Medical Genetics
American and Taiwanese program, 2020/2021, SPRING

CLASS 1

Introduction to genetics

Dr. Szymon Zmorzyński

A) TOPICS:

I) Rules and regulations

II) Basic terms: genetics, nucleic acid, DNA and RNA, DNA replication, DNA polymerase, helicase, DNA ligase, gene, allele (dominant and recessive), codominant alleles, exon, intron, transcription, reverse transcription, RNA polymerase, promotor, enhancer, silencer, translation, genetic code, codon, anticodon, gene expression, homozygous (dominant and recessive), heterozygous, hemizygous, chromatin, chromosome, genome, genotype, phenotype, haplotype, haploid cells, diploid cells, mitosis, meiosis, mutation, polymorphism, single nucleotide polymorphism (SNP)

III) DNA and RNA structure:

-DNA structure (nucleotides, base pairing, DNA as a double helix, the major forms of DNA: A-DNA, B-DNA, Z-DNA)

-ribonucleotides, types of RNA and their function

-messenger RNA structure (cap, leader, coding sequence, trailer, poly-A tail)

B) OBLIGATORY BOOK:

"GENETICS" Ronald W. Dudek – Lippincott Williams & Wolters Kluwer business, 2010. ISBN 978-0-7817-9994-2. CHAPTERS: 1. The nuclear genome; 2. DNA packaging

C) RECOMMENDED BOOK:

"HUMAN GENETICS: From molecules to medicine" C.P. Schaaf, j. Zschocke, L. Potocki, Lippincott Williams & Wolters Kluwer 2012. CHAPTER 2: Molecular basis of human genetics

CLASS 2

Mutagenesis

Dr. Sylwia Popek-Marciniec

A) Topics for presentations:

-TERMS: polymorphism vs. mutation, single nucleotide polymorphism, point mutation, hot spot, wild type allele, null mutation, de novo mutation, somatic mutation, germline mutation, constitutional mutation

-substitutions (transitions and transversions), silent mutation (silent substitution), missense mutation, nonsense mutations. Substitution as a genetic cause of sickle cell anemia.

-deletions, insertions, frameshift mutations. Deletion as a main cause of cystic fibrosis and α-thalasemia

-trinucleotide repeat expansion – genetic cause of Huntington disease, fragile X syndrome, myotonic dystrophy. Terms: genetic anticipation, dynamic mutation, permutation state, full mutation, penetrance (reduced and full penetrance)

-location of mutations and their possible effects (promoter mutation, splice sites mutation, insertion of mobile elements)

-molecular consequences of mutation: gain of gene function, loss of gene function, haploinsufficiency, dominant negative mutation (genetic cause of Marfan syndrome and osteogenesis imperfecta)

-spontaneous and induced mutations

-biological (examples of bacteria and viruses), chemical (base analogs, acridine dyes, role of nitrous acid) and physical (ionizing radiation, nonionizing radiation - pyrimidine dimers) mutagens.

-DNA repair (proofreading, mismatch repair, base excision repair, nucleotide excision repair, homologous recombination, non homologous end joining).

-xeroderma pigmentosum a disease of faulty DNA repair

Topics presented by the teacher:

-Mutations nomenclature (basics).

B) Students may use animations during their presentations, especially for DNA repair.

C) Obligatory book:

L.B. Jorde, J.C. Carey, M.J. Bamshad "Medical Genetics (5th edition)" Chapter 3

D) RECOMMENDED BOOK:

"HUMAN GENETICS: From molecules to medicine" C.P. Schaaf, j. Zschocke, L. Potocki, Lippincott Williams & Wolters Kluwer 2012. CHAPTER 3: Mutations and genetic variability

E) Internet sources: http://varnomen.hgvs.org/

CLASS 3

Single gene alterations I - autosomal dominant disorders and hemoglobinopathies

Dr. Szymon Zmorzyński

A) MENDEL'S PRINCIPLES OF INHERITANCE. TYPES OF INHERITANCE.

B) Autosomal dominant disorders:

I) familial hypercholesterolemia: mutations in *LDLR* gene (6 classes of mutations), symptoms and treatment

II) Fibroblast Growth Factor (FGF) Family – FGF receptors: **achondroplasia** (genetic cause and symptoms) and **Apert syndrome** (genetic cause and symptoms),

III) Huntington disease – genetic cause (CAG repeats, permutation state, terms: penetrance and genetic anticipation), symptoms. Age-dependent penetrance

IV) neurofibromatosis type 1 and type 2 (genetic cause and symptoms of each type) – a disease with highly variable expression

V) Marfan syndrome (genetic cause and symptoms) – an example of pleiotropy

VI) osteogenesis imperfecta – mutations in genes *COL1A1* and/or *COL1A2*. The structure of collagen type I. Osteogenesis imperfecta – types I-IV (main symptoms)

VII) Ehlers–Danlos syndrome (*EDS*) - genetic cause, types and symptoms

C) autosomal recessive disorders:

I) sickle-cell anemia: genetic cause and symptoms

II) the thalassemias (genetic cause and symptoms): α-thalassemia (carrier state and silent carrier state); β-thalassemia (minor and major)

B) Obligatory book:

-"GENETICS" Ronald W. Dudek – Lippincott Williams & Wolters Kluwer business, 2010. ISBN 978-0-7817-9994-2. CHAPTERS: 7. Multifactorial inherited disorders, 12. Genetics of metabolism, 13. Genetics of hemoglobinopathies, 15. Genetics of development, 16. Genetics of cancer, 17. Genetic screening.

or

-D.J. Pritchard, B.R. Korf "Medical Genetics at a Glance (3rd edition). Part 9

-L.B. Jorde, J.C. Carey, M.J. Bamshad "Medical Genetics (5th edition)" Chapters 12 and 4

C) Other sources: Genetics Home Reference: https://ghr.nlm.nih.gov/

CLASS 4

Single gene alterations II - autosomal recessive disorders

Dr. Szymon Zmorzyński

TOPICS:

A) DISORDERS OF METABOLISM. VARIANTS OF METABOLISM – PREVALENCE OF METABOLIC DISEASE, INHERITANCE OF METABOLIC DEFECTS, TYPES OF METABOLIC PROCESSES.

B) AUTOSOMAL RECESSIVE DISORDERS:

-CARBOHYDRATE DISORDERS:

I) **galactosemia**:

-type I (classic galactosemia): genetic cause, symptoms, treatment

-type II and III: genetic causes

-AMINO ACID DISORDERS:

I) **phenylketonuria (PKU) or phenylalanine hydroxylase (PAH) deficiency -** genetic cause, symptoms and treatment

II) **albinism (genetic cause and symptoms)**: Oculocutaneous albinism (type I and II)

-LYSOSOMAL STORAGE DISORDERS:

I) **Gaucher disease** - genetic cause, types (I, II and III) and symptoms

II) **Tay-Sachs disease** - genetic cause and symptoms

III) **Mucopolysaccharidoses** – Hurler Scheie, Hunter and Sanfilippo disease. Genetic cause and symptoms.

-TRANSPORT SYSTEM DISORDERS:

I) **cystic fibrosis**: classes of mutations in the *CFTR* gene, symptoms, treatment

II) **haemochromatosis**:

-type I: genetic cause and symptoms

-type II and III: genetic causes

C) Obligatory books:

-"GENETICS" Ronald W. Dudek – Lippincott Williams & Wolters Kluwer business, 2010. ISBN 978-0-7817-9994-2. CHAPTERS: 12. Genetics of metabolism.

or

-L.B. Jorde, J.C. Carey, M.J. Bamshad "Medical Genetics (5th edition)" Chapter 4

D) Other sources: Genetics Home Reference: https://ghr.nlm.nih.gov/

CLASS 5

Single gene alterations III – X-linked disorders

Prof. Agata Filip

A) TOPICS:

-Sex-linked disorders, transmission patterns, incidence in males and females

-X-linked recessive disorders:

-X-linked color vision deficiency (red-green color blindness),

-glucose-6-phosphate dehydrogenase deficiency (G6PD),

-hemophilia A, hemophilia B,

-Duchenne muscular dystrophy, Becker muscular dystrophy,

-Menkes disease (kinky hair disease),

-Lesh-Nyhan syndrome

-X-linked dominant disorders:

-Bloch-Sulzberger disease (*Incontinentia Pigmenti*),

-Rett syndrome,

-hereditary hypophosphatemic rickets (X-linked hypophosphatemia)

B) Obligatory books and internet sources:

-L.B. Jorde, J.C. Carey, M.J. Bamshad "Medical Genetics (4th edition)" Chapter 5

-R.W. Dudek "BRS Genetics" Chapter 4, pages 30-38

-http://www.ncbi.nlm.nih.gov/books/NBK1449/ (summary only)

-http://ghr.nlm.nih.gov/condition/menkes-syndrome

-C.P. Schaff, J. Zschocke, L.Potocki Human Genetics: from molecules to medicine **p.258** (Lesch-Nyhan), **p.73-47, 201** (Incontinentia Pigmenti only)

C) Other sources: Genetics Home Reference: https://ghr.nlm.nih.gov/

CLASS 6

Multifactorial diseases and population genetics

Dr. Sylwia Popek-Marciniec

A) TOPICS:

I) Multifactorial diseases:

-multifactorial versus single gene inheritance

-classes of multifactorial traits (quantitative traits and threshold traits)

Mutifactorial disorders of the adults:

-cardiovascular disorders: atherosclerosis and hypertension

-diabetes mellitus – type 1 (*HLA DR3-DQ2* allele and *HLA DR4-DQ8* allele), type II and maturity-onset diabetes of the young (MODY)

-Alzheimer disease (genetic cause and symptoms)

-obesity.

-psychiatric disorders: schizophrenia and autism spectrum disorder

II) Population genetics:

-terms: population genetics, population, gene pool, gene flow

-the significance of heterozygosity

-the Hardy-Weinberg Law (assumptions of this law)

-calculation of genotypes and alleles frequency -in the case of autosomal recessive and dominant disorders

-calculation of codominant alleles frequency

-significance of mutations, migrations, genetic drift, random mating, natural selection

-consanguinity in human populations – consanguinity and the frequency of recessive diseases, health consequences of consanguinity

STUDENTS ARE OBLIGED TO BRING SIMPLE CALCULATORS (USING MOBILES IS NOT ALLOWED)

B) ANIMATION:

-the Hardy-Weinberg Law

C) Practical part

I) presentation and discussion

II) calculation of genotypes and alleles frequency

D) Obligatory books:

-L.B. Jorde, J.C. Carey, M.J. Bamshad "Medical Genetics (5th edition)" Chapters 3, 4 and 12.

-"GENETICS" Ronald W. Dudek – Lippincott Williams & Wolters Kluwer business, 2010. ISBN 978-0-7817-9994-2. CHAPTERS: 7. Multifactorial inherited disorders.

E) Other sources: Genetics Home Reference: https://ghr.nlm.nih.gov/

CLASS 7

Chromosomes

Prof. Agata Filip

A) TOPICS:

-Mitosis and meiosis.

-Chromosome structure and classification

-Numerical chromosome abnormalities (aneuploidy, polyploidy, meiotic nondisjunction, anaphase lag, mosaicism).

-Balanced and unbalanced chromosome aberrations and their clinical significance -Structural chromosome abnormalities (deletions, duplications, paracentric and pericentric inversions, reciprocal translocations, isochromosome, Robertsonian translocations), marker chromosomes.

-Chromosome analysis (banding techniques, fluorescent *in situ* hybridization - FISH)

-Cytogenetic nomenclature.

B) Obligatory book: L.B. Jorde, J.C. Carey, M.J. Bamshad "Medical Genetics (5th edition)" Chapters 2 and 6

C) RECOMMENDED BOOK:

"HUMAN GENETICS: From molecules to medicine" C.P. Schaaf, j. Zschocke, L. Potocki, Lippincott Williams & Wolters Kluwer 2012. CHAPTER 3: Mutations and genetic variability

C) Other sources: Genetics Home Reference: https://ghr.nlm.nih.gov/, Atlas of Genetics and Cytogenetics in Oncology and Haematology http://atlasgeneticsoncology.org

CLASS 8

Chromosomal disorders

Prof. Agata Filip

A) TOPICS:

-Sex determination, sex chromosomes, sex-chromatin body.

-Sex-chromosome anomalies (Turner syndrome, Klinefelter syndrome, XXX syndrome, XX male syndrome – de la Chapelle syndrome, XYY syndrome, Swyer syndrome- XY gonadal dysgenesis).

-Autosomal aberrations (Down syndrome, translocation Down syndrome, Patau syndrome, Edward's syndrome, cat's cry syndrome).

- fragile X syndrome.

-Microdeletions (Di George syndrome, Williams syndrome, Smith-Magenis syndrome)

- Imprinting disorders (Prader-Willi syndrome, Angelman syndrome, Beckwith-Wiedemann syndrome).

-Indications for karyotype examination.

B) Obligatory book: L.B. Jorde, J.C. Carey, M.J. Bamshad "Medical Genetics (5th edition)" Chapter 6

C) Other sources: Genetics Home Reference: https://ghr.nlm.nih.gov/, Atlas of Genetics and Cytogenetics in Oncology and Haematology http://atlasgeneticsoncology.org

CLASS 9

Oncogenesis part I

Prof. Agata Filip

A) TOPICS:

-oncogenic transformation – definition, stages of transformation and their characteristics

-cancer cell characteristics

-tumor classification with respect to cell biology and histology

-benign, malignant and locally malignant tumors – differences

-molecular pathways of tumor development: protooncogenes– definition, most important examples, role in normal cells

-mechanisms of protooncogene activation – amplification, point mutation, reciprocal translocation – examples; role of viral infection

-molecular pathways of tumor development: tumor suppressor genes – definition, most important examples, role in normal cells

-mechanisms of tumor suppressor gene inactivation – deletion, point mutation, promoter hypermethylation

-molecular pathways of tumor development: stabilizing (mutator) genes – definition, most important examples, role in normal cells

-mechanisms of mutator gene inactivation – deletion, point mutation, promoter hypermethylation

-role of miRNA in tumor development

-cell cycle and its checkpoints (alterations in oncogenesis)

-apoptosis and necrosis – characteristics, physiologic function, regulation, alterations in oncogenesis

-neoangiogenesis – role in tumor development, regulation (pro- and anti-angiogenic factors, angiogenic switch)

-metastases – stages of development, typical sites

B) Obligatory book: L.B. Jorde, J.C. Carey, M.J. Bamshad "Medical Genetics (5th edition)" Chapter 11, W.S. Klug and M.R. Cummings "Essentials of Genetics" (5th edition or newer), Chapter 21

C) Recommended Book: M.A. Vasef, A. Auerbach. Molecular Oncology, Elsevier 2016, Lauren Pecorino "Molecular Biology of Cancer", Oxford University Press 2012 (third edition) or newer

D) Internet Sources: Atlas of Genetics and Cytogenetics in Oncology and Haematology http://atlasgeneticsoncology.org, The Cancer Genome Atlas https://cancergenome.nih.gov/

CLASS 10

Oncogenesis part II

Prof. Agata Filip

A) TOPICS:

Germline and somatic mutations

Loss of heterozygosity (LOH) phenomenon

Two-hit hypothesis for tumorogenesis

Cancer predisposition – role of germline mutations

Familial cancer – Lynch syndrome, retinoblastoma, breast cancer – molecular cause, pattern of inheritance, age of onset, symptoms

Familial cancer: familial adenomatous polyposis of colon, hereditary diffuse gastric cancer, Li-Fraumeni syndrome, Multiple Endocrine Neoplasia type 2 (MEN 2) – molecular cause, pattern of inheritance, age of onset, symptoms

Features of inherited cancers

Targeted treatment

B) Obligatory book: L.B. Jorde, J.C. Carey, M.J. Bamshad "Medical Genetics (4th edition)" Chapter 11, pages 212-230, W.S. Klug and M.R. Cummings "Essentials of Genetics" (5th edition or newer), Chapter 21

C) Recommended Book: M.A. Vasef, A. Auerbach. Molecular Oncology, Elsevier 2016, Lauren Pecorino "Molecular Biology of Cancer", Oxford University Press 2012 (third edition) or newer

D) Internet Sources: Atlas of Genetics and Cytogenetics in Oncology and Haematology http://atlasgeneticsoncology.org, National Comprehensive Cancer Network https://www.nccn.org/

CLASS 11

Genetic counseling

Dr. Szymon Zmorzyński

A) TOPICS:

-genetic counseling – definition and principles

-integral steps of genetic counseling

-taking a family history (pedigrees, pedigrees symbols, generations, individuals, miscarriages and stillbirths, the ethnic origin of the family, consanguinity)

-modes of inheritance (how to recognize modes of inheritance based on the pedigree)

-Bayesian analysis (calculation of probabilities - prior, conditional, joint and posterior)

-relationship factor (RF) [the coefficient of relationship] - how to calculate this factor?

-clinical genetics evaluation and services

B) Practical part:

I) presentation and discussion – Who is a genetic counselor? What do genetic counselors do? In what settings do genetic counselors work? What skills and personal qualities make a good genetic counselor? What is the future of genetic counseling?

II) drawing the pedigrees, "talking" to the parents of a newborn with Down syndrome, the estimation of recurrence risk – Bayes Theorem, birth of a child with trisomy 18, calculation the relationship factor.

C) Obligatory book:

-L.B. Jorde, J.C. Carey, M.J. Bamshad "Medical Genetics (5th edition)" Chapter 15

CLASS 12

Clinical cases

Dr. Szymon Zmorzyński

A) TOPICS:

I) CHROMOSOMAL DISORDERS:

-Down syndrome, Turner syndrome, Klinefelter syndrome, Patau syndrome, Edward's syndrome, cat's cry syndrome, Prader-Willi syndrome, Angelman syndrome.

II) AUTOSOMAL DISORDERS:

-Oculocutaneous albinism (type I and II), cystic fibrosis, galactosemia (type I), Gaucher disease, hemochromatosis (type I), phenylketonuria, sickle-cell anemia, Tay-Sachs disease, the thalassemias, familial hypercholesterolemia, achondroplasia, Apert syndrome, Huntington disease, neurofibromatosis type 1 and type 2, Marfan syndrome, osteogenesis imperfecta.

III) X-LINKED DISORDERS:

-Alpha-thalassemia/mental handicap syndrome, Ehlers-Danlos syndrome type IX, glucose-6-phosphate dehydrogenase deficiency (G6PD), hemophilia A, hemophilia B, Duchenne muscular dystrophy, Becker muscular dystrophy, Menkes disease, Lesh-Nyhan syndrome, Bloch-Sulzberger disease (*Incontinentia Pigmenti*), Rett syndrome, hereditary hypophosphatemic rickets

CLASS 13

WRITTEN QUIZ AND POINTS CALCULATION

Dr. Szymon Zmorzyński

According to RULES and REGULATIONS a Student is obliged to take a written quiz (covering topics from the whole semester),

if the total score from the classes is less than 60%, but more than 40%.