Genetic diseases

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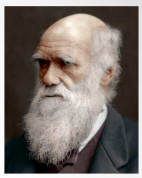
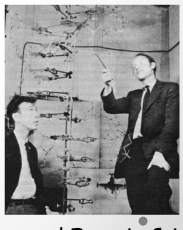
History of genetics

- 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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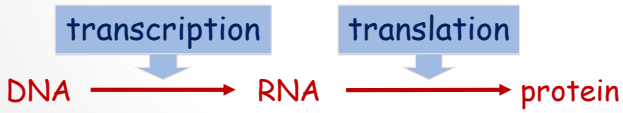
Genetic code

- 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

6	CGA CGC CGG CGT AGA AGG	Arg	4	ACA ACC ACG ACT	Thr		
	CTA CTC CTG CTT TTA TTG	Leu		CCA CCC CCG CCT	Pro		
	TCA TCC TCG TCT AGC AGT	Ser		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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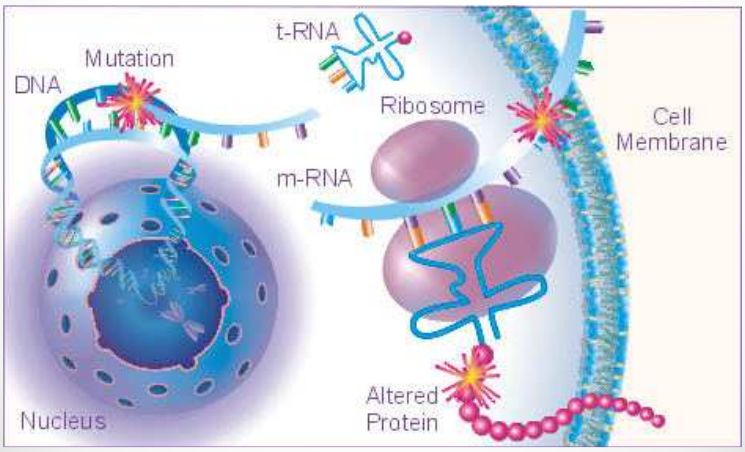
Mutations



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Mutations - definition

- Changes in DNA structure, changes in nucleotide sequence

Mutations - classification

- Etiology
  - spontaneous – mistakes in replication, mistakes in 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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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)
    - Polymorphisms of FTO gene – increased risk of obesity
- Typically, gene polymorphism manifests itself as a change in one nucleotide (single nucleotide polymorphism SNPs).

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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 diseases

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

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

- Disorders of gene expression (epigenetic diseases)

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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
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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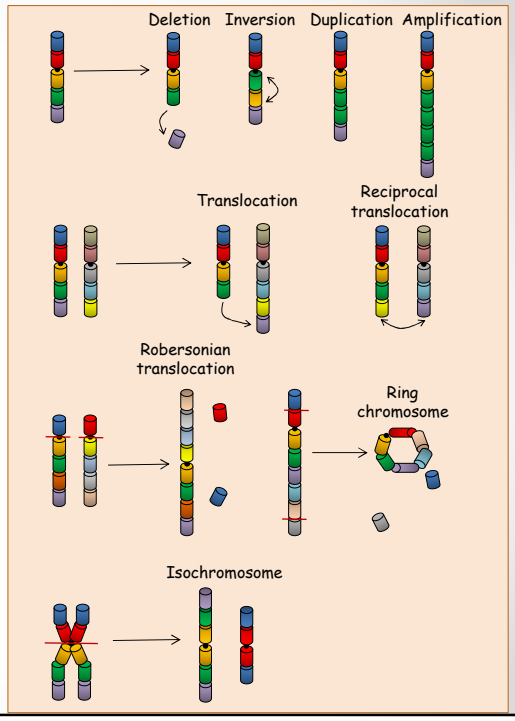
Chromosomal mutations

Structural chromosomal aberrations



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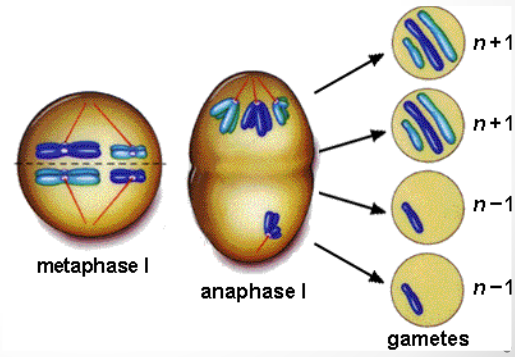
Abnormalities in number of chromosomes

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

Nondisjunction

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



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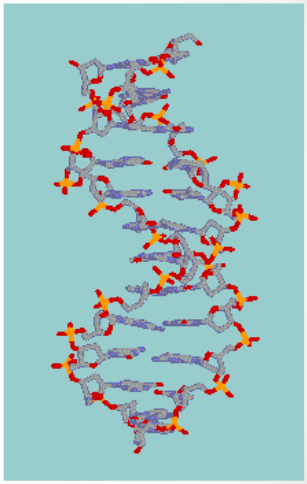
Monogenic diseases



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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

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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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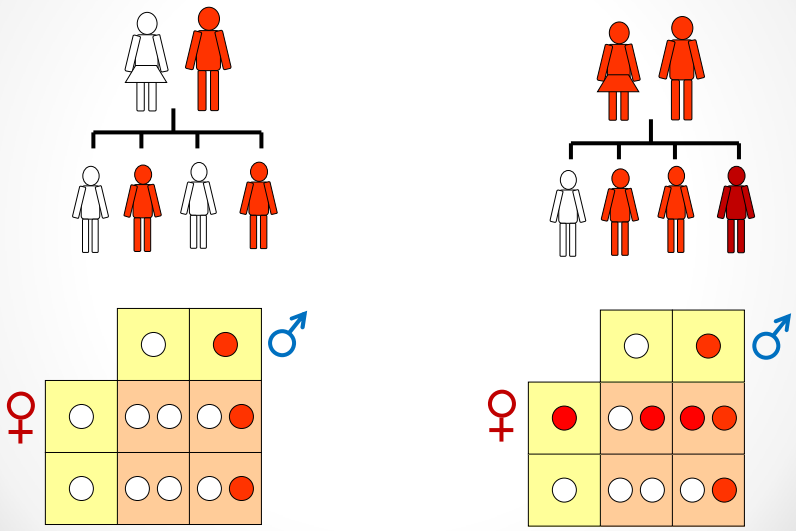
Autosomal dominant diseases



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Autosomal dominant diseases

Characteristic features

- Frequent neomutations – a new spontaneous mutation (parents or siblings are not affected)
- Variable expressivity – qualitative variations of phenotype between people with the same genotype, 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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Marfan syndrome

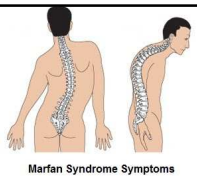
- a genetic connective tissue disorder

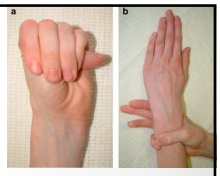
Cause

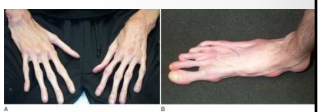
- AD inherited mutation in the *FBN1* gene on chromosome 15, which encodes fibrillin-1, a glycoprotein component of the extracellular matrix.

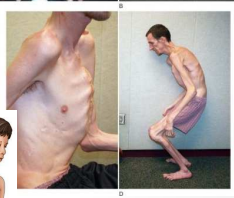
Clinical signs

- 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
Usama Bin Ladin

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Familial hypercholesterolaemia

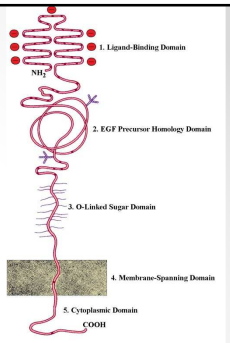
- AD inherited mutation of LDL receptor gene

Symptoms

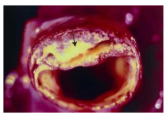
•high plasma cholesterol concentration (LDL)
•rapid development of coronary artery disease

•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

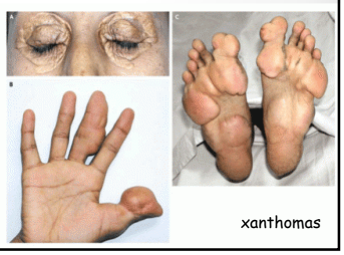
•homozygotes
  - very high LDL concentration (total chol. up to 25 mmol/l)
  - atherosclerosis, myocardial infarction (2.-3. decenium), xantomas



LDL receptor



Atherosclerosis



xanthomas

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Achondroplasia

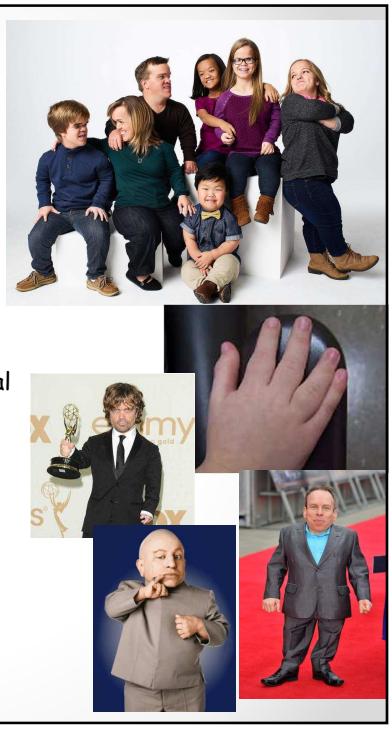
- Bone growth disorder manifested by disproportionate short stature with short limbs.The most frequent cause of dwarfism.

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 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
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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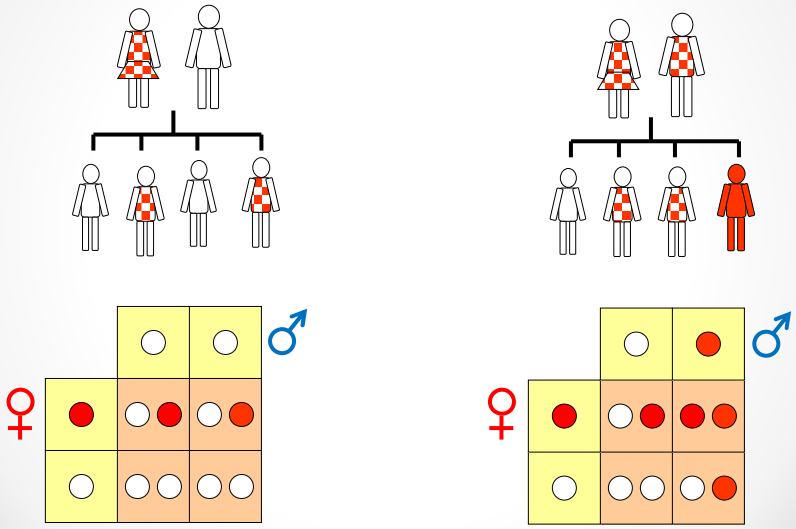
Autosomal recessive diseases



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Phenylketonuria

(hyperphenylalaninemia, Oligophrenia phenylpyruvica)

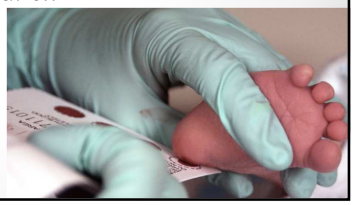
- Inborn disorder of metabolism

Cause

- Phenylalanine hydroxylase deficiency
- disorder of amino acid phenylalanine metabolism
- phenylalanine + 3 phenylalanine 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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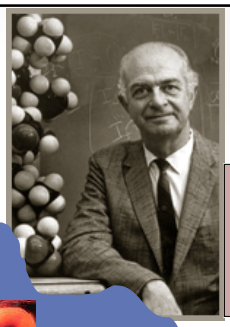
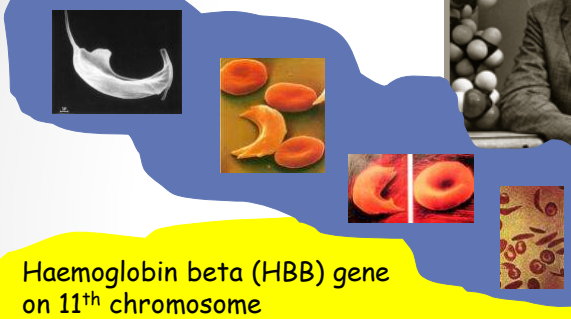
Sickle cell anaemia



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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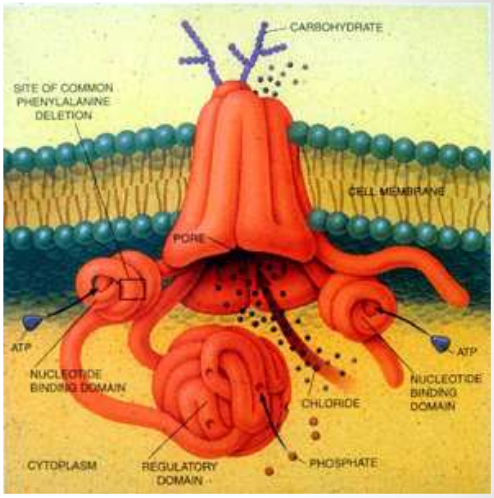
Cystic fibrosis

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

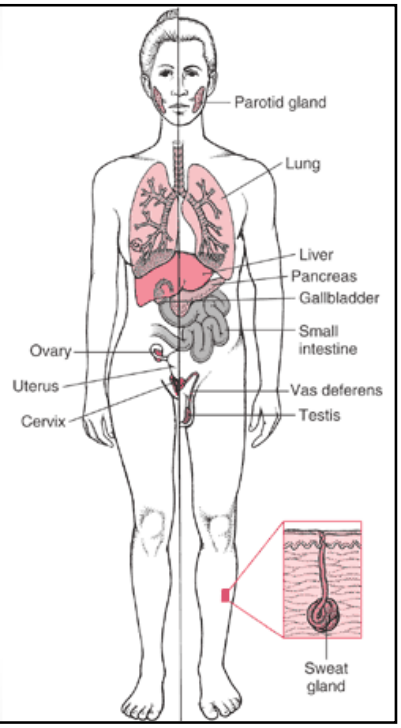
- persistent cough, frequent inflammations
- wheezing, shallow breathing
- frequent lung and respiratory infections
- asthma and sinus infections progressing to lung damage

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 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 resistent 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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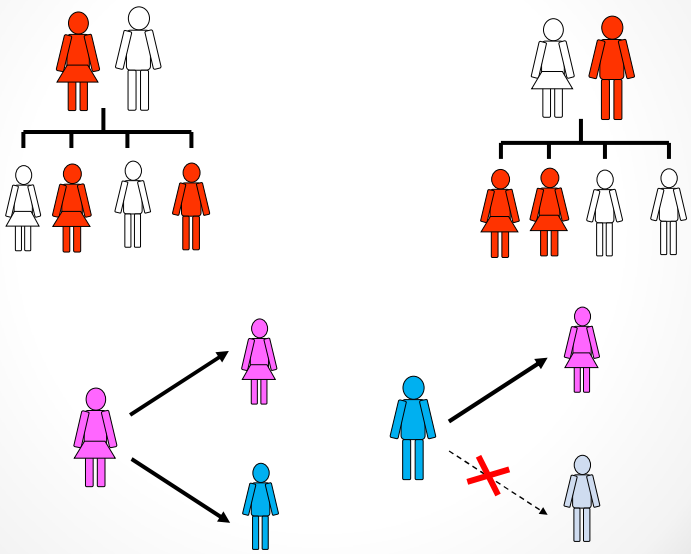
X-linked dominant diseases



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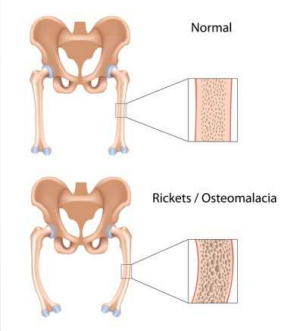
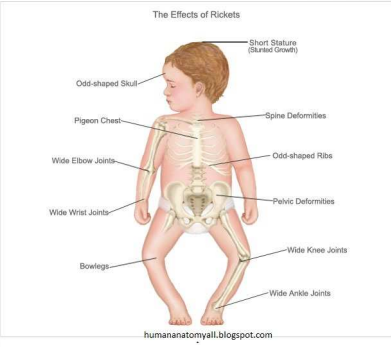
X-linked vitamin D-resistant rickets

- 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 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 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 dystrophia Becker muscular dystrophia Lesh-Nyhan syndrome Ocular albinism (type I and II) Color blindness

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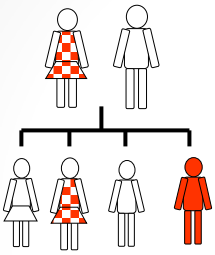
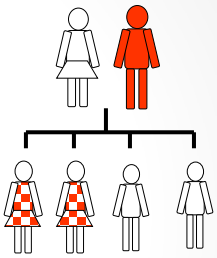
X-linked recessive diseases





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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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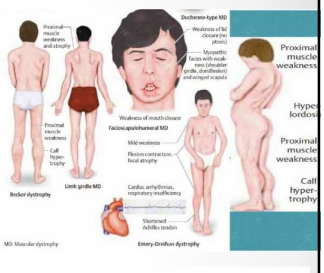
Duchenne muscular dystrophy

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)

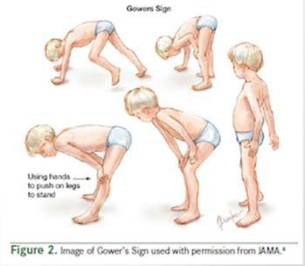
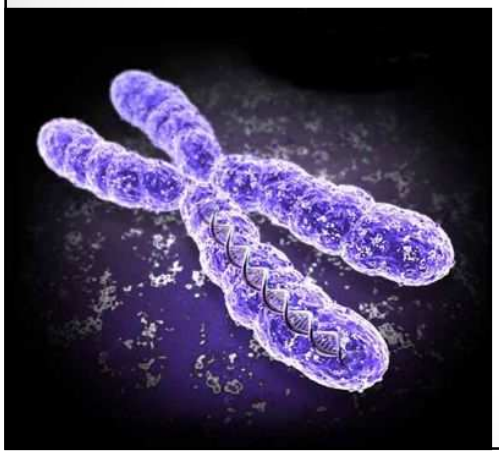


Figure 2. Image of Gower's Sign used with permission from JAMA.[4]

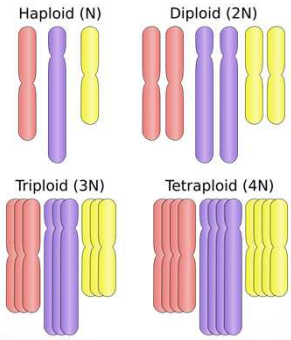
37

Chromosomal aberrations



38

Numeric aberrations of chromosomes



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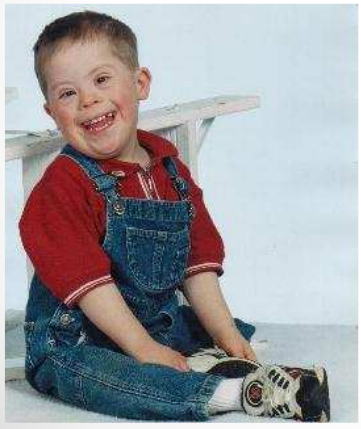
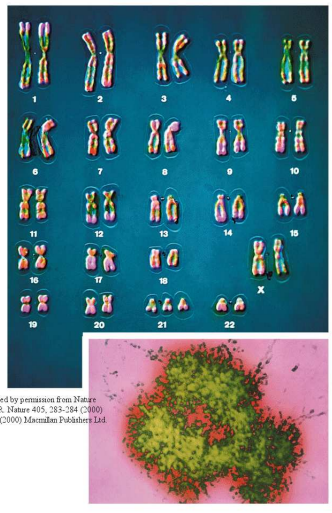
Autosomal aneuploidy

Down syndrome

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

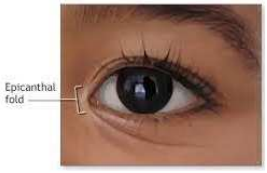




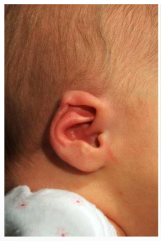
40

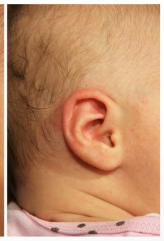
Symptoms

- 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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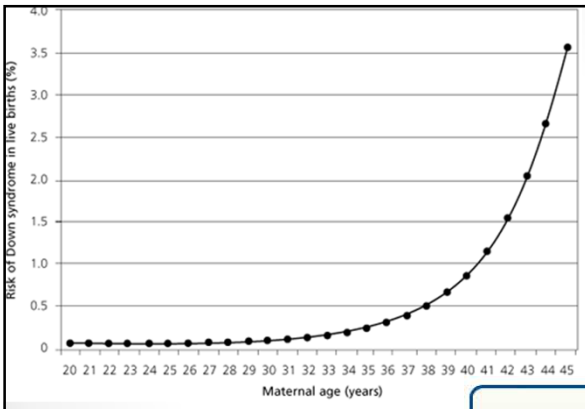

Maternal age and risk of Down syndrome

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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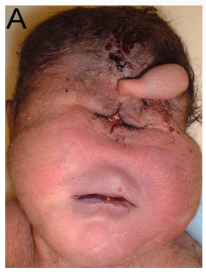
Patau syndrome

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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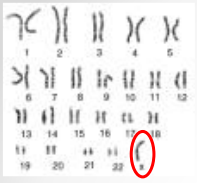
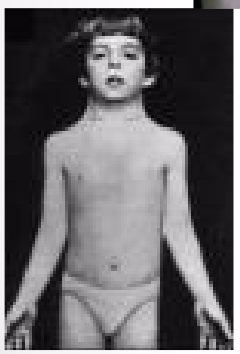
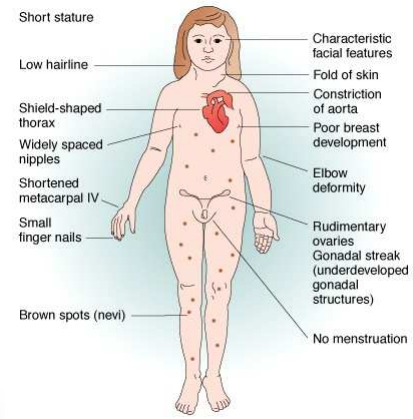
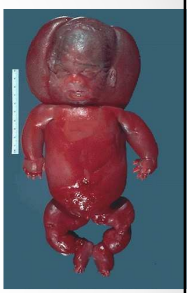
Sex chromosome aneuploidy



Turner syndrome
45, X0







Signs and symptoms

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

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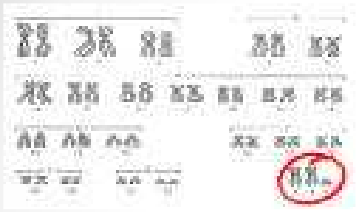
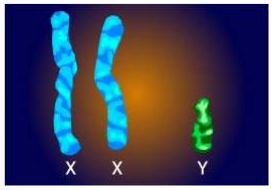
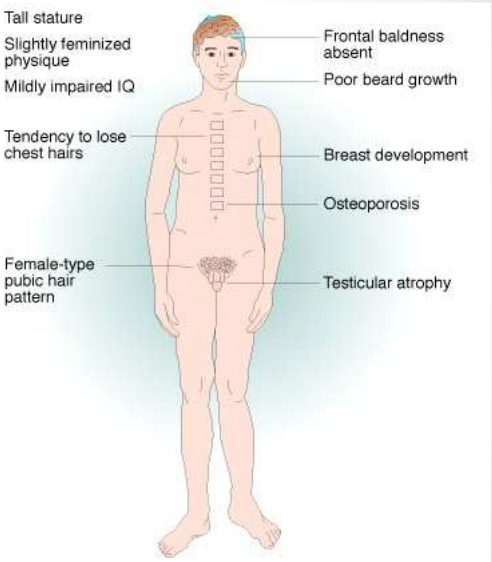
Klinefelter syndrome 47,XXY



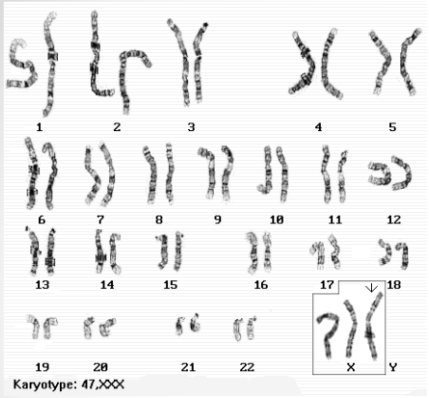




Signs and symptoms
- tall stature
- feminisation
- infertility
- can be mild mantal retardation

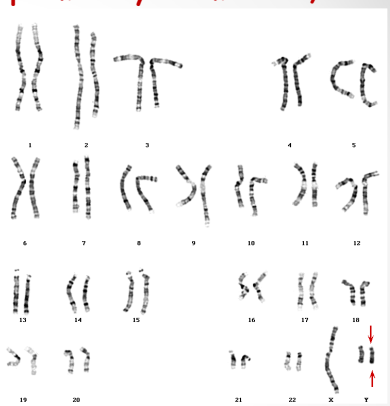
45

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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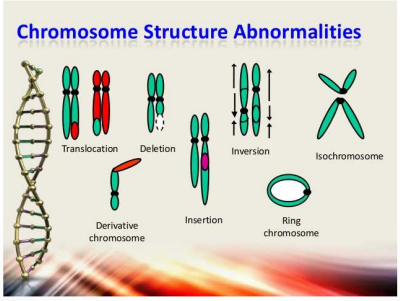
Structure aberrations of chromosomes



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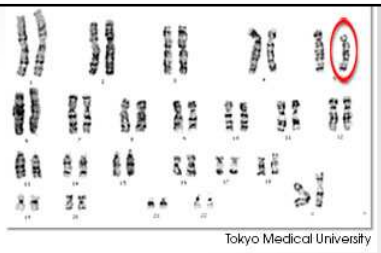
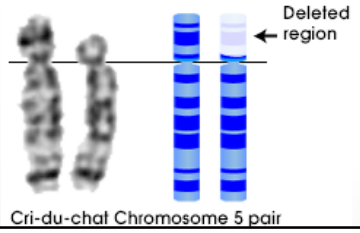
Cri du chat

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, epicantus, other typical face features
- other developmental problems – heart, kidneys...


Tokyo Medical University



Cri-du-chat Chromosome 5 pair

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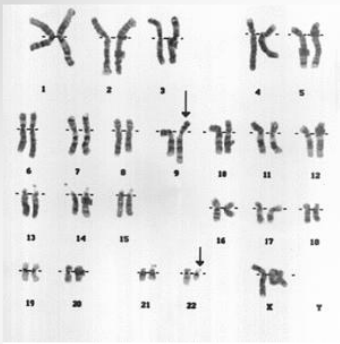
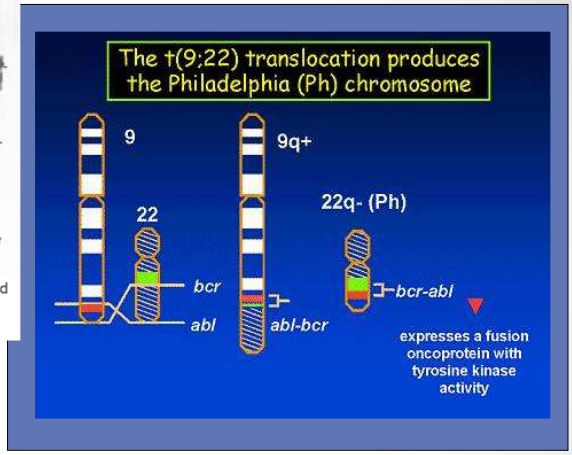
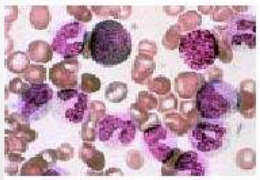
Philadelphia chromosome



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





Slide 75

translocation between 9th and 22nd chromosomes

chronic myeloid leukemia

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Non Mendelian inheritance

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MENDEL'S LAW OF INHERITANCE

- **Law of Dominance:** states that some alleles, which are variants of a particular gene found at the same chromosomal locus or location, are dominant over the other alleles for a given gene.
- **Law of Segregation:** states that the two alleles for each gene separate from each other during gametogenesis so that the parent may only pass off one allele; thus, the offspring can only inherit one allele from each parent.
- **Law of Independent Assortment:** states that the alleles of different genes segregate independently of one another during gametogenesis and are distributed independently of one another in the next generation.

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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 genotyp
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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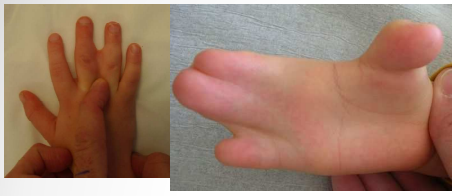
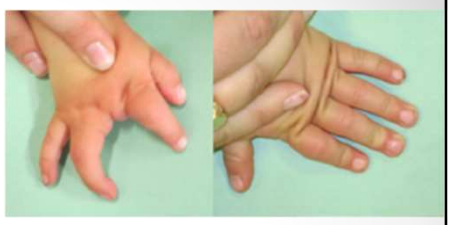
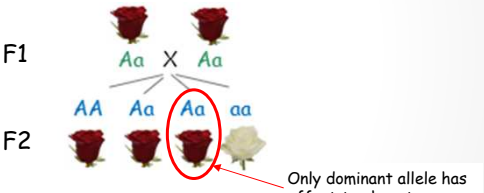
Variabile expresivity
Syndactyly



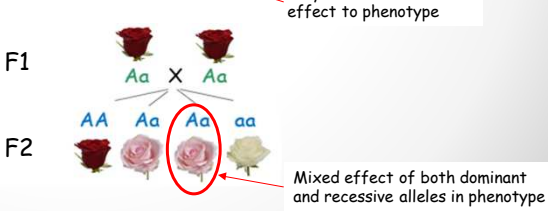
Incomplete penetrance



Complete dominance
(Mendel´s)



Incomplete dominance
(Non Mendelian)



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Dynamic mutations
Trinucleotide repeat disorders

- Genes with polymorphic regions of repeating triplets
- The region with repeating triplets may be located in an exon, intron, or regulatory region of the gene.
- A pathological expansion of the number of triplets may occur.
- The more repeats, the more severe the disease.

Characteristic features

- Inheritance of the diseases – AD, AR, and X-linked
- Anticipation – worsening of the disease, increasing severity of symptoms, and earlier onset of the disease in next generations. The severity of the disease depends on the number of repeats, which usually increases with transmission from generation to generation.
- Dependence of trinucleotide expansion on the sex of the transmitting parent. For example, in fragile X syndrome the number of repeats is higher and the disease is more severe if the mutation is transmitted from mother to son. In contrast, in Huntington's disease the disease is more severe in the offspring if the transmitting parent is the father.

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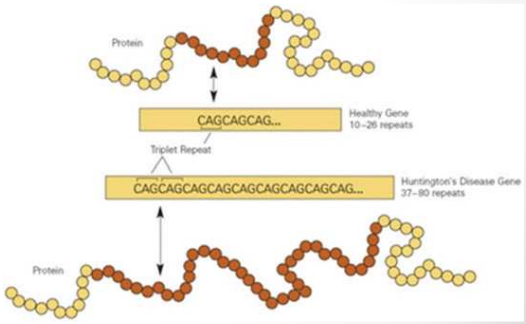
Dynamic mutations
Trinucleotide repeat disorders

Cause
- Mistake in the DNA replication or DNA reperation

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



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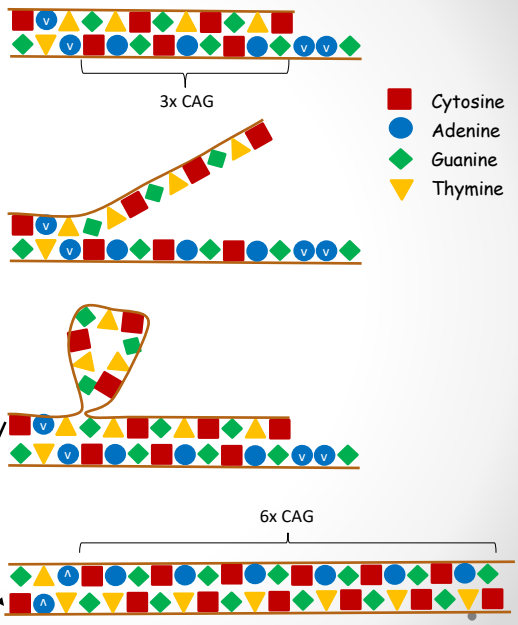
Mechanism of expansion

During replication, DNA polymerase creates a new strand.

This strand partially separates.

A loop is formed, and DNA polymerase synthesizes the same section again.

During the subsequent replication, when the new strand serves as a template, the number of repeats is multiplied.



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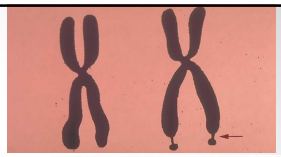
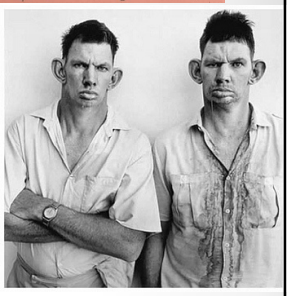
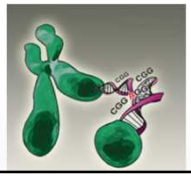
Fragile X chromosome
(Martin-Bell syndrome)

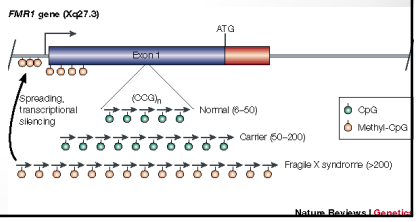




- Mental retardation (IQ 60 – 20)
- Face signs – prolonged face, protruding ears
- Autism, stereotyic movement, speech
- Makroorchidism
- Prolapse of mitral valve

- 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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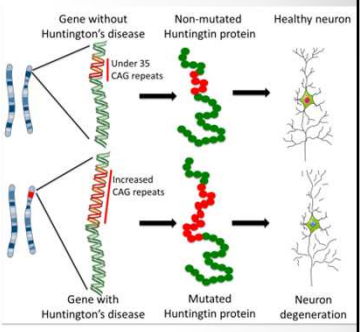
Huntington´s disease
(Huntington´s chorea)

- 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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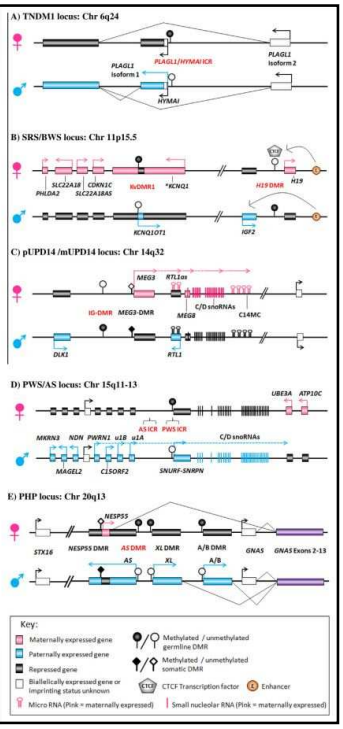
Genomic imprinting

- 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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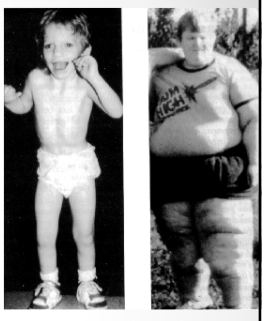
Genomic imprinting

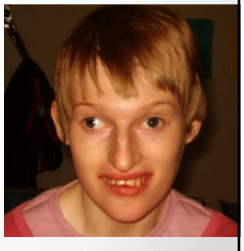
- Prader-Willi and Angelman synfromes
- Two different diseases caused by the same deletion – deletion of 15th chromosome

- 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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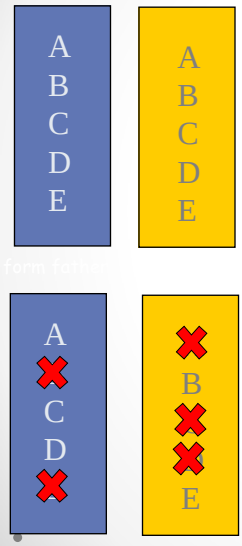
Different expression of alleles from father and from mother



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 or histone modification.

This situation is normal for small group of genes – physiological reduction of genetic information.

Active is only one set of genes - 1xABCDE

(Do not confuse this with dominance and recessivity. A recessive gene is expressed and produces a protein, it just does not manifest in the phenotype. Imprinted gene, however, is blocked and not expressed).

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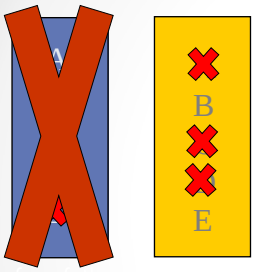
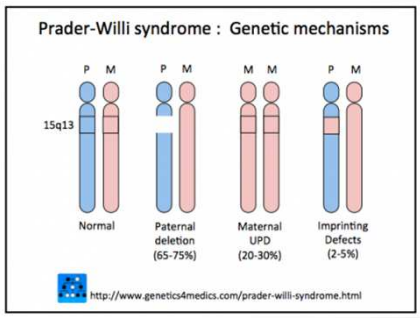
deletion



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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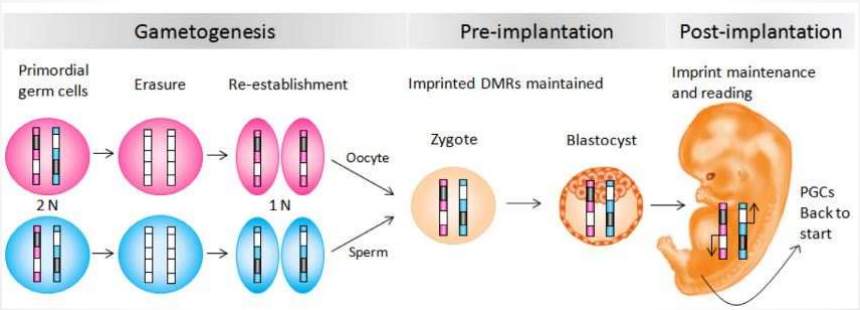
- During gametogenesis – imprinting is erased
- New imprinting is re-established
  - Men – only „father´s" imprinting
  - Women - only „mother´s" imprinting



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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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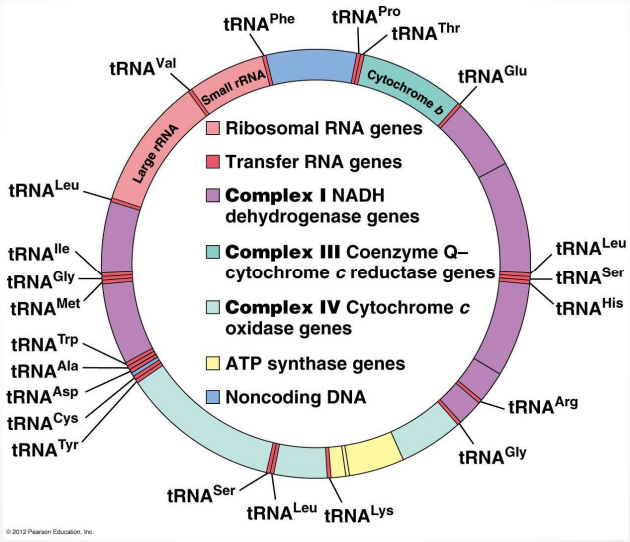
Mitochondrial DNA



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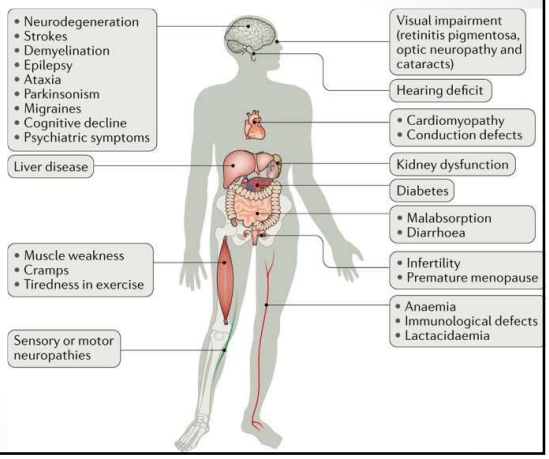
Mitochondrial diseases

- 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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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 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*?

Definition

- 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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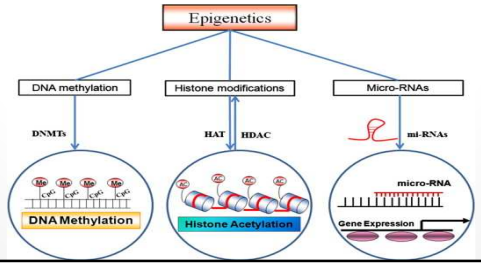
Mechanisms

- 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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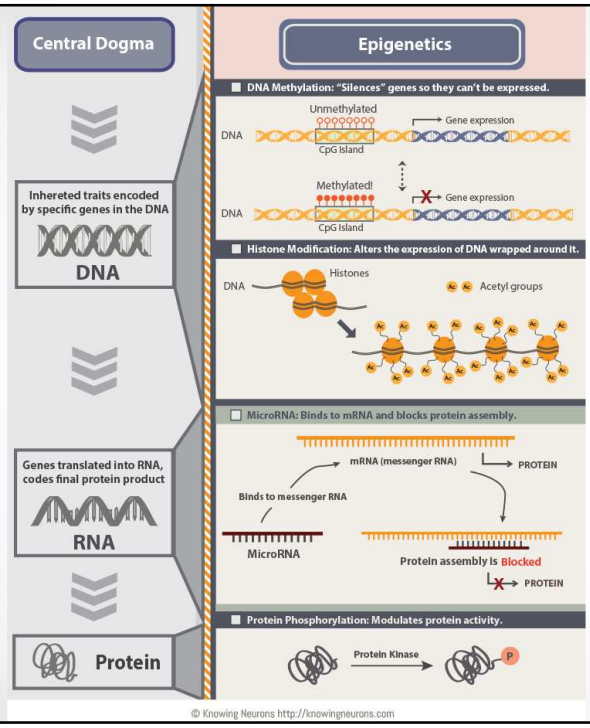

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Factors that influence epigenetic mechanisms

- Diet
  - Starvation
  - Too much fat in diet
  - Fytoestrogenes
- Polutants
- Smoking, alcohol, drugs
- Sedentary lifestyle
- Stress
- Neglect and abuse

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Classification accorfing to heredity

Epigenetic mechanisms with a direct effect

- They manifest during the lifetime of the individual who was directly exposed to environmental factors.
- For example, insufficient care or child abuse at an early age leads to changes in the expression of the glucocorticoid receptor, which later results in an increased risk of developing depression or anxiety disorders.

Epigenetic mechanisms with an indirect effect

- They manifest only in the following generation.
- For example, animal experiments have shown that if a pregnant female is repeatedly exposed to the scent of a predator, her offspring also display a stress reaction to that scent, even though they themselves have never encountered the predator. The explanation lies in a form of "epigenetic programming" of the fetus to adapt to stimuli the mother is exposed to during pregnancy.

Epigenetic mechanisms with a transgenerational effect

- They manifest in the third or subsequent generations.
- The most well-known example is the Dutch famine in 1944. Women who were pregnant at that time gave birth to children who, in adulthood, had an increased risk of obesity, insulin resistance, and cardiovascular diseases. A significantly higher incidence of these conditions was also observed in the offspring of those children, i.e., in the grandchildren of women affected by the famine. Researchers discovered changes in the methylation of the gene encoding insulin-like growth factor 2 (IGF2) in the descendants of these women, which may be related to the increased prevalence of the mentioned diseases.

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Epigenetic diseases

- Diseases caused by (or partially influenced by) defective regulation of gene expression

Neurological disorders

- Fragile X chromosome
- Huntington disease

Metabolic disorders

- Obesity
- Diabetes mellitus

Cancers

- Changes in expression of oncogenes or tumor supressor genes

Psychical disorders

- Depression, anxiety

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