GENETICS AND GENOMICS

Department of Genetics, Cell- and Immunobiology
Course director: ***Prof. Dr. Edit Buzás***
Course coordinator: ***Dr Hargita Hegyesi***
Credit: 3
Number of lessons per week: 3.5 **lecture:** 2 **practical course:** 1.5
Academic year: 2021/2022 II. semester
Subject code: AOKGEN738_1A
Name of the course leader: Prof. Edit Buzás
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Position: Professor and Chairman

Objectives of the subject, its place in the medical curriculum:
Introductory course in classical and molecular genetics and functional genomics, as well as basic course for the clinical module. It addresses the types, general laws of human inheritance, characteristics, organization and structure of the human genome, and the most important methods and / or their application in theoretical and clinical medicine, according to the needs of medical students, and evaluates the results (in practice). It presents the forms of genetic and epigenetic variability, their mechanisms and their consequences for human health. Through selected examples, the pathway from gene to disease is analyzed using a systems biology approach.

Place where the subject is taught (address of the auditorium, seminar room, etc.):
Semmelweis University, Department of Genetics, Cell- and Immunobiology, H-1089 Budapest, Nagyvárad tér 4. Hungary, NET building lecture rooms, L13-L16

Successful completion of the subject results in the acquisition of the following competencies:
Basics of cytogenetics. Setting up and interpreting pedigrees. Basic knowledge of human genetics and human genomics. Background of monogenic and multifactorial diseases. Basics of prenatal diagnosis, detection of monogenic diseases by molecular genetic methods. Basic knowledge of oncogenetics, epigenetics, population genetics, nutrigenetics, evolutionary genetics, pharmacogenetics with biomedical approach. Role of gene-gene and gene-environment interactions in various diseases. Basic knowledge of bioinformatics and systems biology related to medical genetics and genomics. Basics of gene therapy.

Course prerequisites:
Molecular Cell Biology I.,
Medical Biochemistry II.

Number of students required for the course (minimum, maximum) and method of selecting students:
According to Study and Exam Policy

How to apply for the course:
in Neptun system

Detailed curriculum:

Lectures (2 hours per week)[1]***:***

Introduction to human genetics
Genetic variations
Chromosomal aberrations
Autosomal inheritance I.
Autosomal inheritance II.
Role of sex in inheritance
Epigenetics
Genetics of biological processes, oncogenetics
Introduction to genomics
Methods in genomics, systems biology

1 The lectures are given by the senior lecturers of the Institute. The order of the lectures may vary (depending on holidays and workday transfers). Colleagues with senior teaching status may also act as lecturers, if the lecturer on schedule is prevented.* The order of the practices may vary (depending on holidays and workday transfers). Practice instructors: Colleagues with teaching status at the Institute of Genetics, Cell and Immunobiology

Genomic approach of complex inheritance Populationgenetics
Genetherapy
Pharmaco- and nutrigenomics
Genome and environment, Evolutiongenetics

Practices (1.5 hours per week)*:
Genetic aspects of cell cycle and cell division disruptions (Atypical mitosis / meiosis)
Cytogenetics I.
Cytogenetics II.
Introduction to pedigree analysis
Autosomal dominant inheritance I.
Autosomal dominant inheritance II.
Autosomal recessive inheritance I.
Autosomal recessive inheritance II.
Sex-linked inheritance
Complex inheritance I.
Complex inheritance II.
Gametogenesis, prenatal genetic testing
Genetherapy
From genes to bedside

Other subjects concerning the border issues of the given subject (both compulsory and optional courses!). Possible overlaps of themes:

Understanding of Genetics and Genomics is based on the knowledge of molecular biology and molecular genetic techniques studied at Medical Biochemistry I-II. Elective subjects taught by our institute (Sex Genetics, Epigenetics, Genomics) elaborate on some of the subchapters of "Genetics and Genomics", with overlaps needed for understanding, focusing on topics not covered in the main subject. Understanding the subject of Clinical Genetics is based on the knowledge of Genetics and Genomics.

Requirements for participation in classes and the possibility to make up for absences:

Completion of prerequisite subject.

Practices can only be attended to in an appropriate mental and health condition. Practical absence can be remedied during the current training week, in parallel courses, after prior consultation with the practice instructors.

Methods to assess knowledge acquisition during term time:

Bonus lecture scores can be collected at lectures and midterm tests. Written midterm from the topics of taught lectures and practices. We provide an opportunity to retake the midterm, only for students who have proven absence.

Requirements for signature:

According to the Study and Exam Policy the students must visit at least 75% of the lectures and practices.

Type of examination: written (lectures and practices) Moodle test

Requirements of the examination:

1.) Introduction to human genetics and genomics.

MGGe: Chapter 1, pages 9-21; Lecture: Introduction to human genetics

Basic genetic terms, e.g.: genome, genetics, genomics, **homologous chromosomes,** gene, locus, allele, wild type allele, genotype, phenotype, homozygote, heterozygote, hemizygote, dominant, recessive, cytogenetics; Mendel's laws, Model organisms in genetics; DNA: structure, function, amount, organization (chromatin, chromosome). Replication, transcription, mRNA maturation (splicing, alternative splicing), types of RNA-s, features of genetic code. Translation and posttranslational modifications. Human genome: nuclear and mitochondrial. Structure of eukaryotic gene. Intergenic DNA; Specific sequences of nuclear genome. Repetitive sequences. Human Genome Project, ENCODE Project

2.) Transmission of genetic information from cell to cell in an organism.

MGGe: Chapter 2, pages 22- 41, Practice presentation: Atypical mitosis

Features of mitotic phases. Functional parts of chromosomes (telomere, centromere, kinetochore, sister chromatids. Cytokinesis. Changes of DNA amount and chromosome number during cell cycle. Types, causes and consequences of atypical mitosis.

3.) Transmission of genetic information from generation to generation.

MGGe: Chapter 2, pages 41-51; Practice presentation: Typical and atypical meiosis

Significance and source of genetic variability. Significance of meiosis. Stages of meiosis: meiosis I. and II.

Features of phases of first prophase (leptotene, zygotene, pachytene, diplotene, diakinesis; synapsis, crossing over, chiazma). Random alignment and assortment of homologous chromosomes in meiosis I anaphase. Atypical meiotic process: non-disjunction. Change of DNA amount and chromosome number during meiotic process.

4.) Pedigree analysis

Practice: Introduction to pedigree analysis

Mendelian or monogenic inheritance, Construction of pedigree: main symbols that are used in pedigrees. Pedigree analysis (characteristics pedigree patterns of monogenic inheritances: AD, AR, XD, XR, Y-linked, mitochondrial). Disease examples for monogenic inheritances (AD, AR, XD, XR, mitochondrial); ***Important terms****:* gene, genome, locus, allele, multiple allelism, wild type (normal) allele, genotype: homozygote, heterozygote, complex heterozygote, hemizygote, phenotype: dominant, codominant, recessive.

5.) Mendelian Inheritance: autosomal inheritance

MGGe: Chapter 6, pages 102 -121; Lecture: Monogenic inheritance (Autosomal inheritance); Practice: Autosomal dominant inheritence

Properties and disease examples of autosomal inheritance: AD (osteogenesis imperfecta, acondroplasia, Marphan syndrome, familial hypercholesterolemia, Huntington disease, Polycystic kidney disease). Ecogenetic diseases (porphyria, malignant hyperthermia). AR (albinism, phenylketonuria, xeroderma pigmentosum, deafness, cystic fibrosis, sickle cell anemia, thalassemias). ***Important terms****:* gene, genome, locus, allele, multiple allelism, wild type (normal) allele, genotype: homozygote, heterozygote, complex heterozygote, hemizygote, phenotype: dominant, codominant, recessive. Genetic heterogeneity (locus heterogeneity, allele heterogeneity), Factors affecting pedigree patterns: reduced penetrance, variable expressivity, pleiotropy, heterogeneity (locus and allele), phenocopy, anticipation, „de novo", new mutation, Influence of the age, Lethal/sublethal genes, „Modifier genes", Epistasis; Heterozygote advantage, The influence of the environment,

6.) Role of sex in inheritance

MGGe: Chapter 7, pages 122-131; Lecture: Role of sex in inheritance

Properties and disease examples of Sex-linked inheritance: XR (hemophilia A and B; Duchenne and Becker muscular dystrophy), XD (hypophosphatemia, incontinentia pigmenti, Fragile X). Y-linked inheritance; Sex influenced inheritance (e.g. boldness). Sex limited inheritance (e.g. precocious puberty). Genomic imprinting, X-chromosome inactivation. Mitochondrial inheritance (homoplasmy, heteroplasmy)

7.) Cytogenetics

Practice: ***Cytogenetics I***

Structure and types of eukaryotic chromosome. Karyotyping (chromosome preparation, principle, significance and types of banding techniques, principle and significance of multicolor-FISH, and M-banding); kariogram, idiogam; X inactivation. Study of sex chromosomes in interphase. Characteristics of human karyotype. Mutagenicity tests: micronucleus and sister chromatid exchange. Chromosome territories.

Light microscopic slides: 54, 60, 64

8.) Structural chromosome mutations

MGGe: Chapter 4, pages 69-80; Lecture: Chromosomal aberrations; Practice: ***Cytogenetics II***

Structural chromosome aberrations. Types of structural aberrations: deletion (terminal, interstitial), duplication, translocation (reciprocal, Robertsonian), inversion (paracentric, pericentric), ring chromosome, isochromosome. Balanced and unbalanced mutations. Chromosomal translocations in leukemia. Consequence of structural aberrations.

9.) Numerical chromosome mutations

MGGe: Chapter 4, pages 80-90; Lecture: Chromosomal aberrations; Practices: Cytogenetics

Numerical chromosome aberrations: euploidy, polyploidy, aneuploidy, mixoploidy (mosaicism, chimerism). Possible cause of aneuploidy (non-disjunction in meiosis I and II). Autosomal (Patau, Edwards and Down syndromes) trisomies. Numerical aberrations of sex chromosomes (Klinefelter, XYY, triplo X, Turner syndromes). Uniparental disomy (UDP). Cause and consequence of of polyploidy and mixoploidy (mosaicism and chimerism).

10.) Mutations and polymorphisms

MGGe: Chapter 3, pages 52-68; Lecture: Genetic variations

Different meanings of mutation and polymorphism. Significance of mutation. Classification of mutations: by cause (spontaneous, induced, different DNA repair mechanisms, consequence of their failure), by site (in the organism: somatic, germline, in the gene), by function (loss-of-function, gain-of-function, dominant negative, lethal, back), by fitness (neutral, beneficial, harmful), by size (genome, chromosome, gene: insertions, deletions, substitutions). Repetitive insertions, triplet repeat: polyglutamine and polyalanine disorders. inDel mutations: frame shift and in frame mutations.

Nucleotide substitutions: transition, transversion, sense (synonymous) missense and nonsense (non-synonymous) mutations. Types, size and significance of genetic polymorphism.

11.) Epigenetics

MGGe: Chapter 5, pages 91-101; Lecture: Epigenetics

Meaning of epigenetics. Relationship of genome, epigenome and phenotype. Epigenetic mechanisms: transcriptional (DNA methylation, histone modifications), posttranscriptional (RNAi, miR). X chromosome inactivation, role of XIST. Autoimmunity and X inactivation. Genomic imprinting, evidences of nonequivalence of parental genome. Mechanism of genomic imprinting. Causes of Prader Willi and Angelman syndromes. Possible role of genomic imprinting. Relationship between genomic imprinting and cancer. Position effect. Epigenetic changes caused by aging and by in vitro fertilization. Transgenerational effects.

12.) Introduction to genomics. Methods in genomics

MGGe: Chapter 9, pages 148-173; Lecture: Introduction to genomics. Methods in genomics; Practice: Molecular genetic methods and applications in human genetics I-II.

Genomics, Human Genome , DNA sequencing, Participants in the Human Genome Project, Some results of the HGP, Variations in the human genome, Some novel data about gene expression and genetic variability, Junk DNA in the human genome, Comparative genomics, ENCODE project, Genetic markers, GWAS, Principle of molecular genetic methods: hybridization, restriction enzymes, DNA isolation, Visualization of genomial DNA, separation of DNA fragments by gelelectrophoresis, capillary gelelectrophoresis), non-specific staining of DNA (EtBr), Allele-Specific Oligonucleotide (ASO) test, RFLP, , microarray, PCR, PCR-RFLP, Multiplex PCR, MLPA, Significance of real time-PCR. Significance and detection of VNTR. VNTR and trinucleotid diseases. Significance of polymorphism detection in forensic medicine. DNA fingerprint. Foreign DNA (bacterial, viral) detection. Sequencing in genotyping. NGS, RT(reverse transcriptase)-PCR.

13.) *Complex inheritance.*

MGGe: Chapters 10, pages 174-177; Lecture: Complex inheritance, Practice: Complex inheritance

Features of complex inheritance. Environmental factors. Heritability of the complex diseases. Disease examples

14.) Pharmacogenomics

MGGe: Chapter 14, pages 266-286; Lecture: Pharmacogenomics and nutrigenomics

Pharmacogenetics and pharmacogenomics. Pharmacokinetics, -dimamics, ***Drug development Adverse drug response***, **Genomic background of adverse effects**, **CYP (cytochrom P-450) gene family**, **Warfarin**, **Mercaptopurine**, **Genes influencing pharmacodynamics**, **Examples of pharmacogenetic studies**, ***Pharmacogenetics of statins***, ***Clopidogrel***, ***Pharmacotherapy of asthma, MODY***, Succinylcholine sensitivity, Thiopurin methyltransferase variations, Role of membrane receptors in drug effects.

15.) Nutrigenomics

MGGe: Chapter 13, pages 255-263; Lecture: Pharmacogenomics and nutrigenomics

Genetic variations and food, food and gene expression.

16.) Gene therapy

Practice: Genetherapy

Genetherapy types (real, gene expression modification) and forms (in vivo, ex vivo). Nucleic acids applied in gene therapy: DNA, RNA. Forms of introduction of nucleic acids into target cells. Vectors applied in gene therapy: adenovirus, adeno associated virus, retrovirus, lentivirus, nonviral integrating vectors. Comparison of viral vectors. Examples of successful gene therapy trial.

17.) Population genetics

MGGe: Chapter 12, pages 215-224; Lecture: Population and evolution genetics

Types of sample collection, prospective and retrospective studies. Selection of populations for genetic studies. Hardy Weinberg equilibrium. Linkage, haplotype, linkage disequilibrium. Founder populations. Association studies, population stratification, population admixture. Risk calculation, odds ratio and relative risk, p-value.

18.) Evolution genetics

MGGe: Chapter 12, pages 225-236; Lecture: Population and evolution genetics

Gene environmental interactions and the human genome. Natural selection. Role of infections in formation of the genome. Genetic drift, bottleneck effect. Why are some lethal mutations frequent? Examples for effects forming the genome.

19.) Genome and environment

MGGe: Chapter 13, pages 238-254; Lecture: Population and evolution genetics

Penetrance of the genetic variants; Interactions between highly and low penetrant variations and the

environment; smoking-genome interaction, gene-environmental interactions;

20.) Gametogenesis, prenatal genetic testing

Practice: Gametogenesis, prenatal genetic testing

Comparison of spermatogenesis and oogenesis; Genetic aspects of infertility; Genetic aspects of assisted reproduction techniques; CGH; aCGH prenatal genetic testing; Non-invasive prenatal testing

21.) Genetics of biological processes

MGGe: Chapter 8, pages 132-147; Lecture: Genetics of biological processes

Genetics of development: development potentials (totipotent, pluripotent, multipotent, unipotent), cell differentiation, significance of stem cells. Role of morphogens and their concentration gradient (Sonic hedgehog), homeotic genes. Genetics of sex: sex determination, male sex determination. Causes of maldevelopment. Oncogenetics: oncogenes and tumor suppressor and mutator genes. Activation mechanisms of oncogenes. Tumor suppressor genes, LOH. Immunogenetics: somatic gene rearrangement, role of epigenetics, genetic background of antibody diversity.

Method and type of evaluation:

Final grade will be calculated from the result of the exam scores and bonus scores. Bonus scores are the grade calculated from the scores collected at the midterm, homeworks and lectures. Competition will be organized during the semester.

How to register for the examination?:

In the Neptun system, according to current university and faculty settings.

Possibilities for exam retake: According to the Study and Exam Policy

Printed, electronic and online notes, textbooks, guides and literature (URL address for online material) to aid the acquisition of the material:

Cs. Szalai (Editor): Medical Genetics and Genomics e-book, 2018

Power Point presentations of the lectures and practices; The e-book and presentations available at the homepage: http://gsi.semmelweis.hu/index.php/en/education/