UNIVERSITÀ
DEGLI STUDI DI MILANO-BICOCCA

COURSE SYLLABUS

Functional Genomics

2627-1-F0902D001

Aims

The Human Genome Project and subsequent technological advancements, particularly the massive parallel DNA sequencing technologies and techniques for studying the three-dimensional organization of chromatin, have changed the landscape of the relationship between genetics and medicine. The era of medical genetics, focused on chromosomal abnormalities and monogenic diseases, is giving way to the era of clinical genomics and public health. Genome-wide analyses of genetic variability are beginning to comprehensively link the genome to the phenome. Researchers have therefore shifted their focus towards understanding gene functions and the regulatory mechanisms that control gene expression. This includes studying gene-gene and gene-environment interactions to better understand complex traits and diseases.

Specific Objectives

1. Knowledge and understanding
   Students will acquire an in-depth understanding of functional genomics technologies and experimental approaches, with a focus on high-throughput DNA sequencing, chromatin 3D structure analysis, and gene expression regulation. They will also gain knowledge on genetic variability and gene-gene and gene-environment interactions in the determination of complex traits.

2. Applying knowledge and understanding
   Students will be able to design and interpret experimental studies in the field of functional genomics, critically selecting the most appropriate methodologies. They will be capable of applying this knowledge to advanced biomedical research and clinical settings in translational genomics.

3. Making judgements
   Students will develop critical thinking skills in the analysis of genomic data, independently assessing the reliability and significance of scientific results, formulating coherent hypotheses, and evaluating the ethical, clinical, and scientific implications of their analyses.

4. Communication skills

Students will gain the ability to clearly, effectively, and professionally communicate the content and results of complex genomic analyses, both in academic contexts and within multidisciplinary teams, using appropriate scientific terminology and communication tools.

5. Learning skills
   Students will develop a high degree of autonomy in learning and continuous updating, acquiring the ability to critically access scientific literature and independently explore technological and methodological innovations in functional genomics.

Contents

The Functional Genomics course offers an advanced educational path aimed at decoding the structural, functional, and epigenetic complexity of the human genome. In the first part, students will explore the conceptual evolution of the gene, the architecture of non-coding DNA, and the mechanisms of gene duplication, incorporating the latest developments from international consortia. Subsequently, the program examines molecular epigenetic codes, including DNA methylation, histone modifications, and the three-dimensional organization of chromatin, linking them to complex phenomena such as imprinting and X-chromosome inactivation. Particular emphasis is placed on next-generation technological platforms, covering in detail NGS sequencing on DNA and RNA, single-cell genomics, methylation studies, and 3D conformation capture techniques. Finally, the course provides foundational methodological skills for in vitro and in vivo functional validation, analyzing plasmid and viral vectors, programmable gene editing strategies (CRISPR/Cas9), molecular interaction assays, and the development of transgenic animal models or gene silencing approaches applied to biomedical research and gene therapy.

Detailed program

PART I: Conceptual Evolution and Global Genome Organization (Lectures 1-5)
• Lecture 1: From Genetics to Genomics
Conceptual evolution of the term "gene" from the classical and Mendelian eras to the modern era; polymorphisms; genetic and physical maps; linkage studies and GWAS.
• Lecture 2: Sanger Sequencing and Gene Identification
Chain-termination DNA sequencing; historical positional cloning strategies for disease-gene identification; forward and reverse genetics.
• Lecture 3: The Human Genome Project and Protein-Coding Genes
Milestones and methodologies of physical mapping and clonal contigs of the Human Genome Project (HGP); quantitative analysis and distribution of protein-coding genes.
• Lecture 4: Gene Duplication, Gene Families, and RNA Genes
Molecular mechanisms of gene duplication (neofunctionalization, pseudogenes); classification of gene families and the evolution of biological complexity; introduction to non-coding RNA genes (rRNA, lncRNA, miRNA, piRNA).
• Lecture 5: Gene Distribution, Non-Coding DNA (ncDNA), and Human Genome Project Developments
Heterogeneity of gene density, gene deserts, and the isochore model; analysis of ncDNA; innovations by the Telomere-to-Telomere (T2T) consortium and the Human Pangenome Project.
PART II: Molecular Epigenetics, Omics, and 3D Topology (Lectures 6-11)
• Lecture 6: Basic Chromatin Structure and Histone Modifications
Hierarchical levels of DNA packaging and nucleosome biology (histone octamer, variants, and linker histone H1); chromatin dynamics, histone modifications and the histone code, reader and writer enzymes.
• Lecture 7: DNA Methylation: Biological Role and Epigenetic Mechanisms
DNA methylation and its functional significance; DNMT enzymes; the role of methylation in gene repression and development; euchromatin, constitutive heterochromatin, and facultative heterochromatin.

• Lectures 7-8: Next-Generation Sequencing (NGS) Techniques and Functional Genomics Applications
Second- and third-generation NGS platforms. RNA sequencing and transcriptomics. Applications of NGS on DNA and RNA: ChIP-Seq, CUT&RUN, Metagenomics.
• Lecture 9: 3D Genome Organization and Techniques for Studying Chromatin Conformation
Interphase three-dimensional architecture: chromosome territories, A/B compartments, topologically associating domains (TADs), and promoter-enhancer loops. Chromosome conformation capture techniques (Hi-C, Micro-C, MCC) and ligation-independent methods.
• Lecture 10: Genetic Imprinting and X-Chromosome Inactivation
Parent-of-origin-specific monoallelic expression and evidence from pronuclear transfer experiments; uniparental disomies (UPD) and human genetic syndromes (Prader-Willi, Angelman, Silver-Russell, Beckwith-Wiedemann); biological significance, phases, and molecular mechanisms of X-chromosome inactivation.
• Lecture 11: Single-Cell Genomics
Principles, techniques, and implications of single-cell genomic analyses; single-cell RNA sequencing (Single-cell RNA-Seq) for studying transcriptional heterogeneity; introduction to spatial transcriptomics and multi-omics analyses.
PART III: In Vitro Systems, Transduction Engineering, and Gene Editing (Lectures 12-14)
• Lecture 12: Cell Culture and Stem Cell Biology
In vitro manipulation and maintenance of cell cultures; biology, self-renewal, and differentiation of pluripotent stem cells (ESCs, iPSCs) and multipotent stem cells as biological models.
• Lecture 13: Genome Engineering Technologies and Plasmid Vectors
Principles of molecular cloning and the main plasmid vectors used to manipulate gene expression. DNA cloning methods, types of plasmids (cloning, expression, reporter, and knock-down), promoters, transfection strategies, and systems for achieving constitutive or inducible gene expression in eukaryotic cells. Use of zinc finger nucleases (ZFNs), TALENs, and the CRISPR/Cas9 platform; utilization of DNA repair pathways (NHEJ and HDR).
• Lecture 14: Viral Vectors for Gene Transfer
Molecular biology and engineering of retroviral and lentiviral vectors; architecture of self-inactivating (SIN) vectors via 3'-LTR deletion; structural comparison between 2nd and 3rd generation platforms and titration methodologies.
PART IV: Functional Assays, Interactomics, and In Vivo Animal Models (Lectures 15-18)
• Lecture 15: Functional Study of Promoters and Transcription
Biochemical and functional characterization of regulatory regions: reporter vector design (luciferase, GFP) and site-directed mutagenesis of transcriptional binding motifs.
• Lecture 16: Characterization of Protein-Protein Interactions
Methodologies for mapping the protein interactome: yeast two-hybrid assay (Y2H), co-immunoprecipitation (Co-IP), high-resolution biophotonic assays (FRET/BRET); ChIP.
• Lecture 17: In Vivo Gene Targeting Strategies I
Biological principles of homologous recombination in embryonic stem (ES) cells and targeting vector design; generation of knockouts and conditional knockouts using Cre-Lox systems. Construction and selection of genetically modified cells and animals. In vivo genome editing technologies: transposons, Zinc Finger Nucleases (ZFNs), and CRISPR/Cas9. Applications of genome editing in biological research and gene therapy.
• Lecture 18: In Vivo Gene Silencing Strategies I
Principles of gene silencing using antisense oligonucleotides (ASOs); RNA interference (RNAi), siRNA, and shRNA. Delivery strategies and vectors for gene silencing. Biogenesis and function of microRNAs (miRNAs). Applications of small RNAs in studying gene function and developing new therapeutics.

5 interactive Lectures/workshops will be dedicated to student presentations and critical discussion of scientific articles.

Prerequisites

To successfully engage with the advanced and specialized topics of this Functional Genomics course, students are highly recommended to have a solid foundational background in the following areas:

Molecular Biology: Structure of nucleic acids (DNA and RNA), mechanisms of replication, transcription, RNA processing, and translation in both prokaryotes and eukaryotes; classical regulation of gene expression.

General Genetics: Mendelian laws of inheritance, chromosome structure and abnormalities, concepts of mutation, recombination, genetic linkage, and mapping.

Biochemistry and Cell Biology: Protein structure and function, cellular compartmentalization, cell cycle control, intracellular signaling pathways, and basic techniques for handling in vitro cell cultures.

Basic Recombinant DNA Technology: Core principles of molecular cloning, restriction enzymes, gel electrophoresis, and polymerase chain reaction (PCR).

The Human Genome Project and subsequent technological developments are to be considered an indispensable tool for understanding study strategies.

Teaching form

- 12 two-hour erogative lectures delivered in-person;
- 2 two-hour interactive lectures delivered in-person;
- 6 two-hour erogative lectures delivered remotely;
- 6 two-hour interactive workshops conducted in-person.

The course will be taught in Italian. The provided teaching materials will be in English.

Textbook and teaching resource

- Lecture slides

- Reviews and articles published in international journals will be indicated during the course.

Recommended Textbooks:

- "Genetica & Genomica nelle scienze mediche"; Tom Strachan, Anneke Lucassen. Seconda Edizione Italiana - Zanichelli
- "Genetica Molecolare Umana"; Tom Strachan, Andrew Read. Seconda edizione italiana condotta sulle 5 edizione inglese - Zanichelli
- "Functional Genomics: Methods and Protocols" (Methods in Molecular Biology); Michael Kaufmann, Christine A. Wells, Athanasios Alexiou.

Semester

I Semester

Assessment method

Assessment will take place during the scheduled exam sessions through a written exam composed of multiple-choice questions covering the entire course program to evaluate the student's general preparation, and an open question chosen by the student from three proposed questions to assess comprehension abilty and in-depth understanding of the topics.

During the course, students will also be prompted to prepare an oral presentation (optional) on an original scientific article on a topic relevant to the program, to evaluate their presentation and synthesis skills.

The final grade will be determined by the average obtained from the scores obtained in the multiple choice test and the open question. The exam will be passed only if the student will reach a minimum score in both the multiple choice and the open question. The optional presentation will contribute to the final grade by adding a maximum of 3 additional points.
Upon request by the professor or the student, a brief oral exam may be conducted, consisting of an interview on the topics covered in class and/or a discussion of the written exam.

Office hours

on appointment, by e-mail arrangement (emanuele.azzoni@unimib.it)

Sustainable Development Goals

GOOD HEALTH AND WELL-BEING | QUALITY EDUCATION | GENDER EQUALITY