# Genetic diseases
# Genetics in dentistry

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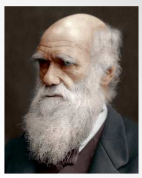
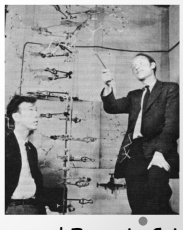
## History of genetics

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


Charles Darwin


Johann Gregor Mendel


James Watson and Francis Crick

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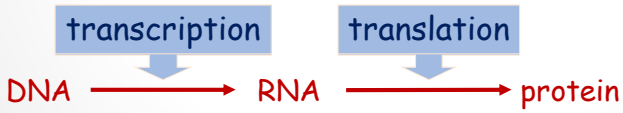
## Genetic code

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

## Central dogma of molecular biology (F. Crick 1958)

How genetic information is expressed

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## Genetic information

Redundancy (degeneration) of genetic code

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 6 | CGA CGC CGG CGT AGA AGG | Arg | 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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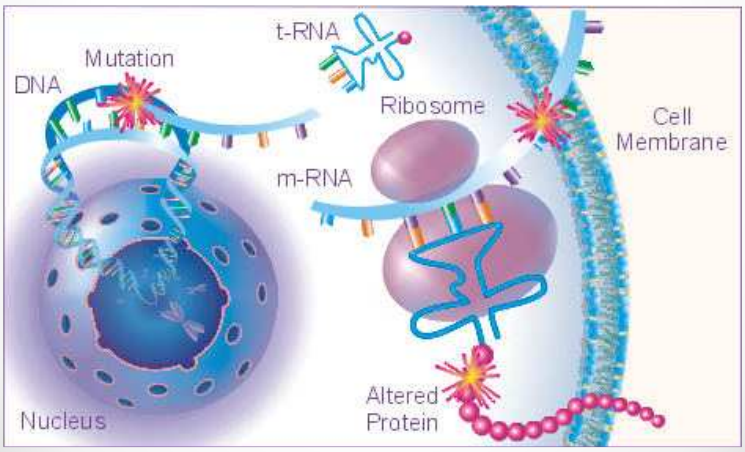
# Mutations

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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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# 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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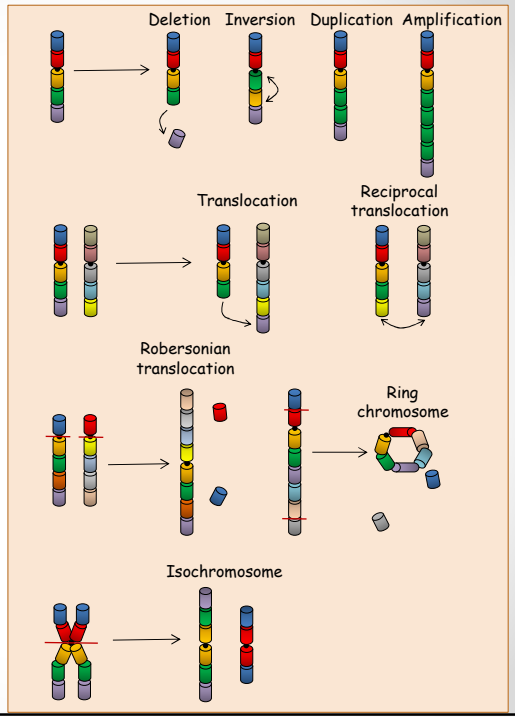
## Chromosomal mutations

Structural chromosomal aberrations

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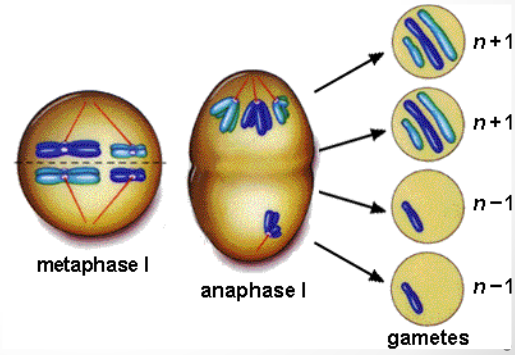
## Abnormalities in number of chromosomes

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

# Genetic disorders

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


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


- Disorders of gene expression (epigenetic diseases)

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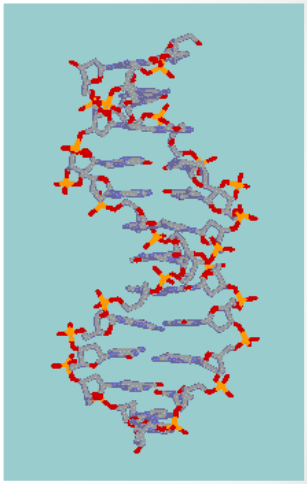
# Monogenic diseases



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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


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## Affected proteins

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

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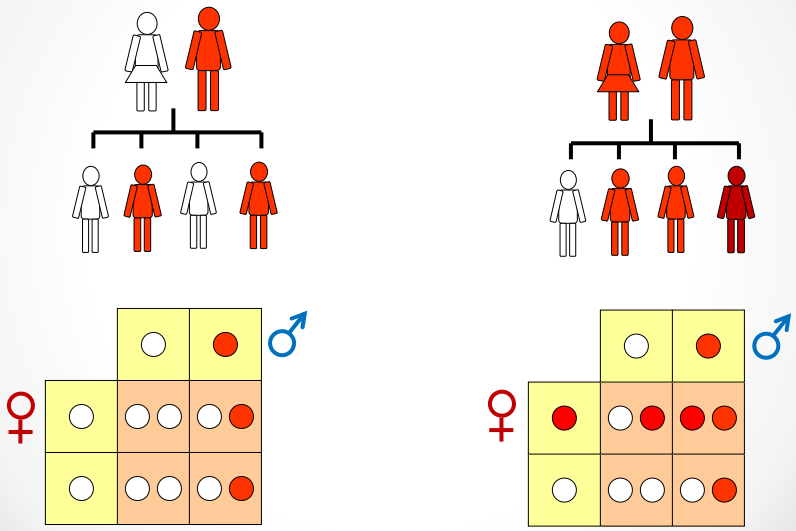
## Autosomal dominant diseases



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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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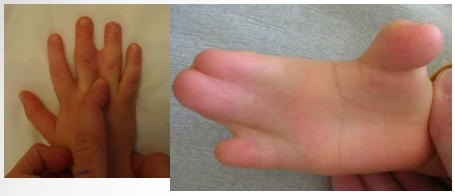
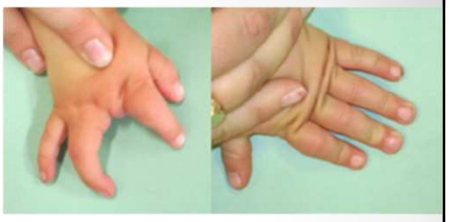
Variabile expresivity
Syndactyly



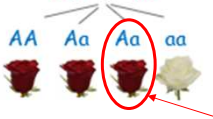
Incomplete penetrance



Complete dominance

F1


F2




Only dominant allele has effect to phenotype

Incomplete dominance

F1


F2


Mixed effect of both dominant and recessive alleles in phenotype

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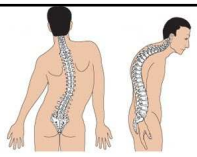
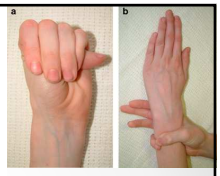
# Marfan syndrome

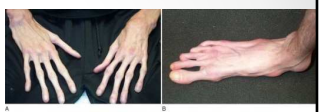
- a genetic connective tissue disorder

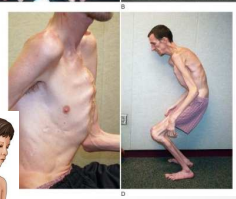


*Cause*

- 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

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# Familial hypercholesterolaemia

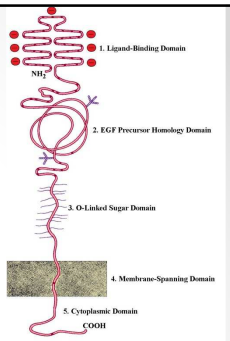
- AD inherited mutation of LDL receptor gene

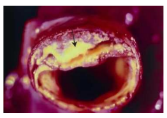
Symptoms

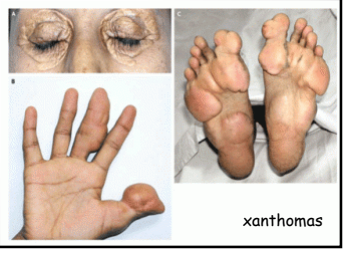
•high plasma cholesterol concentration (LDL)
•rapid development of coronary artery disease

•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





xanthomas

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# Achondroplasia

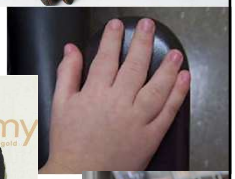
- Bone growth disorder manifested by disproportionate short stature with short limbs.The most frequent cause of dwarfism.

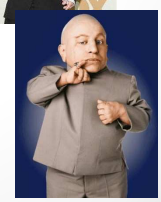
Cause

- 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<br>Sickle cells anaemia<br>Cystic fibrosis<br>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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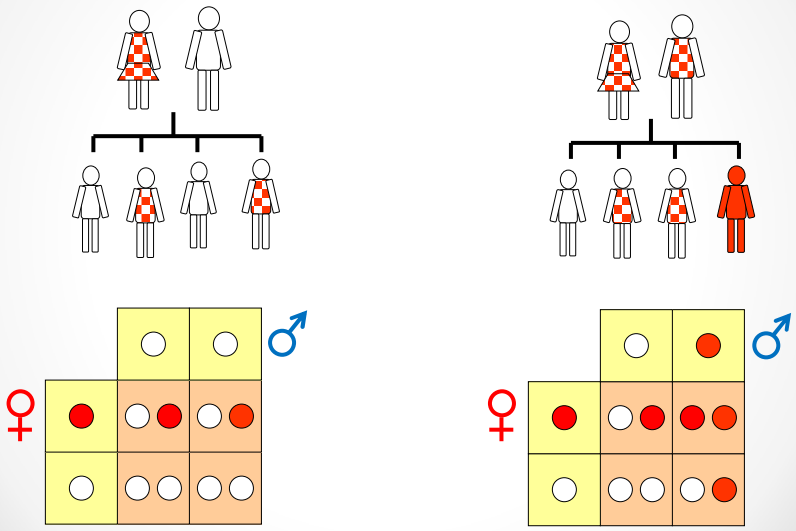
# Autosomal recessive diseases

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# Phenylketonuria

(hyperphenylalaninemia, Oligophrenia phenylpyruvica)

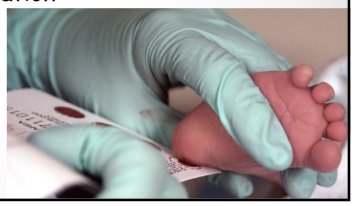
- Inborn disorder of metabolism

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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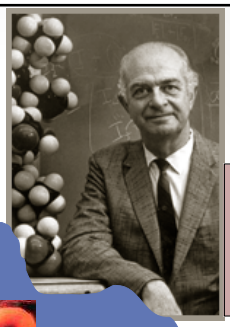
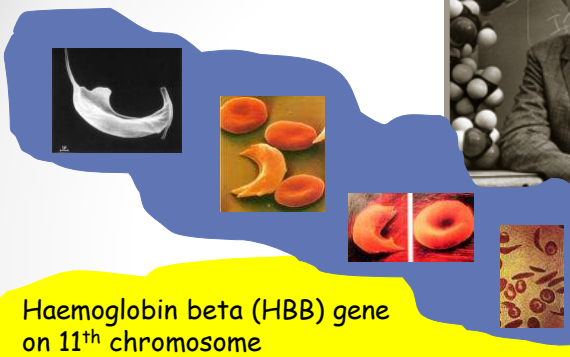
# Sickle cell anaemia



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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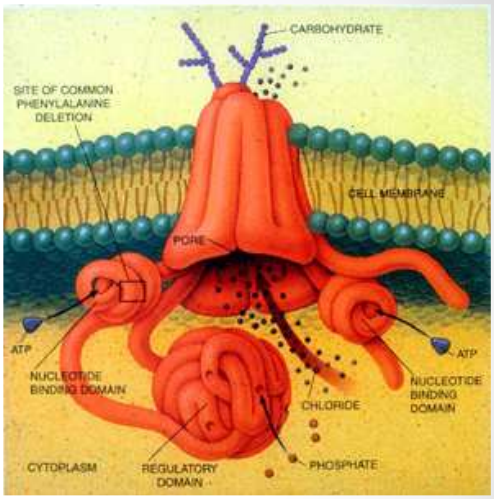
# Cystic fibrosis

## 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

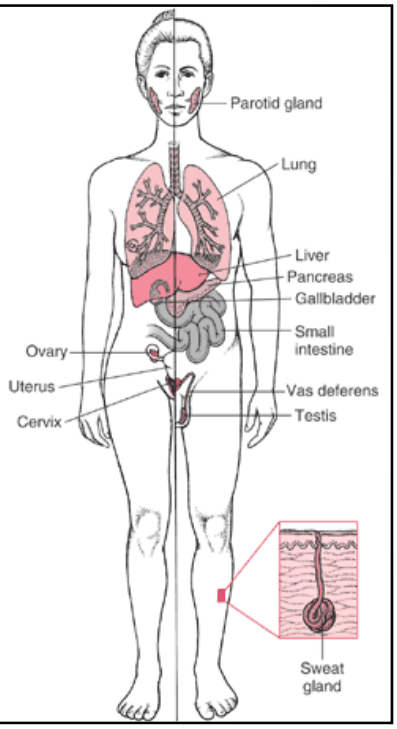
- persistent cough, frequent inflammations
- wheezing, shallow breathing
- frequent lung and respiratory infections
- asthma and sinus infections progressing to lung damage

### 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<br>Transmission from father to son is not possible<br>If the mother is affected (heterozygous), 50% probability of affecting daughters (heterozygotes) and 50% of sons (hemizygotes)<br>If the father is affected, all daughters are affected (heterozygotes), all sons are healthy |
| **Diseases** | Vit. D resistent rachitis<br>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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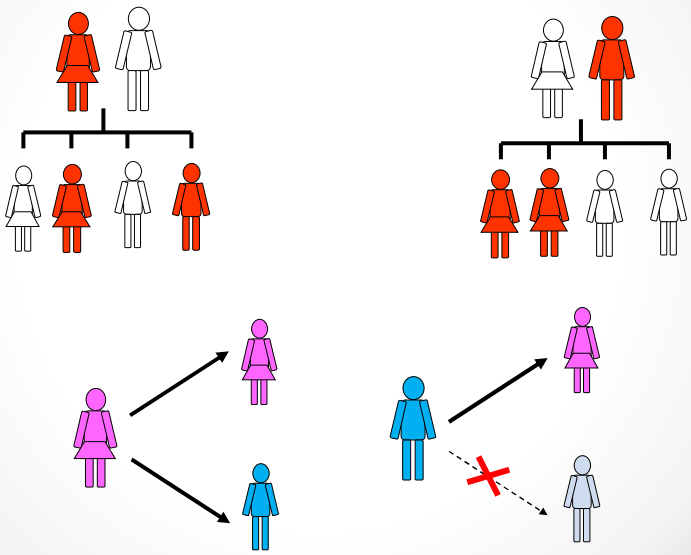
## X-linked dominant diseases



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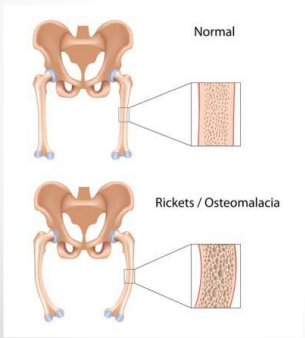
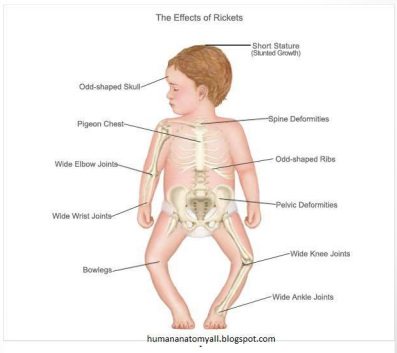
## X-linked vitamin D-resistant rickets

- 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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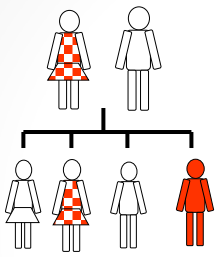
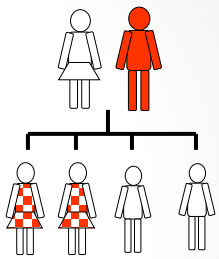
# X-linked recessive diseases

| | |
|---|---|
| **Localisation of pathological gene** | X chromosome |
| **Clinical manifestation** | Men<br>In women very exceptionally (e.g. the union of an affected man – hemizygous with a carrier woman – heterozygous)<br>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<br>Duchenne muscular dystrophia<br>Becker muscular dystrophia<br>Lesh-Nyhan syndrome<br>Ocular albinism (type I and II)<br>Color blindness |

35

## X-linked recessive diseases





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# Hemophilia A

- XR inherited mutation of clotting factor VIII

Signs and symptoms

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

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

The best known patient with hemophilia A – russian tsarevich Alexei

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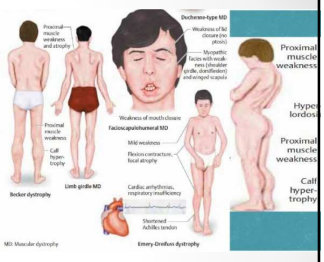
# Duchenne muscular dystrophy

Causes:

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

Signs and symptoms

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



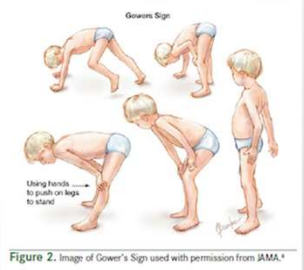



Figure 2. Image of Gower's Sign used with permission from JAMA.[4]

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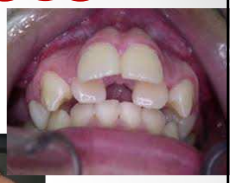
## Genetics in dentistry

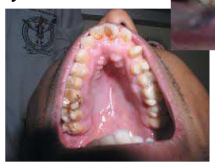
# Monogenic diseases



Marfan´s syndrome

(AD genetic connective tissue disorder )

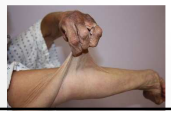
- high-arched soft palate
- crowding of the teeth



Ehlers-Danlos syndrome

(AD genetic connective tissue disorder)

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



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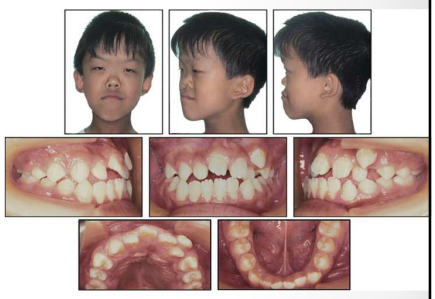
## Genetics in dentistry

# Monogenic diseases

Achondroplasia

(AD skeletal dysplasia, dwarfism)

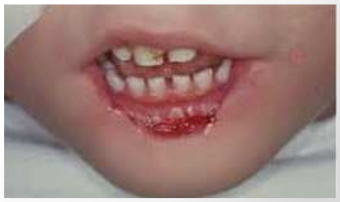
- characteristic craniofacial features, relative macrocephaly, depressed nasal bridge, maxillary hypoplasia, macroglossia, gingivitis...



Lesch-Nyhan syndrome

(AR purine metabolism disorder)

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



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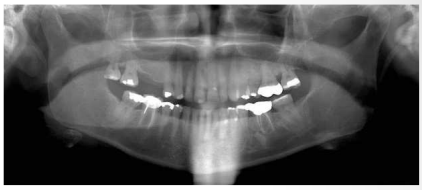
## Genetics in dentistry

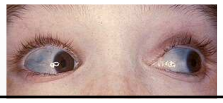
# Monogenic diseases



Gaucher´s syndrome
(AR, sphingolipid metabolism disorder)
- radioluscent lesons in the jaw
- loosing of teeth

Osler-Weber-Rendu sy.
(AD, blood vessel disorder)
- teleangiectasia of the tongue, oral cavity and nasal mucosa

Osteogenesis imperfecta
(britle bone disease, AD collagen metabolism disorder)
- opalescent freely movable teeth



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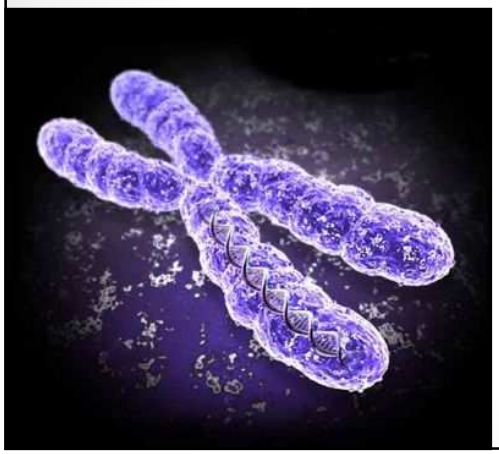
# Chromosomal aberrations



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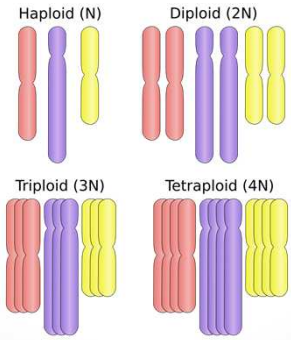
# Numeric aberrations of chromosomes

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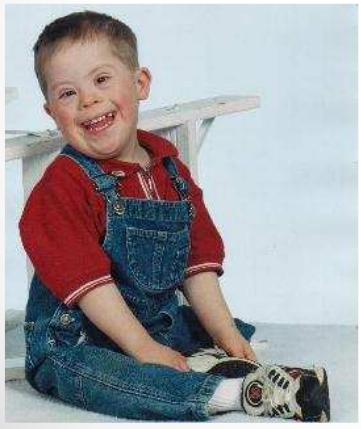
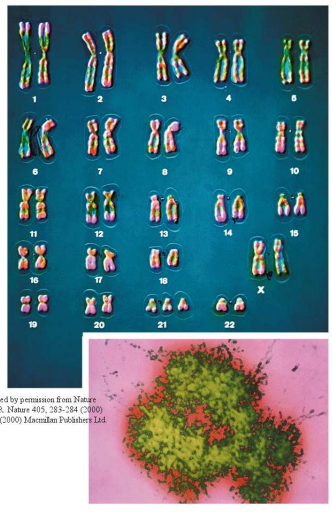
## Autosomal aneuploidy

### Down syndrome

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







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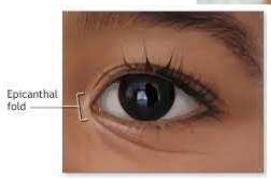
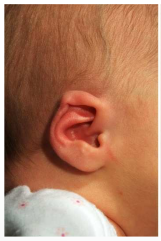
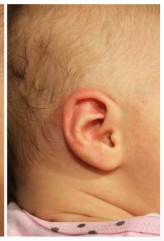
## Symptoms

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

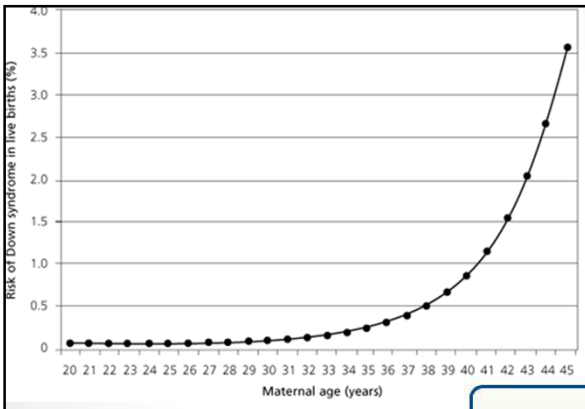



- Flat face
- Epicantus
- Hand deformation – short fingers, abnormal lines on hand
- Deformities of toes
- Heperglossia
- Flattened nose
- Small ears
- …





45




**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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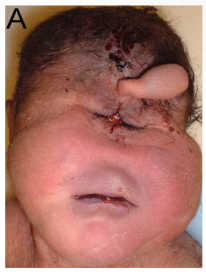
## Patau syndrome

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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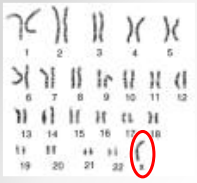
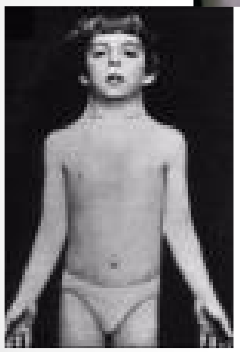
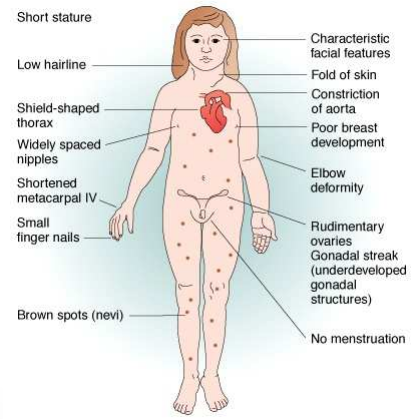
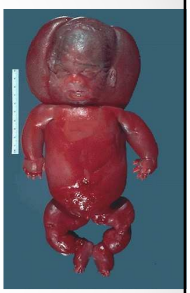
# Sex chromosome aneuploidy



## Turner syndrome
## 45, X0





Signs and symptoms

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

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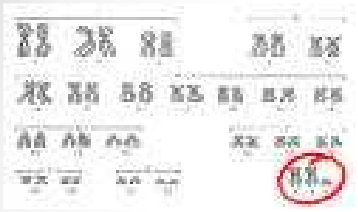
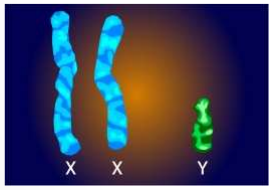
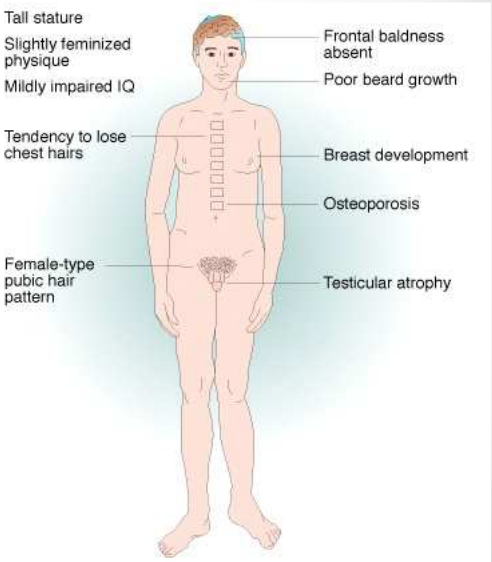
# Klinefelter syndrome 47,XXY






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

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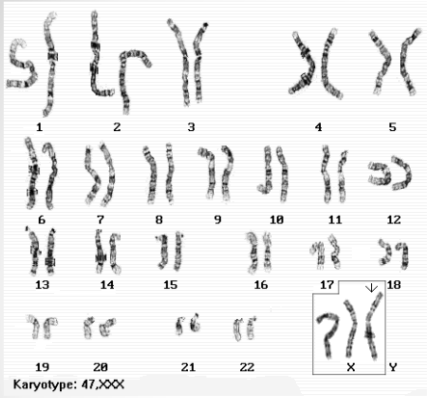
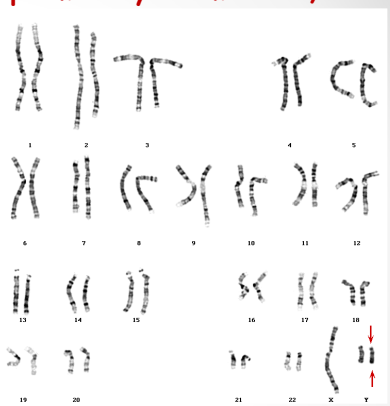
## Superfemale syndrome 47,XXX




Signs and symptoms
- normal appearance
- tall stature
- normal fertility
- mild mental problems – learning problems
- hypotonia

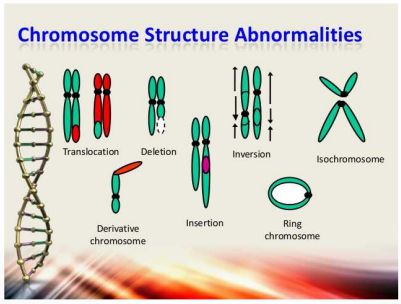
## Supermale syndrome 47,XYY



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

50

# Structure aberrations of chromosomes

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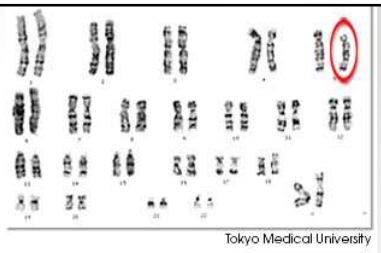
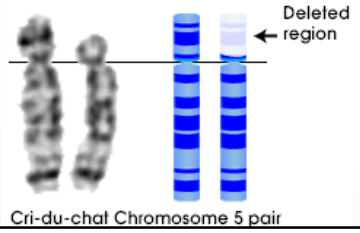
## Cri du chat

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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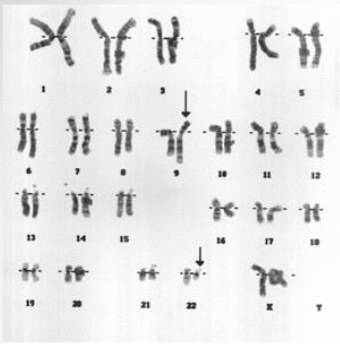
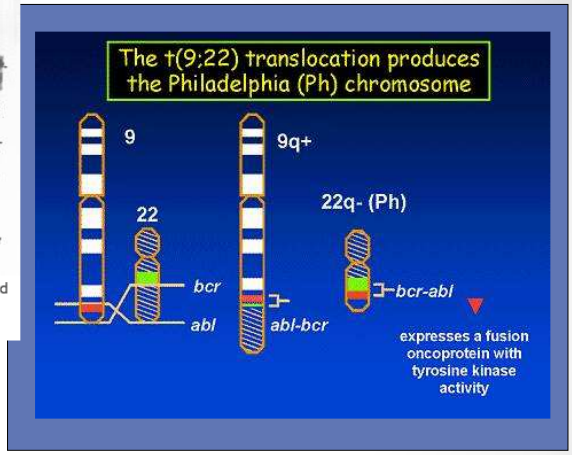
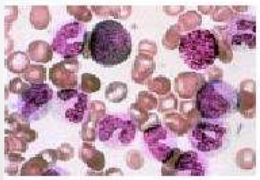
## Philadelphia chromosome



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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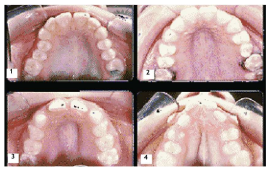
## Genetics in dentistry

# Chromosomal diseases

Turner syndrome

(45,X0)

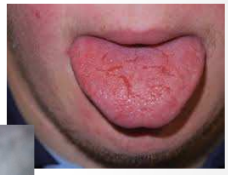
- high palatal vault



Down syndrome

(trisomy 21)

- macroglosia with hypertophic papillae
- cleft or high-arched palate



Cri-du-Chat syndrome

(partial chromosome 5 monosomy)

- mandibular microretrognathia, high palate, enamel hypoplasia, generalized chronic periodontitis, delayed tooth eruption

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# Non Mendelian inheritance

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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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# Dynamic mutations
# Trinucleotide repeat disorders

- genes with physiological repetitive triplet sequences of various lenghts

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

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

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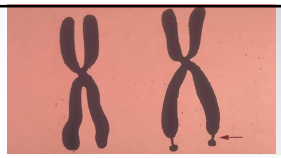
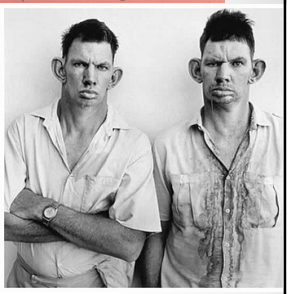
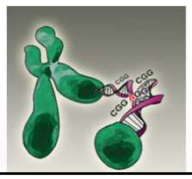
# Fragile X chromosome
## (Martin-Bell syndrome)

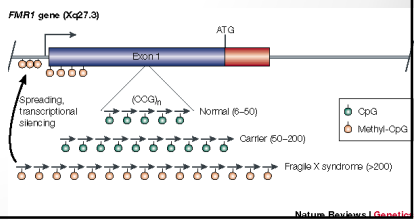




- Mental retardation(IQ 60 – 20)
- Face signs – prolonged face, protruding ears
- Autism, stereotyic movement, speech
- Makroorchidism
- Prolapse of mitral valve

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



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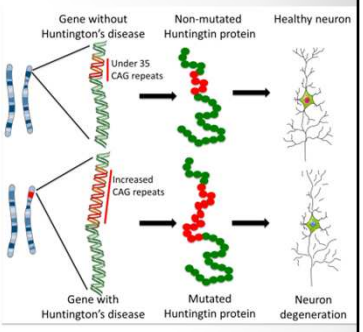
# Huntington´s disease
## (Huntington´s chorea)

- Inherited neurodegenerative disease




Cause

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

Clinical signs

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

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# 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)
  - 1% (3% ?????) of human genes

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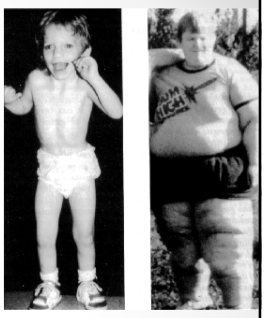
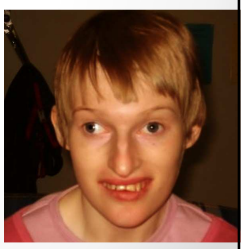
# Genomic imprinting

- 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





Angelman syndrome

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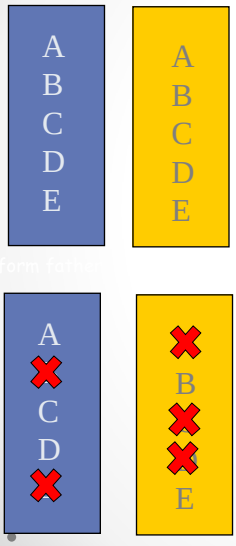
# Different expression of alleles from father and from mother




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

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

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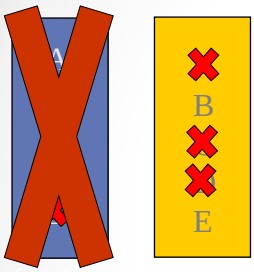
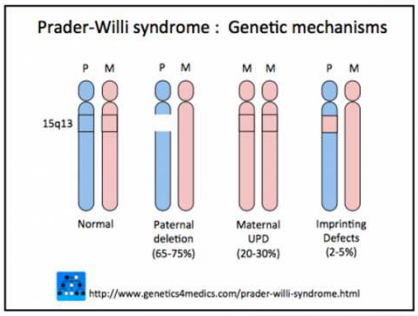



Deletion (loss) of the only active allele causes disease.

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

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# Mitochondrial inheritance

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

Structure

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

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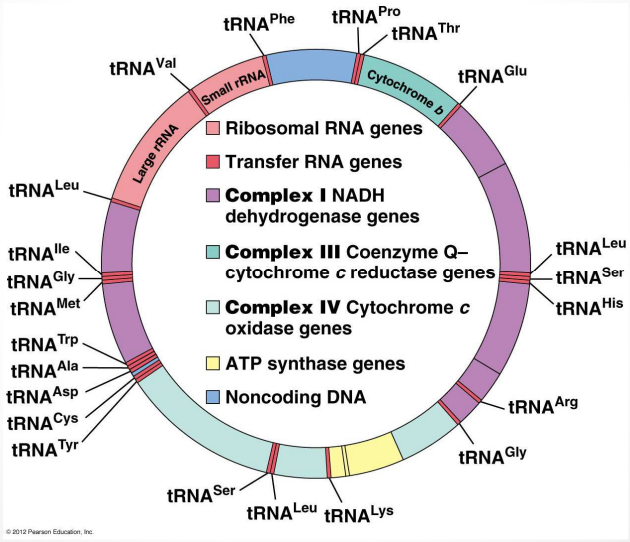
# Mitochondrial DNA

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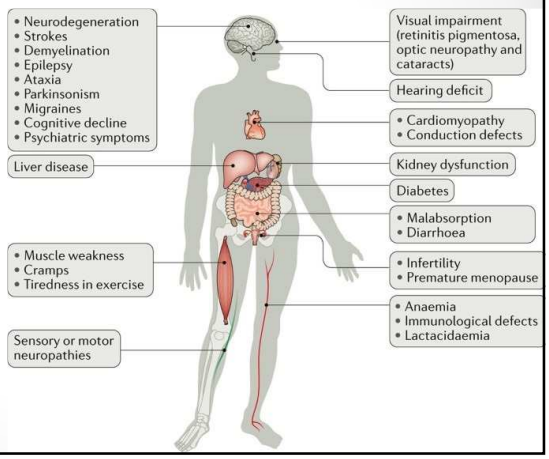
# Mitochondrial diseases

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

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

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## Genetics in dentistry

# Non Mendelian diseases

### Fragile X syndrome

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

### Angelman syndrome

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

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# 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*?

- 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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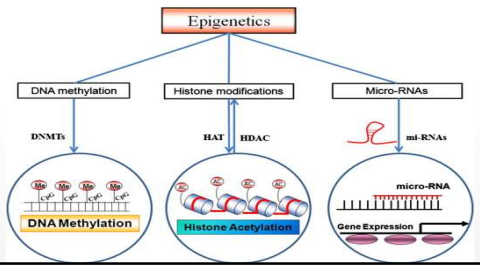
## Mechanisms

- 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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