AlBalqa Applied University
Faculty of Medicine
2nd semester 2020
31501261/ Principles of Genetics and Molecular Biology (3 credit hours)

References:

1. Textbook of Biochemistry with Clinical Correlations, 7th Edition
Thomas M. Devlin.
2. Essentials of Genetics 7th. Ed. 2010 William S. Klug, Michael R. Cummings, Charlotte A. Spencer & Michael A. Palladino
Publisher :PEARSON

Instructor:
Dr. Nabil Amer

Course Description and Objectives:

Objectives of this course are designed to understand the basic principles of molecular Biology and Molecular Genetics. Emphasis will be given to those principles that have application in medical practice. The structure of DNA and RNA as genetic material, DNA organization and its replication, mutation and repair in both prokaryotes and eukaryotes will be covered. Furthermore, gene expression will also be discussed. Finally, the course will cover some aspects of cancer genetics, cytogenetics and molecular biology techniques.

Molecular genetics is one of the most rapidly advancing fields of medicine and is now integral to all aspects of biomedical science. Every physician who practices in the 21st century will require a basic knowledge of the principles of molecular genetics and their application to a wide variety of clinical problems .

The practice of modern medicine includes recognition of the role of genetic factors in health and disease. This requires knowledge of the structure, function, and transmission of genes and understanding of interactions both among genes, and between genes and the environment .

The following outline lists the objectives of the course material in Molecular medical genetics .

Students in Molecular genetics at BAU should know and understand :

1. What are genes and how they are organized .
2. How genes are arranged in chromosomes and how chromosomes replicate.
3. How genes are transmitted from parent to child, how genes segregate, and the patterns of inheritance for dominant and recessive, autosomal and X-linked traits.
4. The nature of mutations and how they are repaired, and how they contribute to human variability and disease .
5. What genes do: the flow of genetic information from DNA to RNA to protein?
6. How gene expression is controlled.
7. The significance of the Human Genome Project to medicine.
8. The molecular basis of inherited disease.
9. The role of genetics in the pathogenesis of neoplasms and in the predisposition to malignancies.
10. The multifactorial nature of most human traits and the principles of multifactorial inheritance.

11. The clinical manifestations of the common chromosomal anomalies.
12. Common molecular and cytogenetic diagnostic techniques and how they are applied to genetic disorders

Assessment :

MIDTERM EXAM: there will be 50 multiple choice questions for 50% of the total
FINAL COMPREHENSIVE EXAM: there will be 50 multiple choice questions (40 of them from the part that you were not examined in + 10 questions from the material of the midterm exam) for 50% of the total

Lecture #	Date	Topic	Outlines	Instructor
1	Sunday	Structure Of Nucleic Acids I	General Base pairs Double helix B-DNA helix vs. A-DNA helix Z-DNA helix ABZ Summary	
2	Tuesday	Structure Of Nucleic Acids II	a). Genetic dogma b). forces that affect DNA double helical stability c). Complexity of chromosomal DNA i). DNA denaturation ii). Repetitive DNA and Alu sequences iii). Genome size and complexity of genomic DNA d). Gene structure i). Introns and exons ii). Properties of the human genome iii). Mutations caused by Alu sequences e). Chromosome structure - packaging of genomic DNA i). Nucleosomes ii). Histones iii). Nucleofilament structure	
3	Thursday	Structure Of Nucleic Acids III		
4	Sunday	Structure of genes and chromosomes I		
5	Tuesday	Structure of genes and chromosomes II		
6	Thursday	DNA Replication I	DNA Replication Mechanisms • DNA Polymerase structure (Klenow fragment) ○ Metal ions in catalysis • Primase priming • DNA ligase catalysis • Helicase SSB, Topoisomerase • DNA Polymerase III holoenzyme • Sliding clamp • Replication fork • Okazaki fragments / Leading/lagging considerations • Leading/lagging strand "trombone" coordination • Topological Considerations • Topoisomers (relaxed versus supercoiled) • Linking, Twisting, Writhing) • Topoisomerases - enzymes affecting DNA topology	
7	Sunday	DNA Replication II		
8	Tuesday	DNA Replication III		

			• Topoisomerase I • Topoisomerase II /Inhibitors • Replication Initiation • *E. coli* replication origin • Binding of dnaA • Pre-priming complext - dnaA, dnaB, dnaC, dnaG, beta Clamp • DNA polymerases • Eukaryotic cell cycle • Telomere formation Shortening	
9	Thursday	DNA Recombination	• Scheme • Strand Invasion • Holliday junction	

10	Sunday	Mutations and DNA repair	DNA Damage
			• 8-Oxoguanine-adenine base pair
			• Adenine deamination
			• Aflatoxin activation
			• Thymine dimers
			• Cross linking agent
			DNA Repair
			• Proofreading
			• Mismatch repair
			• Nucleotide excision repair
			• Uracil repair
			• Huntington's disease
			• Cancer from DNA repair defects
			  ○ HNPCC (Lynch syndrome)
			  ○ p53 damage
			  ○ Agents for treating damage DNA
			• Ames test	

11	Tuesday	Transcription I	RNA Polymerase
			• Structures Subunits
			• Template versus coding strands
			• Polymerase movement
			Promoters
			• Prokaryotic sequences / -35 / -10 sequences
			• Alternative promoters - governed by sigma factors
			Prokaryotic RNA Synthesis
			• Transcription bubble
			• Termination signal
			  ○ Stem loop
			  ○ FMN-specific termination
			  ○ Rho protein
			• Antibiotic inhibition
			  ○ Rifampicin / Site of action - elongation blocker
			  ○ Actinomycin D (binds DNA double helix	

12	Thursday	Transcription II		
13	Sunday	Transcription III		
14	Tuesday	RNA Processing I		
15	Thursday	RNA Processing II		

			• tRNA and rRNA Processing in prokaryotes
			  ○ Ribonuclease P (generates 5' terminus of tRNAs)
			  ○ Ribonuclease III (excises 5S, 16S, 23S rRNAs from primary transcript)
			  ○ CCA addition to tRNAs
			  ○ Base modifications
			  ▪ Uridylate modifications
			Eukaryotic RNA Synthesis
			• Transcription/Translation - Prokaryotes vs. Eukaryotes
			• RNA Polymerases
			• Amanitin structure and source
			• Promoter elements
			• Eukaryotic TATA box / CAAT and GC boxes
			• Transcription Initiation
			• TATA-binding protein - DNA complex
			• Transcription factor HSTF
			  ○ Sequence recognized = 5' CNNGAANNTCCNNG 3'
			  ○ Binding sites
			• Enhancer sequences
			  ○ No promoter activity of own
			  ○ Act up to several thousand bp away from gene
			  ○ Act upstream, downstream, in middle of gene, and orientation independent
			  ○ Specific to specific cells
			• Eukaryotic rRNA
			  ○ Made by RNA Polymerase I as pre-rRNA and
			• Eukaryotic tRNA
			  ○ Made by RNA Polymerase III
			  ○ Processing
			• Eukaryotic mRNA
			  ○ Made by RNA Polymerase II
			  ○ Capping 5' end of mRNAs
			• Polyadenylation 3' end of mRNAs
			• microRNAs
			  ○ made by RNA Pol II or III
			  ○ processed from larger precursors
			  ○ roles in controlling gene expression
			• RNA editing
			  ○ apo B-100/apo B-48
			  ○ Cation channel proteins
			  ○ Trypanosomes (insertion of uridines after transcription using guide RNAs)
			• Splicing
			  ○ Sites
			  ○ Splicing mechanism
			  ○ Lariat branch point	

			○ Spliceosome assembly ○ Splicing catalytic center ○ snRNPs ○ Transcription and processing coupled ○ Splicing mutations and disease ▪ Thalassemia ▪ Examples ○ Alternative splicing patterns (calcitonin/CGRP - ○ Self splicing intron ▪ Schematic ○ Splicing pathway comparisons	
16	Sunday	Regulation Of Gene Expression I	Prokaryotes Sequences, Proteins, and Regulation • Lac regulatory site • lac repressor/DNA interaction • Helix-Turn-Helix / Beta Strands & DNA • B-galactosidase induction in cell • B-galactosidase catalytic action on lactose / Action on X-Gal • Operons • *lac* repressor structure • Allolactose / IPTG • *lac* operon repressed / *lac* operon induced • *E. coli* binding sites • CAP binding Attenuation • trp mRNA structure • Attenuation scheme - Termination with plenty of Trp) / No Termination - low Trp • Leader peptide sequences Eukaryotes • Chromatin 'beads on a string' • Nucleosome core particle • Histone structural similarities • Higher order chromatin structure • Structures - Leucine Zipper / Zinc Finger • Mediator • Enhancer binding sites • Specificity of enhancer action • DNA Methylation slows transcription - Methylcytosine) • Hormones and gene expression - estradiol) / All-trans-retinoic acid and thyroxine • Nuclear hormone receptor ○ Domains ○ Ligand binding affects structure ○ Coactivator Recruitment ○ Tamoxifen/raloxifene structures ○ Estrogen receptor - tamoxifen complex	
17	Tuesday	Regulation Of Gene Expression II		

			• Altering chromatin structure
			  ○ Histone acetyltransferase catalytic activity
			  ○ Bromodomain proteins
			  ○ Chromatin remodeling
			Translational Regulation in Animals
			• Ferritin structure
			• Iron response element
			• Transferrin receptor mRNA
			• IRE-BP
			• Small RNAs - microRNA action	

18	Thursday	Translation I
		Translation II
		Protein processing and targeting
			General
			• Ribosome structure
			• Amino acid addition in translation
			• Translation accuracy
			Genetic Code
			• Genetic Code
			• Codon/anticodon base pairs
			  ○ Inosine
			  ○ Allowed pairings)
			tRNAs
			• Codon/anticodon pairing
			• Alanine tRNA structure/sequence
			• General tRNA structure / Shape / Schematic
			Amino Acid Activation
			• Amino acid + ATP + tRNA + H2O -> aminboacyl-tRNA + AMP + Ppi
			  ○ Aminoacyl-tRNA bond
			• Aminoacyl-tRNA synthetases
			  ○ Threonyl-tRNA synthetase (Editing/activation sites
			  ○ Complex with threonyl-tRNA
			  ○ Recognition sites on tRNA
			• Aminoacyl-tRNA synthetase classes of *E. coli* / Structures
			  ○ Class 1 - links to 2' hydroxyl. Most are monomeric
			  ○ Class 2 - links to 3' hydroxyl (except Phe-tRNA). Most are dimeric
			Ribosomes
			• Images
			• Ribosomal RNA
			• Formylation of methionine
			• Prokaryotic translation initiation sequences
			• tRNA binding sites in the ribosome
			Translation Mechanism
			• Translation initiation in prokaryotes
			• Translation elongation
			  ○ Peptide bond synthesis
			  ○ Translocation	

19	Sunday			
20	Tuesday			

			• EF-Tu
			• Termination
			• Eukaryotic Translation
			  ○ Initiation
			  ○ Elongation
			  ○ Termination
			  ○ Circularization by protein interactions
			Antibiotics and Translation
			• Examples
			• Streptomycin - interferes with binding of formylmethionyl tRNA to ribosome
			• Puromycin - causes premature termination
			• Diphtheria toxin - translocation blocking by modification of elongation factor 2
			• Ricin - N-glycosidase from castor beans that cleaves adenine in 28S rRNA and prevents binding of elongation factors
			Protein Transport/Secretion
			• Ribosomes in E.R.
			• Signal sequences
			• Signal recognition particle / SRP Targeting Cycle
			• Sorting pathways	

21	Thursday	Recombinant DNA Techniques in Medicine I	1.The role of restriction enzymes in recombinant DNA 2.DNA cloning as a method of human gene copying 3.Polymerase chain reaction(PCR) as an amplification method of genes *in vitro*	N.AMER
22	Sunday	Recombinant DNA Techniques in Medicine II	1.The role of restriction enzymes in recombinant DNA 2.DNA cloning as a method of human gene copying 3.Polymerase chain reaction(PCR) as an amplification method of genes *in vitro*	N.AMER
	Tuesday	**REVISION**		
	3/18 - 3/25	**MIDTERM EXAMS**		
23	Sunday	Gene identification I	1. Probing of the gene with complementary labeled sequence 2.Explaining the technique of DNA blotting • Southern Blot • Northern blot	N.AMER
24	Tuesday	Gene identification II	3.DNA sequencing	N.AMER
25	Thursday	Mendelian Inheritance I	Particulate inheritance Genetic terminology Punnet t square Mendel's Pea Plant Experiments	N.AMER
26	Sunday	Mendelian Inheritance Ii	Mendel's Laws Mendel,s law of segregation(monohybrid cross) Law of Independent Assortment	N.AMER
27	Tuesday	Non-Mendelian	Lethal Genotypes Allelic Heterogeneity	N.AMER

		Inheritance I	Incomplete Dominance Codoninance	
28	Thursday	Non-Mendelian Inheritance II	Epistasis Penetrance Expressivity Phenocopies Genetic Heterogeneity	N.AMER
29	Sunday	Chromosomes Karyotyping I	What is karyotype? Performing karyotype Chromosome banding	N.AMER
30	Tuesday	Chromosomes Karyotyping Ii	What can we learn from Karyotypes? Abnormal Number Non-disjunction Deletion or Duplication Translocations Inversions	N.AMER
31	Thursday	Chromosomal anomalies I	1. Monogenic disorders • Autosomal o Recessive o Dominant • Sex linked	N.AMER
32	Sunday	Chromosomal anomalies II	2. Disorders with multifactorial inheritance (Polygenic disorders) • Diabetes mellitus • Hypertension • Gout • Schizophrenia (Psychiatry) • Congenital heart disease …etc.	N.AMER
33	Tuesday	Clinical implications of Molecular genetics I	DNA fingerprinting in forensic medicine 2.Use of repetitive sequence length polymorphism in the diagnosis of congenital diseases	N.AMER
34	Thursday	Methods of gene transfer to human chromosome I	*1.ex vivo* technique 2.*in vivo* technique 3.Gene transfer vehicle	N.AMER
35	Sunday	Gene therapy I	1. Types of gene therapy 2. Gene therapy attempts for cystic fibrosis 3. Gene therapy attempts for Duchenne muscular dystrophy	N.AMER
36	Tuesday	Gene therapy II		N.AMER
37	Thursday	Human genome I	Goals of the human genome project 2.Sequencing the human genome	N.AMER
38	Sunday	Human genome Ii	Goals of the human genome project 2.Sequencing the human genome	N.AMER
	Tuesday	REVIEW		N.AMER
	Thursday	FINALS		