

Genetic diseases

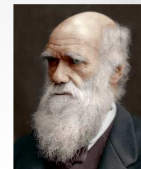
Genetics in dentistry

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2025/2026

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History of genetics

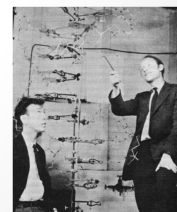
- The first theories of heredity - Aristoteles, Hypokrates, Epikuros
- 1859 - Charles Darwin - „On the Origins of Species“
- 1866 - Johann Gregor Mendel - scientist, Augustinian friar and abbot of St. Thomas' Abbey in Brno - „father of genetics“ - Mendel's laws of inheritance
- 1869 - Friedrich Miescher - discovers "nuclein" (later DNA) in cell nuclei
- 1900 - de Vries, Correns, Tschermak - Rediscovery of Mendel's laws
- 1944 - Avery, MacLeod, and McCarty - 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 prize
- 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“
- 2020 - Nobel Prize - J.A.Doudna and E.Charpentier for CRISPR-Cas9 method for genome editing
- 2022 - the complete sequence of a human Y chromosome



Charles Darwin



Johann Gregor Mendel



James Watson and Francis Crick

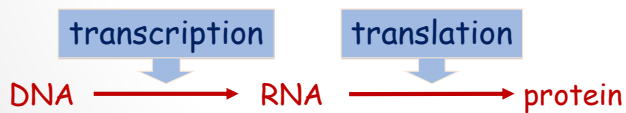
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Genetic code

- 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)

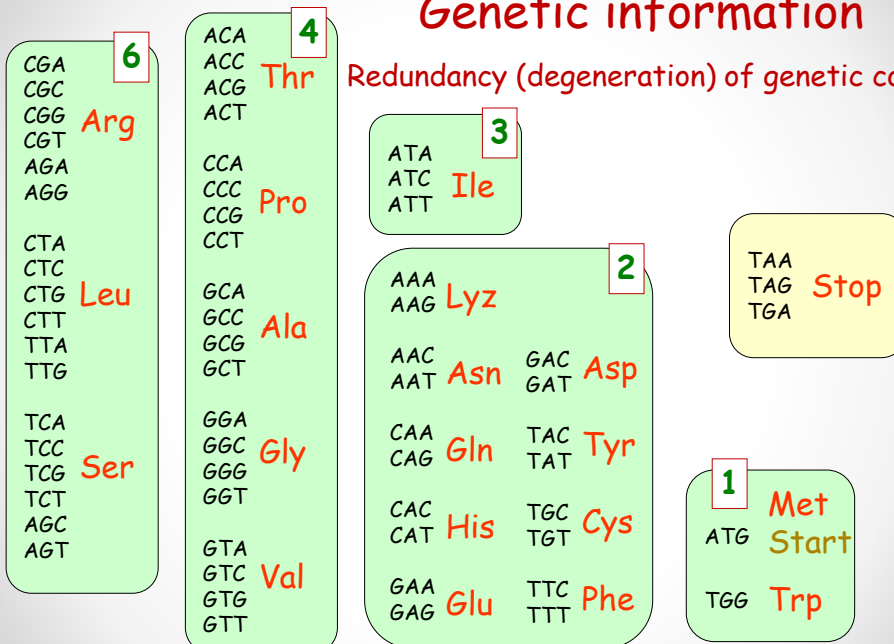
How genetic information is expressed



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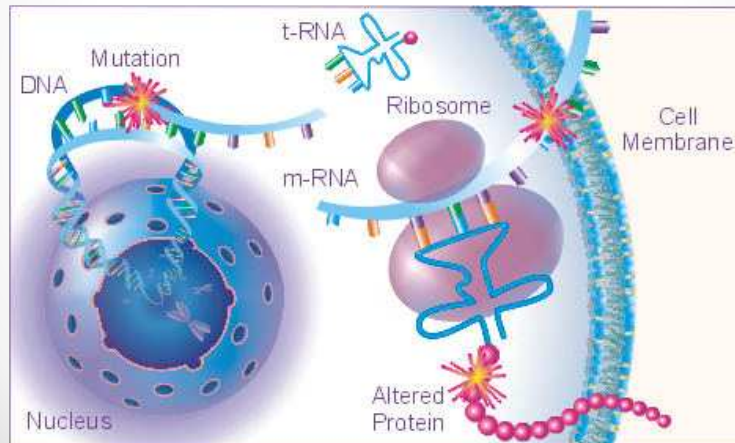
Genetic information

Redundancy (degeneration) of genetic code



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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, mistakes in DNA repair mechanisms
 - induced - mutagens (physical, chemical, biological)
- Localisation
 - gametic
 - somatic
- Extent
 - 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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Mutation vs. polymorphism

- **Gene mutation** - change in DNA structure, changes in nucleotide sequence
- **Gene polymorphism** - presence of two or more variants (alleles) of a gene within a population. Differences in DNA structure, in the DNA sequence.

What is the difference between them???

1. Frequency in the population

- **Gene Mutation** - rare, in less than 1% of the population
- **Gene Polymorphism** - more common, more than 1% of the population.

2. Effect on Function

- **Gene Mutation** - can significantly affect gene function, leading to dysfunctional proteins or complete loss of function
- **Gene Polymorphism** - more subtle effects on gene function and are often neutral. It leads to the variability of a certain sign in the population

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Mutation vs. polymorphism

3. Impact

- **Gene Mutation** - often associated with specific diseases or disorders (cystic fibrosis, sickle cell anemia... or cancer)
- **Gene Polymorphism** - subtle or no effects on gene function and its consequence is:
 - Variability and diversity of a some sign in the population (color of eyes, hair, facial features... but also differences in metabolizing a certain substrate, etc.)
 - The polymorphism of some genes increases the probability of some diseases development (so-called **genetic predisposition**), e.g.:
 - Polymorphisms of tumor suppressor genes increase the risk of cancer development (e.g. some BRCA1 or BRCA2 gene variants increase the risk of breast or ovarian cancer)
 - HLA gene polymorphisms increase the risk of autoimmune diseases development (e.g. some DR3 or DR4 gene variants increase the risk of developing type 1 diabetes mellitus)
- Typically, gene polymorphism manifests itself as a change in one nucleotide (single nucleotide polymorphism SNPs).

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Single gene mutations

Point mutations

Classification 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
ACAG	TACAC	
Thr	Tyr	?
ACATACAC		

Inzertion

Ile	Gly
ATTGGA	
Ile	Arg ?
ATT C GGA	

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Single gene mutations

Classification according to amino acids sequence

- **silent mutation**
- same sense mutation

Ile
ATT
ATA
Ile

- **missense mutation**

Glu
GAG
GTG
Val

- **nonsense mutation**

Gly
GGA
TGA
Stop

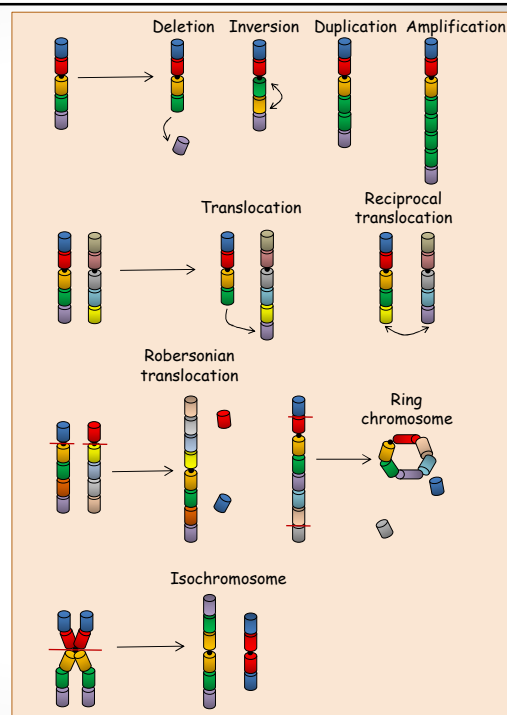
- **frame shift mutation**

Thr Val His
ACA**G**TACAC
Thr Tyr ?
ACATACAC

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Chromosomal mutations

Structural chromosomal aberrations



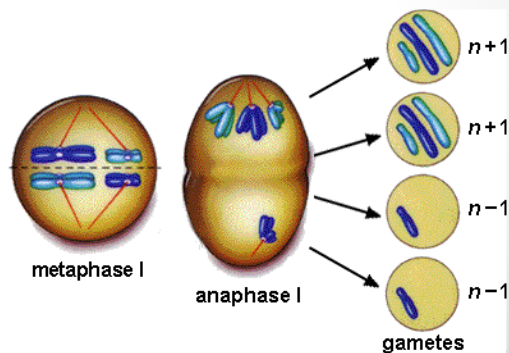
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Abnormalities in number of chromosomes

- **polyploidy** - more than diploid number of chromosomes (diploid number - 46, 69 - triploidy, 92 - tetraploidy)
- **aneuploidy** - abnormal number of chromosomes (normal - 46, aneuploidy - 47- trisomy, 45 - 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 mutation
- **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

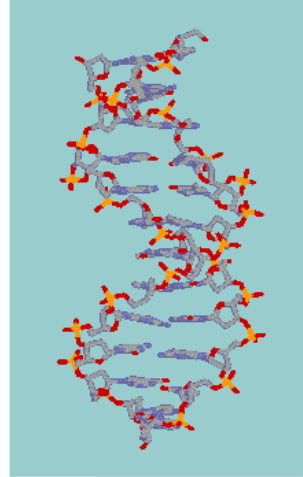
- Genetic alterations of somatic cells (neoplasms)
- Mitochondrial disorders
- Dynamic mutations (trinucleotide repeat disorders)

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

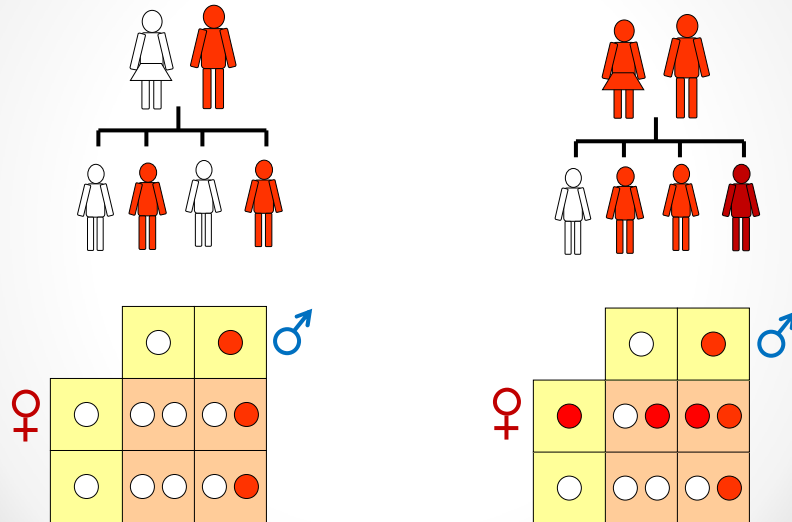
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Autosomal dominant diseases

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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Autosomal dominant diseases

Characteristic features

- **Frequent neomutations** - a new spontaneous mutation (parents or siblings are not affected)
- **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)
- **Incomplete penetrance** - quantitative variations of phenotype between people with the same genotype (e.g. 60 % - from 10 people with the same mutation only 6 have clinical signs, 4 are without clinical signs)
- **Complete dominance** - dominant allele completely masks effect of recessive allele in phenotype, homozygote and heterozygote have the same phenotype
- **Incomplete dominance** - not only the dominant but also the recessive allele is involved in the phenotypic expression (homozygote and heterozygote have differences in phenotype - clinical signs of homozygote are much intensive than in heterozygote)

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Variable expressivity
Syndactyly



Incomplete penetrance



Complete dominance

F1: $Aa \times Aa$

F2: AA (red), Aa (red), Aa (red), aa (white)

Only dominant allele has effect to phenotype

Incomplete dominance

F1: $Aa \times Aa$

F2: AA (red), Aa (pink), Aa (pink), aa (white)

Mixed effect of both dominant and recessive alleles in phenotype

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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

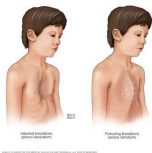
- Tall, long limbs, long fingers - arachnodactyly
- Increased joints flexibility
- Scoliosis, lordosis
- Lens dislocation - fibrillin is one protein of apparatus that fix sclera in position
- Valvular disorders, aneurysm, varices



Marfan Syndrome Symptoms













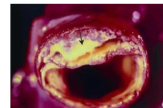
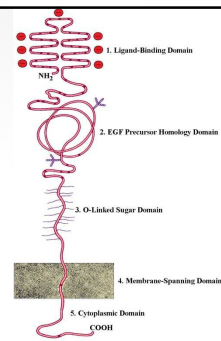
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Familial hypercholesterolaemia

- AD inherited mutation of LDL receptor gene

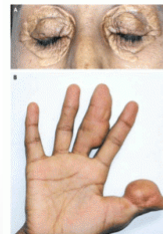
Symptoms

- high plasma cholesterol concentration (LDL)
- rapid development of coronary artery disease
- heterozygotes
 - 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
- homozygotes
 - very high LDL concentration (total chol. up to 25 mmol/l)
 - atherosclerosis, myocardial infarction (2.-3. decenium), xanthomas



LDL receptor

atherosclerosis



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 intelligence



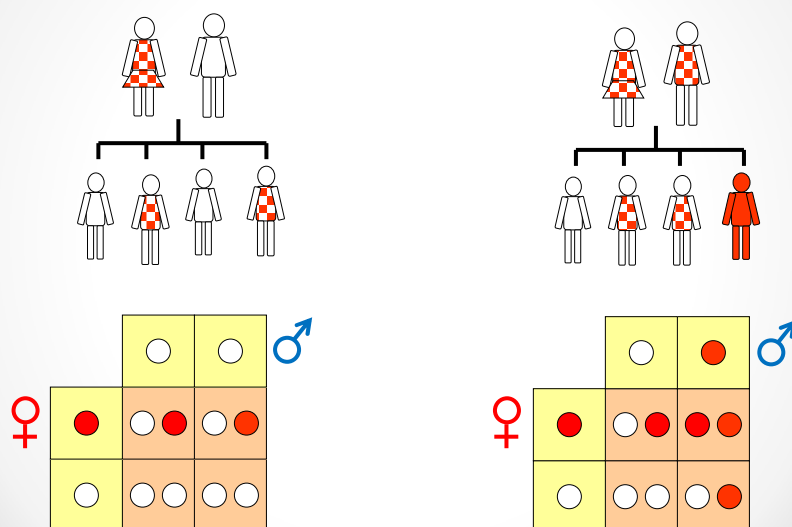
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Autosomal recessive diseases

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
Characteristic features	More frequent in consanguineous marriages, or in a certain population or in a certain geographical location (e.g. cystic fibrosis in Caucasians, sickle cell anemia in Africa, Tay-Sachs disease in Jews of Ashkenazi origin, alkaptonuria in Slovakia, congenital glaucoma in the Roma population...)

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Autosomal recessive diseases



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Phenylketonuria

(hyperphenylalaninemia, Oligophrenia phenylpyruvica)

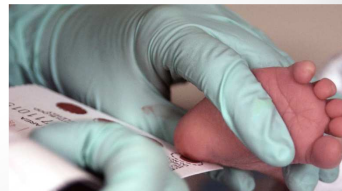
- Inborn disorder of metabolism

Cause

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

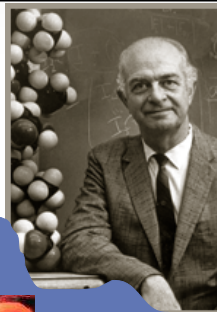
Clinical signs

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



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Sickle cell anaemia



Linus Carl Pauling
Nobel prizes
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

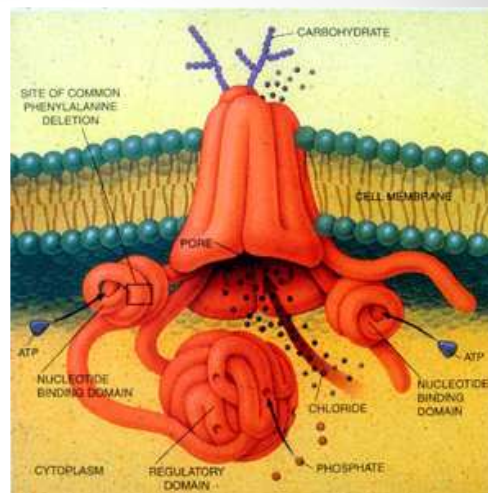
- Carriers, resistant to malaria
- Clinically - AR - without clinical signs
- Hematology - codominant - in blood can be found HbA and HbS

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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

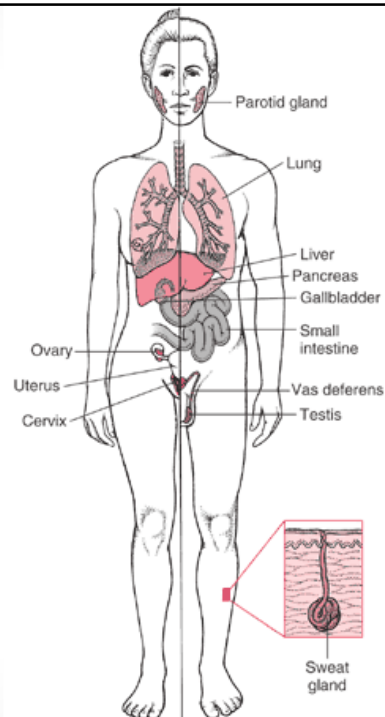
- persistent cough, frequent inflammations
- wheezing, shallow breathing
- frequent lung and respiratory infections
- asthma and sinus infections progressing to lung damage

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



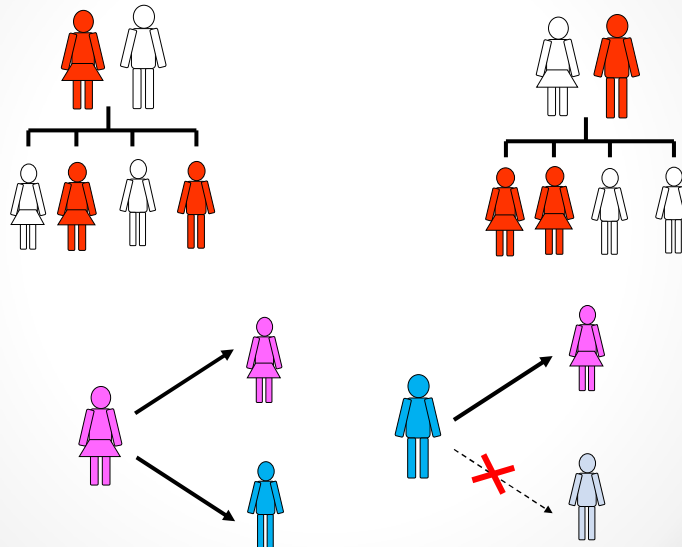
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X-linked dominant diseases

Localisation of pathological gene	X chromosome
Clinical manifestation	Men and women Transmission from father to son is not possible If the mother is affected (heterozygous), 50% probability of affecting daughters (heterozygotes) and 50% of sons (hemizygotes) If the father is affected, all daughters are affected (heterozygotes), all sons are healthy
Diseases	Vit. D resistant rachitis Rett syndrome
Characteristic features	In affected women (heterozygotes), the "normal" gene suppresses the expression of the pathological gene, and therefore in male patients (hemizygotes) a more severe or even fatal course can be expected

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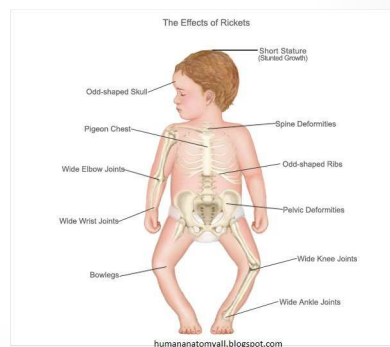
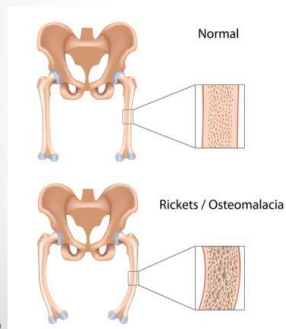
X-linked dominant diseases



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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 1 α -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 In women very exceptionally (e.g. the union of an affected man - hemizygous with a carrier woman - heterozygous) Heterozygous women (carriers) may have clinical symptoms - cause: lyonization - random inactivation of one X chromosome - if more active X chromosomes with mutation remain, symptoms will manifest
Diseases	Hemophilia A, hemophilia B Duchenne muscular dystrophy Becker muscular dystrophy 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
 - o Superficial - skin, tooth extraction...
 - o Joints, muscles, brain, inner organs... - pain, inflammation, degeneration...



Queen Victoria - the most famous carrier of hemophilia, her daughters passed mutation to Germany, Spain and Russia royal families



The most famous 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 difficulties (because of muscular fatigue)

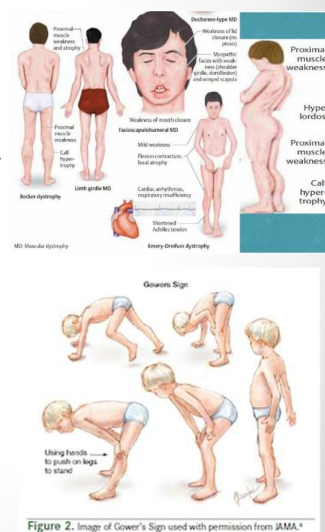


Figure 2. Image of Gower's Sign used with permission from JAMA.*

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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 of the teeth, tongue, and lips



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Genetics in dentistry

Monogenic diseases

Gaucher's syndrome

(AR, sphingolipid metabolism disorder)

- radioluscent lesions in the jaw
- loosening of teeth



Osler-Weber-Rendu sy.

(AD, blood vessel disorder)

- teleangiectasia of the tongue, oral cavity and nasal mucosa



Osteogenesis imperfecta

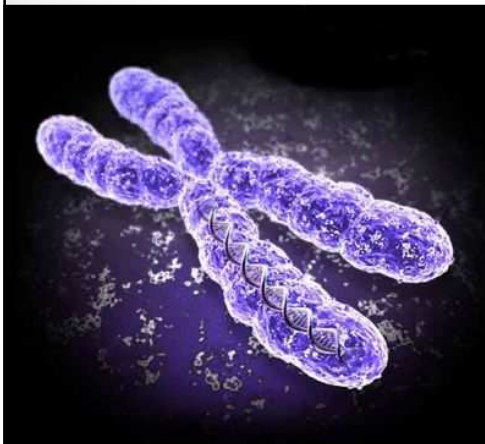
(brittle bone disease, AD collagen metabolism disorder)

- opalescent freely movable teeth



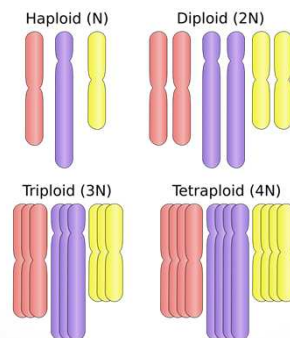
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Chromosomal aberrations



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Numeric aberrations of chromosomes



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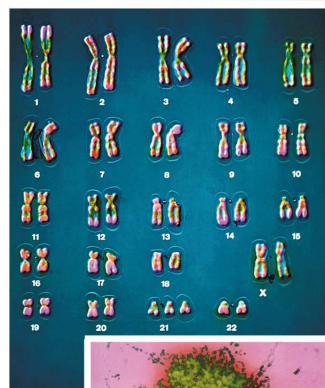
Autosomal aneuploidy

Down syndrome

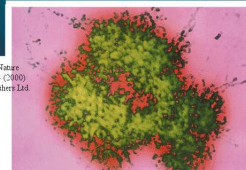
Free trisomy: 47,XY+21; 47,XX+21

Mosaic: 46/47,XY/XY+21

Translocation: 46,XY,t(14q21q)



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Hewes, R. Nature 405, 282-284 (2000)
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Symptoms

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

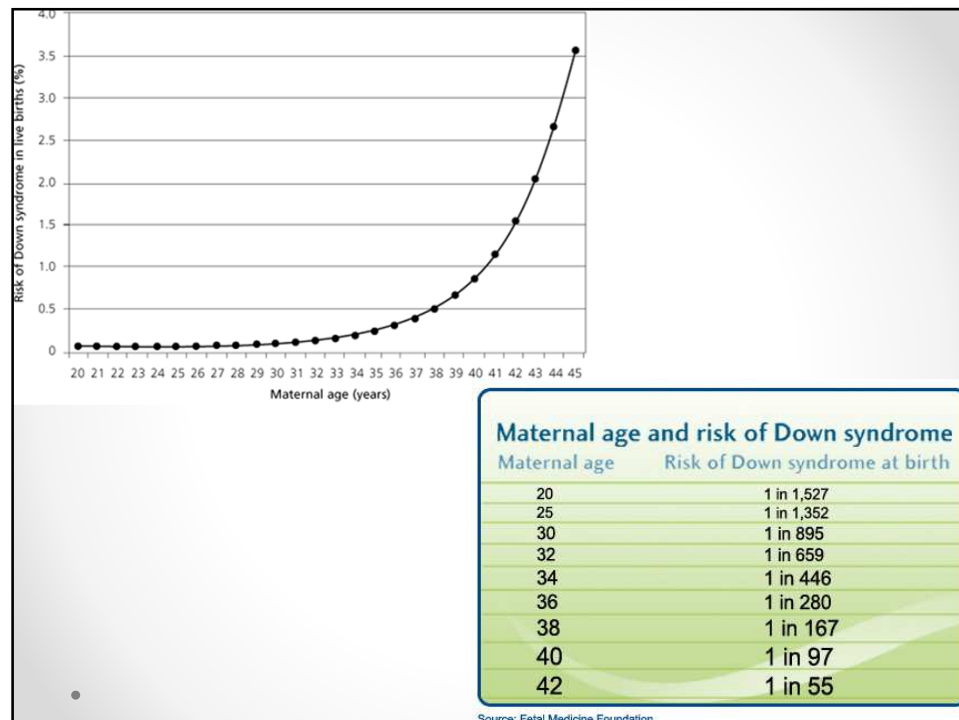


Epicanthal fold

- Flat face
- Epicanthus
- Hand deformation - short fingers, abnormal lines on hand
- Deformities of toes
- Hesperglossia
- Flattened nose
- Small ears
- ...



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Patau syndrome

trisomy of chromosome 13

- Intellectual and motor dissability
- Microcephaly
- Polydactyly
- Cyclopia
- Heart deffects
-



Edwards syndrome

trisomy of chromosome 18

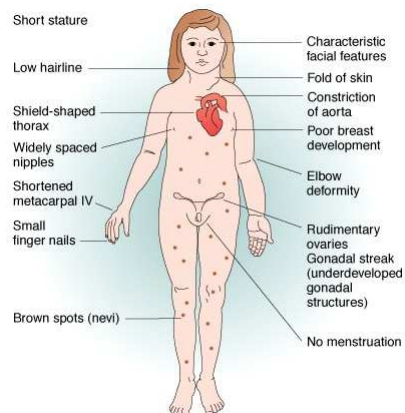
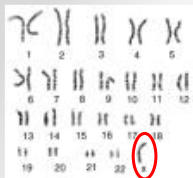
- Intellectual and motor dissability
- Microcephaly
- Cleft palate
- Contractures of joints
- Heart deffects
-



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Sex chromosome aneuploidy

Turner syndrome 45, XO



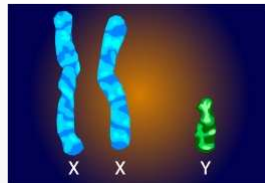
Signs and symptoms

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

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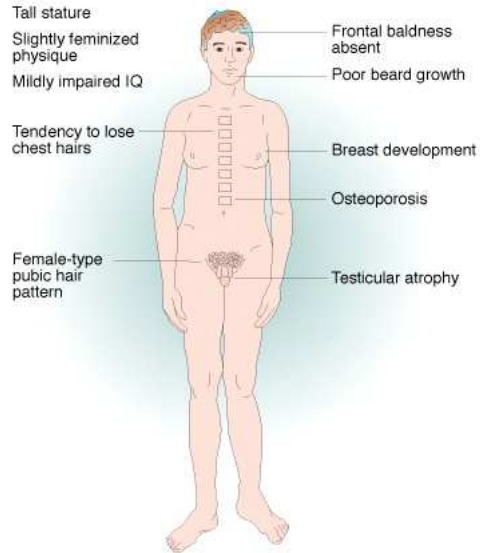
Klinefelter syndrome

47,XXY



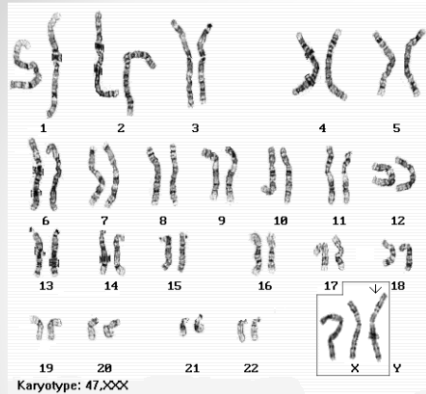
Signs and symptoms

- tall stature
- feminisation
- infertility
- can be mild mental retardation



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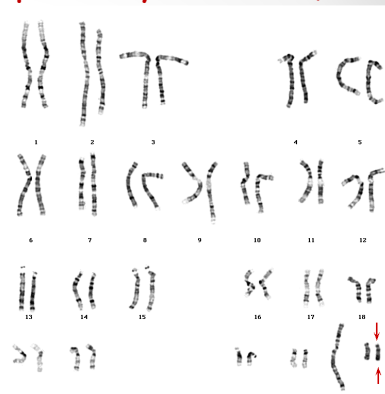
Superfemale syndrome 47,XXX



Signs and symptoms

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

Supermale syndrome 47,XYY

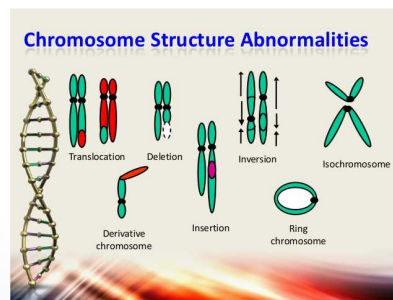


Signs and symptoms

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

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Structure aberrations of chromosomes



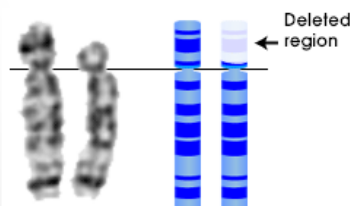
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Cri du chat

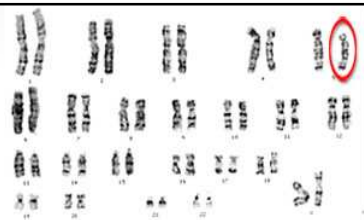
Deletion of the short arm of 5th chromosome

Signs and symptoms

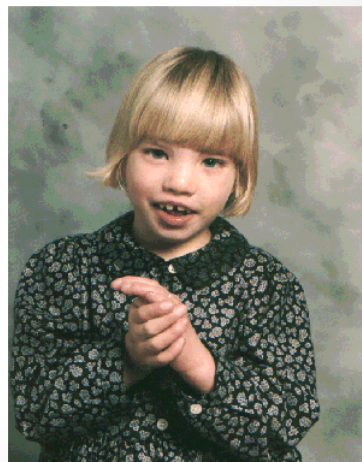
- characteristic cry similar to kitten meowing due to problems with the larynx and nervous system.
- mental retardation
- feeding problems because of difficulty in swallowing and sucking
- hypotonia
- Small head, wide eyes, epicanthus, other typical face features
- other developmental problems - heart,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



Cri-du-chat Chromosome 5 pair

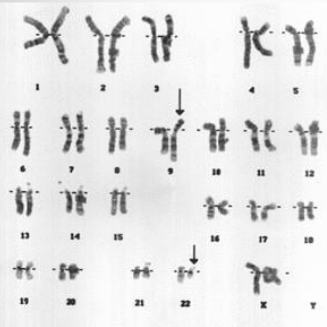


Tokyo Medical University



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Philadelphia chromosome

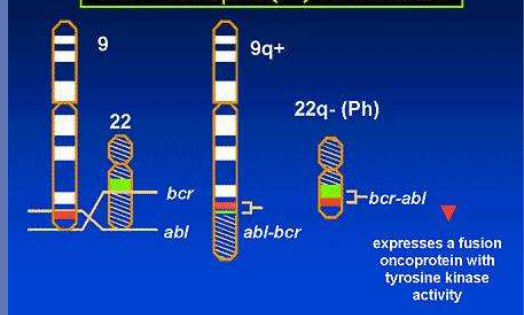


The abnormality seen by Nowell & Hungerford on chromosome 22, Now known as the Philadelphia Chromosome.



Slide 75

The t(9;22) translocation produces the Philadelphia (Ph) chromosome



expresses a fusion oncoprotein with tyrosine kinase activity

translocation between 9th and 22nd chromosomes
chronic myeloid leukemia

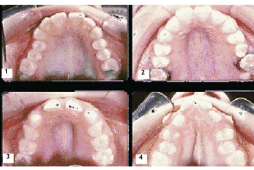
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Genetics in dentistry

Chromosomal diseases

Turner syndrome
(45,X0)

- high palatal vault



Down syndrome
(trisomy 21)

- macroglossia with hypertrophic 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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Non-Mendelian genetics refers to patterns of inheritance that do not follow the basic principles established by Gregor Mendel.

Examples:

1. **Incomplete dominance** - not only the dominant but also the recessive allele is involved in the phenotypic expression. Homozygote and heterozygote have differences in phenotype - clinical signs of homozygote are much intensive than in heterozygote
2. **Codominance** - both alleles in a heterozygote are fully expressed
3. **Variable expressivity** - qualitative variations of phenotype between people with the same genotype
4. **Incomplete penetrance** - quantitative variations of phenotype between people with the same genotype
5. **Pleiotropy** - a single gene influences multiple traits.
6. **Epistasis** - one gene affects the expression of another gene, masking or altering its effects.
7. **Genomic imprinting** - Certain genes are expressed differently depending on whether they are inherited from the mother or the father.
8. **Trinucleotide repeat disorders** - abnormal trinucleotide repeat expansions
9. **Mitochondrial inheritance**

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Variable expressivity
Syndactyly



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Dynamic mutations Trinucleotide repeat disorders

- genes with physiological repetitive triplet sequences of various lengths

Cause

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

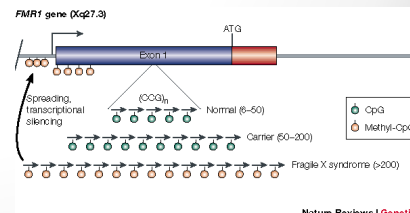
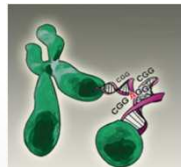
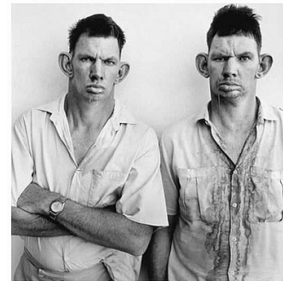
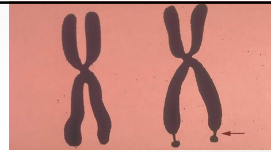
Diseases

- 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, stereotypic 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



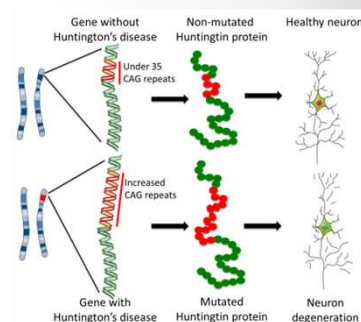
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Huntington's disease (Huntington's chorea)

- 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 → protein 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 disease, muscle atrophy...

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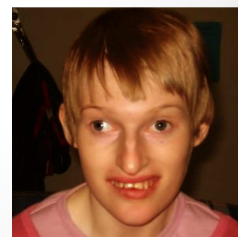
Genomic imprinting

- 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)
 - less than 1% of human genes

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Genomic imprinting

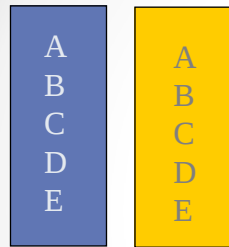
- Prader-Willi and Angelman syndromes
- Two different diseases caused by the same deletion - deletion of 15th chromosome
 - PWS - deletion of CH15 inherited from father
 - AS - deletion of CH15 inherited from mother
- PWS: Hypotonia, mental retardation (milder), hyperphagia, weight gain, hypogonadism
- AS: Happy puppet sy., mental and motor retardation, seizures, spasms, insomnia, epilepsy



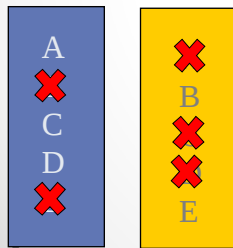
Angelman syndrome

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Different expression of alleles from father and from mother



form father



Majority of genes

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

Imprinting

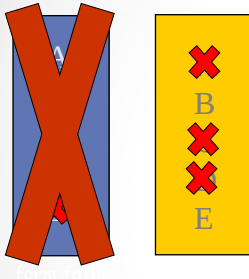
From pair of alleles only one gene is active (e.g. from father) and the second one (from mother) is blocked.

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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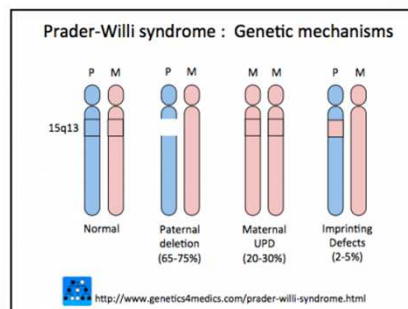
deletion



form father

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

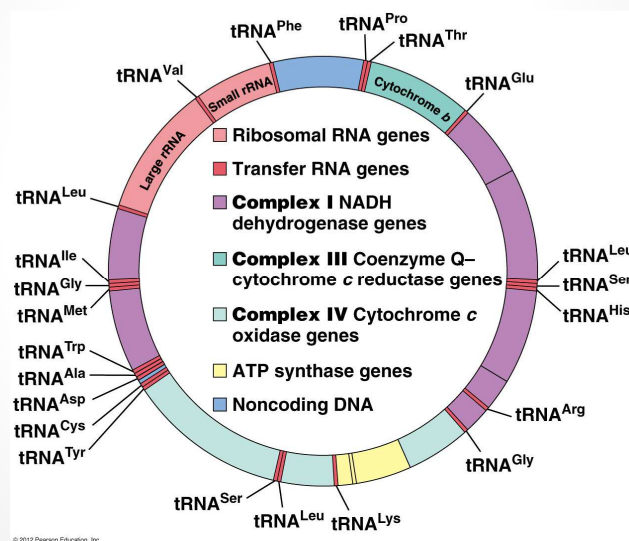
- mtDNA - evolutionary different from nuclear DNA - bacteria
- Maternal inheritance - degradation of sperm mtDNA in the male genital tract or in the fertilized egg.

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



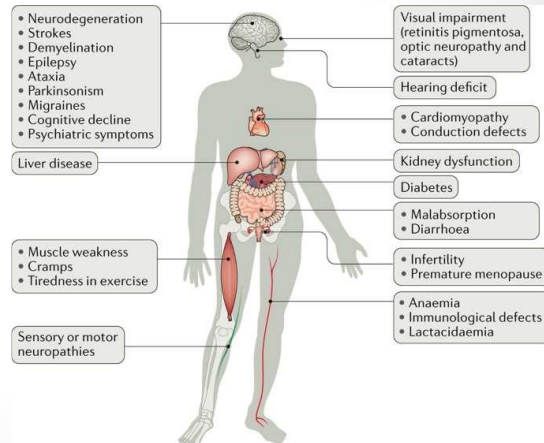
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Mitochondrial diseases

- o KSS - Kearns-Sayre sy.
- o LHON - Leber hereditary optic neuropathy
- o MERFF - Myoclonic epilepsy, ragged red fibers
- o 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 - ageing?



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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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Polygenic and complex diseases



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Polygenic Diseases

- Conditions that result from the cumulative effect of multiple genes, contribution of environmental or lifestyle factors may be minimal or secondary e.g.
 - Hypertension
 - Asthma
 - Schizophrenia

Complex Diseases

- Caused by the interaction of multiple factors, including genetic (often polygenic) and environmental factors. Genetic factors contribute to susceptibility, but environmental factors (such as diet, exercise, or exposure to pathogens) play a substantial role in the disease's development and progression e.g.
 - Obesity
 - Type 2 diabetes mellitus
 - Coronary artery disease

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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 phenotype* (one is a bit taller, one has a bit darker hair, a bit different colour of eyes, different intelligence....)?
- ... *women* with two big X chromosomes (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.

