Genetics I.

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OUTLINE

- LANDSCAPE OF THE HUMAN GENOME, MAIN MILESTONES
- GENETIC ABNORMALITIES (Point mutations, Chromosome aberrations)
- MENDELIAN DISORDERS (DISEASES CAUSED BY SINGLE GENE DEFECTS)
- COMPLEX MULTIGENIC DISORDERS
- CYTOGENETIC DISORDERS
- MOLECULAR DIAGNOSIS OF MENDELIAN AND COMPLEX DISORDERS
- PEDIATRIC DISEASES
Genetic revolution (cracking the code) - 2003
IMPORTANT MILESTONES

- **1953**
  - Structure of the DNA (Watson, Crick, Franklin)

- **1983**
  - Human genome project - HUGO (Venter, Collins)

- **2003**
ABOUT THE GENOME

- 3 billion base pairs
- 25 thousand protein coding genes (only 1-2% of the genome)
- 98% „junk” DNA ??
ABOUT THE GENOME

- 3 billion base pairs
- 25 thousand protein coding genes (only 1-2% of the genome)
- 98% „junk” DNA ?
- ENCODE project (Encyclopedia of DNA elements)
- 75-90% of the genome is transcribed !!
- Emerging critical role for non-coding RNAs
- Various types of ncRNAs:
  - miRNA, IncRNA,
  - piRNA, snoRNA
  - tiRNA, T-UCR, TERRA, ...

Exom
MICRO-RNA REGULATION

- ~22 nt long RNAs
- Post-transcriptional regulation
- More than thousand miR species (*miRBase*)
- Mechanism (DICER, RISC)
- A given miRNA can silence multiple target genes
- Binding determined by the 3’UTR sequence

- Specific expression pattern in several diseases
- Therapeutic approach (RNA interference)
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Long, non-coding RNAs (IncRNA)

- 200nt-100kb long RNAs
- Their number may exceed coding mRNAs
- Diverse functions:
  - Regulation of transcription, splicing
  - Chromatin regulation
  - Binding to histone proteins
  - microRNA
  - Decoy function
  - Scaffold function

- Novel therapeutic targets (?)
- Involved in various disorders
- *XIST*: X-chromosome inactivation
- *FMR4*: fragile X-syndrome
- *BACE1*: Alzheimer’s disease

Is this what makes us „special” ??
EPIGENETIC REGULATION

- Regulation of gene expression without underlying changes in the DNA sequence
- Development, differentiation

- DNA methylation
- Histone modifications (methylation, acetylation)

Developmental disorders
Cancer

MUTATIONS IN PROTEIN CODING GENES

- **GERMLINE** versus **SOMATIC** mutations

**Main types:**

- Missense mutations (sickle cell anemia > hemoglobin mutation)
- Nonsense mutations (leading to nonsense mediated decay)
- Frameshift mutations (alteration in the reading frame)
- Trinucleotide repeat mutations (fragile X-syndrome, Huntington’s disease)

**Chromosomal aberrations**

  - Structural alterations (deletion, amplification, inversion, translocation)
  - Numerical alterations (aneuploidy, monosomy, trisomy)
SNP („single nucleotide polymorphism“)

- 99,5% identity between 2 individuals
- Potentially 15 million nucleotide differences
- Appr. 6 million known SNPs

- More often in regulatory regions compared to coding seq
- Direct effect or „marker SNP“
- Some SNPs associated with increased risk in certain diseases
NATURAL VARIATION IN THE GENOME (polymorphisms)

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**CNV („copy number variation“)**

- 1000-millions bp long DNA regions, deletions/duplications
- Majority in coding regions (phenotype!)

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**DNA sequence from person 1:**
```
...AGGTTCACGATCGATCGCCACATCGCTT
GACGATCGTCGACGTCACGAAACGCACTAC
CTATGCTAGTCGCTTCAAAAGTGGTT
TTCCATGAAAACTAGTGTGCTGAGATT
```

**DNA sequence from person 2:**
```
...AGGTTCACGATCGATCGCCACATCGCTT
GACGATCGTCGACGTCACGAAACGCACTAC
CTATGCTAGTCGCTTCAAAAGTGGTT
TTCCATGAAAACTAGTGTGCTGAGATT
```
Getting started is simple.
Learn more about your health and ancestry.

1: Order
Start by ordering your DNA kit from our online store.
We ship internationally.

2: Register
When it arrives, be sure to register your specific bar code number so we can process your results.

3: Send
Our DNA kit includes detailed instructions on how to provide your saliva sample. Once completed, send your kit back to us in the pre-paid packaging provided.

What happens next.
We keep you informed every step of the way. You'll receive an email confirmation when your sample arrives at the lab and also when your reports are ready.
Once you have been notified your reports are ready, you sign in and your health and ancestry reports will be displayed on your personal homepage.

Health tools
Document your family health history, track inherited conditions, and share the knowledge.

Inherited traits
Explore your genetic traits for everything from lactose intolerance to male pattern baldness.

Scientific advances
Keep receiving updates on your DNA as discoveries are made, so your knowledge grows as you do.
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MENDELIAN DISORDERS (Diseases caused by a single gene)

Inheritance patterns:

- Autosomal dominant
- Autosomal recessive
- X-linked
- Y-linked (not significant)

- **Pleiotropy**: single gene mutation with many phenotypic effects
- **Genetic heterogeneity**: mutations of different loci leading to the same trait
- **Modifier genes** at other loci
Autosomal dominant inheritance

- At least one parent affected
- Manifested in heterozygous state ($AA$, $Aa$, $aa$)
- Both males and females are affected
- 1:2 chance in the offspring of having the disease ($Aa \times aa$)
- Affected child with healthy parents (new mutations in gametes)
- Variable clinical presentation (penetrance, expressivity)
- Delayed age of onset (Huntington’s)
- 50% reduction > symptoms > Dominant negative effect

Most frequently affected protein families:
- Receptors, transport proteins (regulators of metabolic processes, LDL rec.)
- Important structural proteins (spectrin, collagen)
- Enzymes are not affected (very rarely)!
Autosomal recessive inheritance

- Largest group of Mendelian disorders
- Both alleles are mutated (aa)
- The parents are usually not affected (carriers) (Aa)
- Offspring have 25% chance for having the disease (Aa x Aa)
- Complete penetrance is common, early onset of disease
- Enzymes often affected (compensation in heterozygotes)
X-linked recessive inheritance

- Heterozygous females (carriers) transmit to sons only
- Affected males are hemizygous for that trait
- Rarely, heterozygous females may be affected (X inactivation)
- All daughters of an affected male will be carriers
- Offspring of carrier females have a 50% chance for inheriting the mutated allele
X-linked recessive inheritance

Hemophilia in the British royal family
Diseases caused by mutations in genes of structural proteins

- **MARFAN SYNDROME**
  - *Autosomal dominant* connective tissue disorder
  - Fibrillin gene (*FBN1*) mutations
  - Microfibrils (ECM) (aorta, ligaments)
  - Skeletal abnormalities (arachnodactyly, spinal deformities)
  - Overgrowth of bones, Dislocation of the lens (ectopia lentis)
  - Floppy valve syndrome
  - *Cardiovascular symptoms*: aortic dissection, predisposition to aneurisms
  - Most common cause of death: aortic rupture
  - Clinical heterogeneity
  - TGFβ inhibition as experimental therapy
Diseases caused by mutations in genes of structural proteins

- **EHLERS-DANLOS SYNDROME (EDS)**
  - *Autosomal dominant*, (AR also possible)
  - At least 6 variants caused by different mut.
  - Collagen gene mutations
  - Extr. stretchable skin, hypermobile joints
  - Ruptures involving large arteries, colon
  - Impaired wound healing

**Main types:**
- Lack of lysyl hydroxylase (AR)
- *COL3A1* mutations (AD)
- *COL5A1, COL5A2* mutations (AD)
FAMILIAL HYPERCHOLESTEROLEMIA

- One of the most common mendelian disorders (1:500), AD
- LDL receptor mutations, impaired LDL uptake > hypercholesterolemia
- Increased cholesterol uptake by the monocytes and macrophages
- Xanthomas, premature atherosclerosis > myocardial infarction
- Increased risk in homozygous patients (MI before age of 20)
- 5 different types of mutations (I-V)
Diseases caused by mutations in genes of receptor proteins or channels

- **FAMILIAL HYPERCHOLESTEROLEMIA**
Diseases caused by mutations in genes of receptor proteins or channels

- **CYSTIC FIBROSIS (CF)**
  - Most common lethal genetic disease (Caucasian population)
  - *Autosomal recessive, CFTR* gene mutations, Impaired Cl⁻ transport
  - Sweat: high NaCl concentration!
  - Abnormally viscous mucus: recurrent pulmonary infections, pancreatic insufficiency
Diseases caused by mutations in genes of receptor proteins of channels

- **CYSTIC FIBROSIS (CF)**
  - Severe and mild \( CFTR \) mutations
  - \( \Delta F508 \) (deletion of phenylalanine 508) most common severe mutation
  - Pulmonary changes (obstruction and infection)
  - *Most frequent cause of death: cardiopulmonary complications*
  - Pancreatic insufficiency, Liver involvement
  - Viscous mucus in small intestine of infants (meconium ileus)
  - Infertility (bilateral absence of the vas deferens)
  - Median life expectancy: ~36 years (novel therapies)
  - *Gene therapy (!?)*
Diseases caused by mutations in genes of enzyme proteins

- **PHENYLKETONURIA (PKU)**
  - * Autosomal recessive* pattern
  - Lack of Phenylalanine hydroxylase (PAH) > hyperphenylalaninemia
  - Phenylalanine – Tyrosine conversion inability
  - Impaired brain development, mental retardation apparent by 6 months of life
  - Dietary restriction of phenylalanine
  - Lack of tyrosine > decreased pigmentation of hair and skin
Diseases caused by mutations in genes of enzyme proteins

**GALACTOSEMIA**

- *Autosomal recessive pattern*
- Mutations of GALT: systemic accumulation of galactose-1-phosphate, galactitol
- Vomiting, diarrhea within few days of milk ingestion
- Liver, brain and eye damage (jaundice, hepatomegaly, cataracts, mental retardation)
- Dietary restriction of lactose
Lysosomal Storage Diseases

- **Main characteristics:**
  - *Autosomal recessive* inheritance (predominantly)
  - Symptoms in infants and young children
  - Deficiency of the catabolism of complex substrates, (enzyme defects)
  - Storage of insoluble intermediates in phagocytes > hepatomegaly
  - Frequent CNS involvement with neuronal damage
  - Cascade of secondary events triggered (macrophage activation)
Lysosomal Storage Diseases

- **TAY-SACHS DISEASE**
  - $G_M^2$ gangliosidosis, mutation of hexose-aminidase-A $\beta$ subunit
  - Brain is principally involved (neurons, glial cells)
  - Motor weakness, neurologic impairment, severe progressive neur. dysfunction

- **NIEMANN-PICK DISEASE, TYPES A and B**
  - Accumulation of sphingomyelin (SM-ase deficiency) in phagocytes and neurons
  - Spleen, liver, bone marrow, lymph nodes, lungs most severely affected
  - Severe neurologic dysfunction, death within the first 3 years

- **NIEMANN-PICK DISEASE, TYPE C**
  - $NPC1$ and $NPC2$ mutations
  - Primary defect of lipid transport, cholesterol and ganglioside accumulation
  - Ataxia, dystonia, psychomotor regression
Lysosomal Storage Diseases

- **GAUCHER DISEASE**
  - Glucocerebrosidase mutations (cleaves glucose from ceramide)
  - Glucocerebroside accumulation in macrophages >> Gaucher cells
  - *Type I.* (chronic, non-neuropathic): bone involvement, hepatosplenomegaly (99%)
  - *Type II and III.*: characterized by neurological symptoms
  - Therapy: Enzyme replacement

- **MUCOPOLYSACCHARIDOSES (MPS)**
  - Mucopolisaccharide accumulation
  - Depending on the enzyme error types I-VII
  - Hepatosplenomegaly, Skeletal deformities, brain lesions, arterial deposits
  - *Myocardial infarction* as important cause of death
  - *Type I (Hurler syndrome):* dermatan and heparan-sulfate, cardial involvement
  - *Type II (Hunter syndrome),* X-linked recessive, milder clinical course
Glycogen Storage Diseases

- **HEPATIC TYPE**
  - von-Gierke disease: lack of glucose-6-phosphatase
  - Enlargement of the liver due to the stored glycogen
  - Hypoglycemia (failure of glucose production)

- **MYOPATHIC TYPE**
  - McArdle disease: lack of muscle phosphorilase
  - Impaired energy production, muscle weakness
  - Cramps, myoglobinuria

- **POMPE DISEASE (Type II glycogenosis)**
  - Lysosomal storage disease (lack of acid maltase/glucosidase)
  - Glycogen deposition in every organ, cardiomegaly is the most prominent, early death
Single-gene disorders with atypical patterns of inheritance

- **Diseases caused by triplet repeat mutations**
  - Fragile X-syndrome,
  - Huntington’s disease

- **Diseases caused by mitochondrial gene mutations**

- **Diseases associated with genomic imprinting**
  - Angleman and Prader-Willi syndrome

Complex multigenic disorders

- **Multifactorial or poligenic traits/diseases**
  - Skin color, height, intelligence
  - Type-2 diabetes, hypertension
  - Wide range, continuous traits
  - Role of environmental factors („Nature-Nurture“)
Diseases caused by triplet repeat mutations

- **FRAGILE X-SYNDROME**
  - CGG repeat in the *FMR1* gene
  - Mental retardation
  - Macroorchydism
Diseases associated with genomic imprinting

- **Prader-Willi and Angelman syndromes**
  - Chr15 microdeletion
  - AS: maternal, PWS: paternal, (deletion)
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- Prader-Willi and Angelman syndromes
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To be continued ....

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Thanks for your attention!