Molecular Biology of Diseases
Types of diseases

On the basis of genetic background
1. Monogenic diseases
2. Multifactorial diseases
3. Mitochondrial diseases
4. Chromosomal disorders
5. Epigenetic diseases
6. Non-inherited genetic diseases
7. Non-genetic diseases

Mixed system
1. Cardiovascular diseases
2. Cancer diseases
3. Autoimmune diseases
4. Metabolic disorders
5. Dementia
6. etc.
Penetrance continuum

Monogenic diseases  ..................  Complex diseases

CAUSATIVE FACTOR ← The presence of a single mutant allele Is decisive in the development of the disease

SUSCEPTABILITY FACTOR → The „appropriate” environment and other alleles of different genes are also necessary for the development of the diseases
Selection against the complex diseases

The causes for the high prevalence of complex diseases

1. The negative selection is not efficient – the disease appears at middle or old age
2. Is it a tool in the hand of evolution for providing an optimal life time?
Monogenic Diseases

1. Autosome-linked
2. Sex chromosome-linked (X, Y)

1. Dominant
2. Recessive
3. Co-dominant
4. Intermediate

6000

0,5%
Heterozygote advantage

The survival of heterozygote is better than those of carrying two homozygous normal alleles.

The classic example: sickle cell anemia: the heterozygotes are resistant against malaria.

The elimination of mutant alleles takes time!
The X-linked diseases are frequent in males, but rare in females

Y-linked diseases are rare, since there are few genes on Y chromosome

Why is there difference between the sexes if the X chr. is inactivated?
1. The pseudo-autosomal region is active
2. There is no inactivation in the early stage of embryogenesis
3. The mosaic expression is often enough for the functionality
Cystic fibrosis

Dorothy H. Andersen:
1938

Cystic fibrosis
exon
intron
25 kb
CFTR gene
CFTR protein
Transmembrane
segments
Nucleotide binding
fokls
R domain

Treatment

A normal-functioning CFTR channel moves chloride ions to the outside of the cell while a mutant CFTR channel does not, causing sticky mucus to build up on the outside of the cell.

CFTR: cystic fibrosis transmembrane conductance regulator
Gene therapy of cystic fibrosis

CFTR gene + adenovirus

nucleus, mucosal cell, CFTR gene

lung
CF and the heterozygote advantage

Knockout mouse

diarrhea

cholera

TBC
Sickle cell anemia

Distribution of Malaria

Normal hemoglobin
Sickle Cell hemoglobin forms long, inflexible chains

Normal Red Blood Cells
Sickled Red Blood Cells

Normal red blood cells are compact and flexible, enabling them to squeeze through small capillaries
Sickled red blood cells are stiff and angular, causing them to become stuck in small capillaries

<table>
<thead>
<tr>
<th>Normal Cells</th>
<th>Sickle Cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAA GTA AAC ATA GGA CTT CTT</td>
<td>DNA</td>
</tr>
<tr>
<td>GUU CAU UUG UAU CCU GAA GAA</td>
<td>mRNA</td>
</tr>
<tr>
<td>val his leu thr pro glu glu</td>
<td>Protein</td>
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PKU - phenylketonuria

People with PKU Have a Defective PAH Enzyme

Protein → Amino acids

One of these amino acids is phenylalanine

PAH Enzyme

PKU: Toxic levels of phenylalanine

Normally, the PAH enzyme breaks down phenylalanine

People with PKU have a defective PAH enzyme, so toxic levels of phenylalanine build up in their bodies.

PAH: phenylalanine hydroxylase
SCID
Severe combined immunodeficiency

2 main types:
1. X-linked SCID
2. ADA deficiency
SCID gene therapy
Clinical experiments – Boston Children’s Hospital

1. Isolation of stem cells from the bone marrow of sick child
2. Delivery of functional SCIDX1 gene to the stem cells
3. Retransplantation of genetically improved stem cells to the bone marrow
ADA deficiency
adenosine deaminase

**ADA Converts Deoxyadenosine to a Non-toxic Substance**

- **Normal**
  - ADA binds to deoxyadenosine and converts it to...
  - ...Deoxyinosine NOT toxic

- **Abnormal ADA**
  - Abnormal ADA cannot bind to deoxyadenosine

- **Deoxyadenosine levels rise**

**THERAPY**
- High levels of deoxyadenosine kill B and T cells of the immune system
- The body is open to infection by bacteria and viruses
Duchenne Muscular Dystrophy

Mutations in the dystrophin gene (X chromosome)

gene: 2,4 Mbp – the longest human gene
mRNA: 14 kbp (pre-mRNA: 2,4 kb)
protein: 3,500 amino acids
exon: 79
Thalassemias

Anemia: characteristic feature of thalassemias

Causes:
(1) decrease of the number or (2) the size of red blood cells;
(3) decrease of the number or (4) the $O_2$-binding capacity of hemoglobin molecules

Genetic causes:
(1) mutation in the coding region of hemoglobin: abnormal protein structure
(2) mutation in the regulatory region of hemoglobin gene: few hemoglobin molecules
Galactosemia

Lactose: a sugar found in milk

Milk

Glucose
Galactose

In the body, lactose is cleaved to form glucose and galactose

Used for energy

Normal

GALT binds to galactose...

...and converts it to glucose, which is then used for energy

Galactosemia

No GALT. Galactose concentration rises to toxic levels, causing:

- kidney failure
- enlarged liver
- cataracts
- brain damage

GALT: galactose-1-phosphate uridyl transferase
Hemophilia

Inability of blood clotting

Hemophilia A: VII\textsuperscript{th} factor deficiency
Hemophilia B: VIII\textsuperscript{th} factor deficiency

No fibrin generation

X chromosome-linked
Marphlan syndrome

Genetic disease of the connective tissue; Dominant inheritance

**Mutation:**
- 90% fibrillin 1 gene
- 10% TGF-β gene

Michael Phelps
Achondroplasia

- 85% sporadic
- Rarely: mutation in FGFR3 gene (G → A; Gly → Arg)

Problem in chondrogenesis (cartilage formation) → slow growth of bones
Albinism

1. Tyrosinase gene albinisms
2. P gene albinisms

MRC1 gene mutation: Caucasian race and Neanderthal man
Tay-Sach disease

Mutation of HEXA gene $\rightarrow$
$\rightarrow$ accumulation of toxic amount of gangliozid in the brain

HEXA: hexoseaminidase
Color blindness

X chromosome:
OPN1LW (opsin 1L, red)
OPN1MW (opsin 1L, green)

EVOLUTION:
a person with deuteranopia can distinguish more khaki shades
– better recognition of camouflage
Color blindness

Red

Green

(Not expressed)

Green-red hybrid

(Not expressed)
Color blindness

5A

Protanopic

5B

Red

Green

Green-red hybrid

Red-green hybrid
# Color blindness

## Gene cluster

<table>
<thead>
<tr>
<th>A. Protan color vision</th>
<th>Color vision</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Red-green hybrid</td>
<td>Protanomalous</td>
</tr>
<tr>
<td>2</td>
<td>Protanopic</td>
</tr>
<tr>
<td>3</td>
<td>Protanopic</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>B. Deutan color vision</th>
<th>Color vision</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 Red</td>
<td>Deuteranomalous</td>
</tr>
<tr>
<td>5 Green-red hybrid</td>
<td>Deuteranopic</td>
</tr>
<tr>
<td>6 Green</td>
<td>Deuteranopic</td>
</tr>
<tr>
<td>7 Defective green</td>
<td>Deuteranopic</td>
</tr>
</tbody>
</table>

*Note: Cys203Arg*
Color blindness
Trichromatic vision for squirrel monkey

**L-opsin gene** delivery to retinal cones by adeno-associated virus (AAV) vector