
- Small and widely spaced teeth
- Small chin

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Epigenetic mechanisms

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How it is possible that...

- ... identical (monozygotic) twins (with the *same DNA information*) *can have differences in fenotype* (one is a bit taller, one has a bit darker hair, a bit different colour of eyes, different intelligence....)?
- ... *women* with two big X chomosomes (cca 155 Mbp + 155 Mbp) and *men* with one X and one small Y chromosome (cca 155 Mbp + 57 Mbp) have in fact the *same amount of genetic information*?
- ... though we have the *same genes in all our cells*, *our cells are different* (different shape, size, function, metabolism...)?
- ... in two patients with two *different diseases* with different clinical signs (e.g. Angelman vs. Prader-Willi diseases) genetic examination can prove the *same mutation*?

- Epigenetics is the study of heritable changes in gene function without any change in the nucleotide sequence.
- Changes in chromatin structure and DNA accessibility, leading to switching 'on' or 'off' genes.

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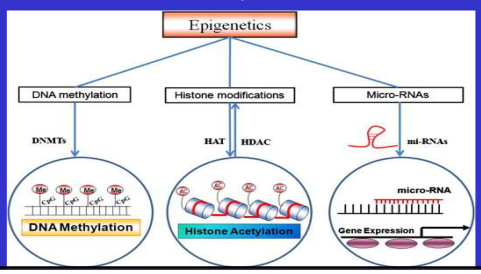
Mechanisms

- DNA methylation - methyl group is added at the 5-carbon of the cytosine to form 5-methylcytosine. DNA methylation generally results in gene silencing or reduced gene expression.
- Histone modification - enzyme catalyzed reactions such as lysine acetylation, lysine/arginine methylation, serine/threonine phosphorylation, and lysine ubiquitination alter their functions resulting in promotion or repression of gene transcription.
- Non-coding RNA-mediated pathways - microRNAs (miRNA) are a class of non-coding single stranded RNAs of 19-25 nucleotides in length, which are reported to have a key role in the regulation of gene expression – binds to mRNA and stop translation.



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