Universitat Autònoma de Barcelona

2020/2021

Molecular Pathology

Code: 100868
ECTS Credits: 6

Degree	Type	Year	Semester
2500252 Biochemistry	OB	3	2

The proposed teaching and assessment methodology that appear in the guide may be subject to changes as a result of the restrictions to face-to-face class attendance imposed by the health authorities.

Contact

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Use of Languages

Principal working language: catalan (cat)
Some groups entirely in English: No
Some groups entirely in Catalan: No
Some groups entirely in Spanish: No

Teachers

Anna Maria Bassols Teixidó
Maria Fátima Bosch Tubert

Prerequisites

There are no official prerequisites, but it is assumed that the student has previously acquired enough solid knowledge on subjects of 1st and 2nd degrees: Biochemistry I and II, Molecular Biology, Genetics and Basic and Advanced Instrumental Techniques.

Objectives and Contextualisation

Provide a general knowledge about the molecular basis of the development of genetic diseases and deepen in the application of biochemical and molecular biology techniques for their study, diagnosis and therapeutics. In order to integrate this information, some selected examples of genetic diseases will be described at the molecular level.

Competences

- Be able to self-evaluate.
- Collaborate with other work colleagues.
- Design experiments and understand the limitations of experimental approaches.
- Display knowledge of the biochemical and genetic changes that occur in many pathologies and explain the molecular mechanisms involved in these changes.
- Interpret experimental results and identify consistent and inconsistent elements.
- Make an oral, written and visual presentation of ones work to a professional or non-professional audience in English and understand the language and proposals of other specialists.
- Manage bibliographies and interpret the information in the main biological databases, and also know how to use basic ICT tools.
- Read specialised texts both in English and ones own language.

- Take responsibility for one's own learning after receiving general instructions.
- Think in an integrated manner and approach problems from different perspectives.
- Use ICT for communication, information searching, data processing and calculations.
- Use clinical laboratory techniques to determine biochemical and genetic markers of different pathologies and critically assess the results, speculating on the nature of any possible underlying pathologies.

Learning Outcomes

1. Analyse and interpret the published data relating to studies on genetic linkage and positional cloning in order to identify genes associated with genetic diseases.
2. Be able to self-evaluate.
3. Collaborate with other work colleagues.
4. Define the concept and general applications of molecular therapy and gene therapy.
5. Describe and use techniques from biochemistry and molecular biology for detecting mutations responsible for genetic diseases in different types of samples and for prenatal diagnosis.
6. Describe the methodologies and limitations for generating animal models of human diseases.
7. Describe the molecular bases of genetic diseases and their different pathogenetic mechanisms.
8. Design experiments and understand the limitations of experimental approaches.
9. Exemplify each type of pathogenetic mechanism, its functional repercussion and its therapeutic approaches.
10. Explain the molecular bases of such phenomena as loss and gain of function, incomplete penetrance, anticipation, variable expressivity, genetic impression and inactivation of the X-chromosome.
11. Interpret and integrate the analytical data from the principal biochemical and molecular genetics tests for the screening, diagnosis, prognosis and monitoring of pathologies.
12. Interpret experimental results and identify consistent and inconsistent elements.
13. Make an oral, written and visual presentation of ones work to a professional or non-professional audience in English and understand the language and proposals of other specialists.
14. Read specialised texts both in English and ones own language.
15. Relate the different types of DNA mutations to their effects on gene expression.
16. Submit a basic query to databases on genes and genetic diseases and interpret the results.
17. Take responsibility for one's own learning after receiving general instructions.
18. Think in an integrated manner and approach problems from different perspectives.
19. Use ICT for communication, information searching, data processing and calculations.

Content

THEORY

1. Introduction to genetic diseases. Definition of health and disease. Definition of genetic disease. Garrod's contribution: Inborn errors of metabolism. Data bases of genetic diseases. Monogenic, polygenic and multifactorial diseases. Mendelian inheritance. Incidence and prevalence of genetic diseases in the population.

2. Mutations in DNA as a cause of genetic diseases. Definition of mutation. Mutation rate. Types of molecular mutations and their effect on gene expression. Haemoglobinopathies. Enzymopathies: Blocking a metabolic pathway. Glucose-6-phosphatase, galactosemia and phenylketonuria deficiencies.

3. Molecular genetics diagnosis. Type and origin of analyzed samples. Prenatal and carrier diagnostics. Non-invasive techniques. Methods for detection of point mutations (SNPs), dynamic mutations, deletions and chromosomal rearrangements. Microarrays.

4. Molecular bases of inheritance and genetic diseases. Loss of function. Recessivity. Dominance. Haploinsufficiency. Negative dominant effect. Gain of function. Variable expressivity. Incomplete penetrance. Epigenetics. Genomic imprinting. Prader-Willi and Angleman syndromes. Chromosome X inactivation. Functional hemizygosity. Mosaic females. XIST gene and chromosome X inactivation center (XIC).

5. Identification of disease-associated genes. Strategies. Functional cloning. Positional cloning. Genetic and physical maps. Linkage analysis. LOD score. Zoo blots. CG isles. Exon trapping. Exon prediction. Chromosome jumping. Candidate genes.

6. Genome Project. Objectives. Chronology. Complete genomes. Strategies: Top-down and bottom-up. High-resolution physical maps: STS. Sequencing and assembling. Contig maps. Result analysis. Functional genomics. System biology. The new paradigm in Medicine: Pharmacogenomics and toxicogenomics.

7. Monogenic diseases:Cystic fibrosis. Alteration on chloride ion transport. Identification of the associated gene. Structure and function of the cystic fibrosis transmembrane regulator (CFTR). Effects of ΔF508 and other mutations. Compound heterozygous. Therapeutic approaches.

8. Diseases caused by dynamic mutations. Classification. Proposed mechanism. General characteristics: Incomplete penetrance, anticipation, premutation. X-fragile syndrome. Effect of trinuclotide CGG expansion. Function of FMR1 gene.

9. Polygenic diseases: Alzheimer's disease. Types of lesions. Candidate and susceptibility genes. Amyloid protein precursor (APP). Role of secretases in APP processing. Presenilins. Drugs: Acetylcholinesterase inhibitors. Additional therapeutic approaches.

10. Chromosomal diseases: Down síndrome (Trisomy 21). Effect of maternal age. Phenotype. Causes. Gene dosage effect. Candidate genes. Down syndrome critical region. Animal models. Prenatal diagnosis.

11. Diseases of amino acid metabolism. Phenylketonuria and other hyperphenylalaninemias. Phenylalanine hydroxylase deficiency. Structure and effect of mutations. Neonatal diagnosis and prevention.

12. Diseases of lipid metabolism. Familiar hypercholesterolemia. Cholesterol metabolism and LDL. Associated loci. Structure and function of LDL receptor. Effect of mutations.

13. Diseases of carbohydrate metabolism. Glycogen storage diseases. Galactosemias.

14. Diabetes mellitus. Type 1 diabetes. Type 2 diabetes.

15. Lysosomal storage diseases. Enzyme replacement therapy.

16. Diseases of collagen biosynthesis and structure. Osteogenesis imperfecta. Ehlers-Danlos syndrome. Alport syndrome.

17. Muscular dystrophies. Duchenne muscular dystrophy. Becker muscular dystrophy. Limb-girdle muscular dystrophy. Structure ofdystrophin and dystrophin-dystroglycan complex.

18. Disesases related to DNA repair systems. Xeroderma pigmentosum. Cockayne syndrome. Ataxia telangiectasia. Fanconi anemia.

19. Biochemistry and molecular biology of cancer (I). Cancer as a multicausal process. Cancer epidemiology and risk factors. Fundamental alterations in cancer cells.

20. Biochemistry and molecular biology of cancer (II). Oncogenes and protooncogenes: Activation mechanisms, membrane, cytoplasmatic and nuclear oncoproteins. Tumor suppressor genes: Molecular bases and their relationship with hereditary cancers. Cancer and apoptosis.

21. Biochemistry and molecular biology of cancer (III). Molecular bases of invasion and metastasis. Therapeutic approaches.

22. Molecular biology techniques to study disease mechanisms (I). Introduction to techniques of transgenesis in animals. DNA microinjection into fertilized oocytes.

23. Molecular biology techniques to study disease mechanisms (II). Introduction to techniques of targeted genomic alterations: Obtaining knock-out and knock-in animals using classical and CRISPR / Cas9 techniques.

24. Introduction to gene therapy. Types of vectors. Development of strategies for gene transfer into specific cells and tissues.

SEMINARS

Suggested topics:

1. Pigmentary retinosis
2. Charcot-Marie-Tooth's disease
3. Parkinson's disease
4. Colorectal cancer
5. Lesch-Nyhan Syndrome
6. Amyotrophic lateral sclerosis
7. Adrenoleukodystrophy
8. Rett syndrome
9. Gaucher's disease
10. Malignant hyperthermia
11. Marfan Syndrome
12. Friedreich's Atlas
13. Neurofibromatosis
14. Colorectal cancer
15. Mitochondrial diseases
16. Immunodeficiencies
17. Narcolepsy
18. Schizophrenia

19. Alcoholism

20. Pharmacogenomics and toxicogenomics

Methodology

Material available on the Intranet of the subject

Teaching guide

Calendar of teaching activities (lectures, tutorials, assessments, deliveries ...)

Visual material used by teachers in the lectures

Self-learning topics (Seminars)

Short questions, clinical cases, statements of problems

Collection test questions as an exam model

The training activities are divided into three sections: lectures and seminars, each one with its specific methodology. These activities will be complemented by a series of tutorial sessions that will be additionally scheduled and a collection of deliveries of tests for continuous evaluation.

Lectures

The content of different subjects will be explained with the support of visual material that will be available to students through the Intranet of the subject. This visual material will be written in Catalan, Spanish or English. Lecture sessions will be the most important part of the theory section.

Seminars

Knowledge of some parts chosen from the content of the different subjects will have to be searched through autonomous learning by students. It will evaluated as oral presentations in the Seminar sessions and it will also be uploaded as a study material on the Intranet for all students to have access. Oral presentations done and presented in English.

The group will be divided into two subgroups (maximum 30 students per subgroup), whose lists will be made public at the beginning of the course. There will be 10 sessions of seminars during the course where students will prepare an oral presentation for a chosen self-study (see seminar contents). Presentations in PowerPoint format and a summary of a maximum half-page will have to be sent to the teacher a week before. She/He may suggest changes or modifications during that week that must be included inthepresentation.

The oral presentation of the seminar will have a minimum duration of 20 min., with the following scheme:

• Inheritance and epidemiology,

• Clinical (symptomatology),

• Molecular genetics (chromosomal location and gene identification),

• Biochemistry (mutations / allelic variants and genotype-phenotype correlation),

• Diagnosis and therapeutics.

The rest of the time will be devoted to solving doubts, answering questions, raising a debate, etc., where all those attending the seminar will be able to participate.

The oral presentation will be shared among the members of the group (2 students), so that everyone has the opportunity to speak al least for 10 min.

Attendance and accomplishing oral presentations at the Seminars are mandatory for all students, except in cases where there is a documented justification. Active participation of the students in the seminars will be rated, so that it will have an impact on the seminar grade. Lack of attendance will discount a percentage of the seminar mark.

Delivery of clinical cases, short questions or problems

Every 10-12 theory topics a collection of questions that may contain clinical cases, short questions or problems will be delivered through the intranet tool and that will have to be answered back within 5 days. Questions will be related to concepts explained in the lectures but also to self-learning topics that must be searched and studied through autonomous learning by the students.

Tutorials

Tutorials will be carried out s requested by students. If the number of requirements is extremely high, especially for midterm exams or the resolution of clinical cases or short questions, up to 3 classroom tutorials would be scheduled and they will be announced on a timely basis through the intranet. The objective of these sessions will be to resolve doubts, review basic concepts, solve problems or clinical cases proposed through intranet short questions, guide on the consulted sources of information and carry out debates on the topics for which there are planned autonomous learning or that have been proposed by the teachers. These sessions will not be lectures nor will be treated new topics from the official content of subjects, but will be sessions of debate and discussion.

Activities

Title	Hours	ECTS	Learning Outcomes
Type: Directed			
Theory lectures	35	1.4	1, 4, 5, 7, 6, 9, 10, 16, 15
Type: Supervised			
Delivery of clinical cases, short questions and problem solving, through the Intranet	3	0.12	19, 5, 8, 11, 12, 14, 18, 16, 17
Seminars	10	0.4	1, 4, 5, 7, 6, 9, 10, 11, 15
Tutorials	6	0.24	1, 4, 5, 7, 6, 8, 9, 10, 11, 12, 18, 16, 15
Type: Autonomous			
Delivery of clinical cases, short questions and problem solving, through the Intranet	12	0.48	1, 19, 5, 8, 11, 12, 14, 18, 16, 15, 17
Preparation of seminars	26	1.04	1, 19, 3, 9, 14, 16, 15, 13, 17
Study	50	2	1, 4, 5, 7, 6, 9, 10, 11, 14, 15, 17, 2

Assessment

The evaluation of this course will have the format of continous assessment with a re-assessment final test. The objective of the continuous assessment is to encourage the students' effort throughout the semester, allowing

them to monitor their degree of follow-up and understanding of the subject. The final test of re-assessment is used to verify that the student has reached the necessary degree of integration of knowledge of the course. To be eligible for the retake process, the student should have been previously evaluated in a set of activities equaling at least two thirds of the final score of the course or module. Thus, the student will be graded as "No Avaluable" if the weighthin of all conducted evaluation activities is less than 67% of the final score.

Seminars

Assessment of teamwork:

The obtained mark will be the same for all the members of the team, as long as all of them have prepared and exhibited in an equivalent manner. The involvement of the different members of the team will be verified through a small individual and confidential survey. The weight of the evaluation of teamwork will be 25% of the total.

Evaluation of individual learning:

The two sections (Theory and Seminars) are inseparable, so that the student must participate, and be evaluated, in both to overcome the matter. Therefore, participation in the seminars is mandatory, both on the day of the oral presentation and the attendance at the other seminars of the peers. Students missing more than 40% of programmed sessions will be graded as "No Avaluable". The active participation of the students in the seminars will have an impact on the seminar grade. A selection of seminars, which are also part of the contents of the subject, will be evaluated with a question to the examination of the 2nd midterm exam, and will contribute in a proportional way to the mark of thisexam. The re-assessment exam will also include a seminar question.

Theory

Individual assessment through:

• Two midterm tests with short questions.

• A final proof of re-assessment that will have the same format as the midterm exams and will cover the entire subject of the course. This exam is intended for students who have not previously passed midterm tests.

• Delivery of answers for clinical cases, problems and continuous assessment tests through the intranet (maximum 2 deliveries)

The weight of the theory evaluation will be 75% of the total. Of this, 15% will correspond to the score of the delivery of answers through the intranet, and 60% to the theory exams (30% for each midterm exam).

In order to be able to do the average between midterm tests, without going to the final re-assessment test, the student will have to obtain in the two midterm exams a qualification equal or higher than 4.5. The topics corresponding to the partial theory tests with a qualification of less than 4.5 will be evaluated in the final re-assessment test, where it will be also necessary to obtain a qualification equal or higher that 4.5 of each midterm topics to be able to average with the scores of the rest of the activities. However, those students who have passedthe partial tests of theory and want to improve their qualification may choose to attend to the final test of re-assessment for the totality of the subject or only one of the midterm exams. The student who is attending a re-assessment exam is resigning the partial / s scores.

It is necessary to obtain a final grade equal to or greater than 5 to pass the course, either through midterm or through the final re-assessment test.

It will be considered that a student will obtain the "not evaluated " qualification when the number of assessment activities carried out is less than 67% of those programmed for the course.

The students from a second enrollement of the course will not have to carry out the educational activities or the evaluations of those activities passed with a score higher than 5, like the seminars and the delivery of questions of continous assessment.

Assessment Activities

Title	Weighting	Hours	ECTS	Learning Outcomes
Delivery of clinical cases, short questions and problem solving, through the Intranet	15%	1	0.04	1, 19, 5, 8, 11, 12, 18, 16, 15, 17
Oral presentation and participation in seminars	25%	1	0.04	1, 19, 3, 5, 7, 9, 11, 14, 16, 15, 13, 17
Theory midterm individual exams	60%	6	0.24	1, 4, 5, 7, 6, 8, 9, 10, 11, 14, 15, 17, 2

Bibliography

Basic Bibliography

Emery, A.E.H., Rimoin, D.L. *Principles and Practice of Medical Genetics.* 4th. ed. Vols. 1, 2 i 3. Churchill Livingstone. New York, 2002.

González-Sastre, F., Guinovart, J.J. *Patología Molecular.* Masson, Barcelona, 2003.

Oliva, R. *Genética Médica.* 3ª ed. Universitat de Barcelona. Barcelona, 2004.

Scriver, C.R., Beaudet, A.L., Sly, W.S., Valle, D. *The Metabolic and Molecular Bases of Inherited Disease*. 8ª ed. Vols. 1-4. McGraw-Hill, Inc. New York, 2001.

Strachan T, Goodhip J, Chinnery P. Genetics and Genomics in Medicine. Garland Science, Taylor & Francis Group. NY & London, 2015.

Strachan, T., Read, A.P. *Human Molecular Genetics 4th Edition*. Garland Science, Taylor & Francis Group. London, 2010.

Strachan, T., Read, A.P. *Genética Humana*. McGraw-Hill Interamericana, México DF, 2006. Versió en castellà de *Human Molecular Genetics 3*. Garland Science. London, 2004.

Sudbery, P. *Genética molecular humana.* 2ª ed. Pearson Educación, Madrid, 2004. Versió en castellà de *Human molecular genetics*, 2nd ed. Pearson Education, 2002.

Complementary Bibliography

Amstrong L. Epigenetics. Garland Science. New York. 2014.

Jackson, I.J., Abbott, C.M. *Mouse Genetics and Transgenics. A practical approach.* Oxford University Press, 2000.

Jorde, L.B., Carey, J.C., Bamshad, M.J., White, R.L. *Genética Médica.* 3ª ed. Elsevier. Madrid, 2005.

Lewin, B. *Genes VIII.* Pearson Prentice Hall. Upper Saddle River, 2004.

Matthes, D.*J. Problems and solutions for Strachan & Read'sHuman Molecular Genetics2.* Bios Scientific Publishers.Oxford, 2001.

Muñoz, A. *Cáncer: Genes y Nuevas Terapias.* Hélice, 1996.

Nussbaum, R.L., McInnes, R.R., Willard, H.F. *Thompson & Thompson Genetics in Medicine with clinical case studies*. 6th ed. W.B. Saunders. Philadelphia, 2004.

Weinberg, R.A. *The Biology of Cancer.* 2nd ed. Garland Science. New York. 2014.

Internet addresses

On-line Mendelian Inheritance in Man (OMIM). http://www.ncbi.nlm.nih.gov/Omim/

Molecular Medicine MedPulse®. http://www.medscape.com/px/splash

Medline Plus®. http://www.nlm.nih.gov/medlineplus/

Genes and Disease.
http://www.ncbi.nlm.nih.gov/books/bv.fcgi?call=bv.View..ShowTOC&rid=gnd.TOC&depth=2