

SUBJECT	MEDICAL GENETICS		
CREDITS	Total: 4.5	Theory 2.5	Practical 2

GENERAL OBJECTIVE

To provide students with terminology and knowledge from the field of human genetics that will enable them to understand physiopathology and develop skills in the areas of clinical description, information search, independent learning, continuous education, recognition of their own professional limitations, respect for the autonomy and individuality of patients, genetic counselling and treatment options for genetic-based disorders.

SPECIFIC OBJECTIVES

The specific objectives set out below follow the guidelines established by the American Society of Genetics (*"Report from the American Society of Human Genetics Information and Education Committee: Medical School Core Curriculum in Genetics" Am. J. Hum. Genet. 56:535-537, 1995*), which are followed by numerous medical faculties. Reference is also made to other complementary recommendations from other societies (*"Association of Professors of Human or Medical Genetics"*, and the *"American Academy of Family Physicians"*). These specific objectives are consistent with both the general objectives of our Faculty of Medicine and the teaching syllabus.

The specific objectives are organized in three parts: Knowledge, aptitudes and attitudes. As some of these objectives are addressed in various classes, their numbering and order is different to that of the classes set out in the syllabus.

Knowledge

The practice of modern medicine includes recognition of the role of genetic factors in health and disease. This requires recognition of the structure, function, mechanisms and rules of genetic transmission, as well as the relationship between genes and between genes and the environment. Therefore, students must understand:

- What genes are, how they are organized and controlled, what they do and how they segregate.
- The nature of mutations and permutations and how these help generate human variability and/or disease.
- The inheritance patterns characteristic of the following kinds of inheritance: autosomal dominant, autosomal recessive, X linked dominant and X linked recessive.
- The factors which affect the phenotypic expression of monogenic alterations, including the concepts of variable expressivity and incomplete penetrance.
- The basis of mitochondrial disorders and the inheritance pattern in mitochondrial (maternal) inheritance.
- How genes are organized in chromosomes, how chromosomes replicate and segregate in mitosis and meiosis, and how they are transmitted to offspring.
- The clinical manifestations of the most common numerical and structural chromosomal anomalies and mosaicism.
- The concepts and importance of gene imprinting and uniparental disomy.
- The principles of population genetics and the implications of genetic epidemiology for public health.
- The medical application of polymorphisms, of linkage analysis and of gene mapping.
- The basic principles of innate metabolic errors, of pharmacogenetic variations and their general clinical manifestations.
- The multifactor nature of most human traits, both normal and abnormal, and the principles of multifactor inheritance.

- The mechanisms of teratogenesis and the main effects of human teratogens.
- How to recognize and classify congenital anomalies and the method for diagnosing congenital disorders.
- The role of genetics in the pathogeny of neoplasias and in the predisposition to cancer.
- How to use evolutionary principles to understand both human biology and disease.
- How the frequency of hereditary disease varies between different ethnic groups.
- The most common molecular and cytogenetic diagnostic techniques and their application to the diagnosis of genetic alterations.
- Current procedures for prenatal genetic diagnosis and the most common disorders detected at the prenatal stage.
- Methods of genetic counselling.
- The advantages, limitations and dangers of predictive tests.
- The existence of and reason for programs designed to prevent hereditary diseases.
- Advances and current approaches in the treatment of genetic disorders.
- How to assess scientific advances in a clinical context and how to apply them in an appropriate way to patient care.
- Organizational and financial aspects of the health system with respect to genetics.
- Legal and ethical aspects in the practice of genetic medicine.
- Helpful and improper approaches in the history of human genetics.

Skills or aptitudes

Students must learn to synthesize the objective facts related to genetic disorders and be able to use this information to draw up an appropriate plan for diagnostic assessment and treatment or prevention with the patient or family. Students must also learn to communicate or transmit the information related to different genetic alterations in a clear and non-directive way, without personal bias, to people from all levels of society, who will differ in terms of their education, socio-economic status, and ethnic and cultural background. Therefore, students must be able to:

- Take a comprehensive medical genetic history and draw up a family tree.
- Carry out a physical examination and be able to recognize the main major and minor anomalies, special attention being paid to the identification of anatomical and anthropometric alterations.
- Formulate a suitable differential diagnosis and draw up a diagnostic plan that includes the use of complementary tests, whether these be biochemical, cytogenetic or molecular.
- Use in an efficient way the various information search systems, including traditional and media libraries and electronic resources, in the process of assessing, diagnosing or offering genetic counselling to patients with genetic disorders, as well as in the diagnosis of congenital disorders and the examination of teratogenic presentations.
- Understand and interpret cytogenetic, biochemical and molecular laboratory reports.
- Appreciate the importance of biomedical research and develop the technique and skills required for critical analysis of current scientific developments.
- Coordinate the information obtained from different sources into a coherent and rational action plan.
 - Ensure that people or patients have access to diagnostic and predictive tests that are appropriate in terms of the alteration present in their family, and to inform patients of the utility, benefits, limitations and risks of these types of tests.
 - Offer patients the appropriate treatment in each case, including options such as enzyme replacement, dietary restrictions, pharmacological treatment, transplants and gene therapy.
 - Communicate genetic information in an appropriate way to each individual patient or family.
 - Understand the different stages of normal development of human behaviour, the maturation process and intelligence in order to facilitate the provision of genetic counselling to individuals of widely varying age and characteristics.
 - Tolerate, or even promote, the reiteration of information by patients with the aim of reducing their anxiety or lack of understanding of the concepts being proposed.
 - Use suitable techniques when required to give bad news.

- Recognize the defence mechanisms used by patients and be able to decide when it is best to leave them intact and when to challenge them.
- Deal with the emotional responses of patients.
- Interpret the ethical, cultural, religious and ethnic attitudes of patients and develop the ability to treat each patient or each family member as an individual.
- Understand and act in accordance with the various cultural, social or religious attitudes of patients with respect to assumptions such as contracting, abortion, the custody of children or the roles of each member of a couple relationship.
- Make appropriate use of community support services.

Attitudes

Students must learn to be empathic, to avoid making value judgements and offer non-directive genetic counselling. They must also recognize their own limitations, know how to seek help when necessary and be motivated towards independent and continuous learning until the end of their professional career. Therefore, students must be able to:

- Appreciate the importance of being able to predict and prevent disease.
- Respect the religious, moral and ethical beliefs of patients, even if they differ substantially from the student's own beliefs.
- Present all available options in a balanced, rigorous and non-directive way.
- Appreciate the importance of confidentiality and the difficulties that arise when it is realized that a relative of a patient has a high risk of developing a serious and potentially avoidable disease.
- Appreciate the advantages and disadvantages of referring patients and their families to associations or support groups.
- Recognize their own limitations and seek help when necessary.

SYLLABUS

Theory

Topic 1. Concept and history of genetics

The science of genetics. Brief history of genetics. Mendel. Areas of genetics. Human genetics, medical genetics, molecular genetics, biochemical genetics, cytogenetics and clinical genetics. Phenotype and genotype. Examples of genetics in medicine. Proportion of the population affected by monogenic, chromosomal and multi-factor alterations. Current organizational and financial aspects of the health system with respect to genetics.

Topic 2. The human genome and gene structure and expression

Composition of the human genome. Nuclear genome and mitochondrial genome. Organization of the genome sequence and the number of genes. Structure of gene. Exons. Introns. *Splicing*. Translation. Genetic code. Regulation of gene expression.

Topic 3. Replication, recombination and mutation of the genome

Cell cycle. Mitosis. DNA replication. Mutagens. Errors in DNA replication. Correcting errors. Mutation rates. Meiosis. Meiotic recombination. Concept of linkage. Consequences of non-homologous recombination.

Topic 4. Methodological bases of genetic analysis

Isolation of nucleic acids. Restriction enzymes. Generation of recombinants. Molecular cloning. PCR. Electrophoresis of nucleic acids. Southern blot analysis. DNA sequencing.

Topic 5. Current state of information regarding the human genome

The genome project. Available results and information drawn from analysis of the genome. Research applications. Consulting databases of genome information and obtaining genetic information. OMIM (*Online Mendelian Inheritance in Man*) and other databases. Medical and clinical applications.

Topic 6. Patterns of monogenic inheritance

Autosomal dominant inheritance. Autosomal recessive inheritance. X linked inheritance. Recognizing the different types of inheritance. Calculating risks of transmission in monogenic inheritance

Topic 7. Aspects of phenotypic expression and non-classical patterns of monogenic inheritance

Penetrance. Expressivity. Age of onset. Pleiotrophy. Sex-related phenotypes. Mitochondrial inheritance. Somatic mosaicism. Germinal mosaicism. Gene imprinting: Prader-Willi and Angelman syndromes. Uniparental disomy. Inactivation of the X chromosome. Dynamic mutations.

Topic 8. Genes in populations

The human population. Hardy-Weinberg law. Hardy-Weinberg equilibrium. Factors which modify the Hardy-Weinberg equilibrium and the consequences: stratification, non-random mating, consanguinity, natural selection, genetic drift, bottlenecks, founder effect, migration. Applications of the Hardy-Weinberg law. Risk calculation.

Topic 9. The examination in clinical genetics

Family tree and family interview. Physical examination in clinical genetics. Dermatoglyphs. Complementary tests. Sources of information and consultation. OMIM. Searching for analysis laboratories.

Topic 10. Cytogenetic tests

Human karyotype. Methodological approach. Chromosome banding. Identification of chromosomes. Chromosomal polymorphisms. Fluorescent *in situ* hybridization (FISH). Comparative genome hybridization (CGH).

Topic 11. Chromosomal alterations: autosomal and gonosomal disorders

Numerical alterations: polyploidy, aneuploidy and mosaicism. Structural alterations: deletion, duplication, inversion, translocation, ring, isochromosome. Mechanisms of production. Autosomal disorders: general aspects, incidence, and clinical description and cytogenetics of the most common forms. Gonosomal disorders: Turner's and Klinefelter's syndromes.

Topic 12. Sex determination, embryo development and alterations associated with reproductive failure

Sex phenotype and criteria for assigning sex. Differentiation of the primitive gonad. Sex chromosomes. SRY gene. Intersexual and hermaphroditic states. Androgen receptor. Genes involved in embryo development and main alterations. Human infertility. Microdeletions in chromosome y, Klinefelter's syndrome and agenesis of the vas deferens. Infertility in women. Deficit of 21-hydroxylase. Reproductive consequences of balanced translocations.

Topic 13. Disorders linked to chromosome X

Criteria for recognizing X linked inheritance. Name and examples of X linked disorders. Alterations of colour vision. Haemophilia. Fragile X syndrome.

Topic 14. Autosomal dominant disorders

Criteria for recognizing autosomal dominant disorders. Name and examples of autosomal dominant disorders. Huntington's disease. Familial hypercholesterolemia. Familial and pre-senile Alzheimer's disease.

Topic 15. Autosomal recessive disorders

Criteria for recognizing autosomal recessive disorders. Name and examples of autosomal recessive disorders. Cystic fibrosis. Hereditary haemochromatosis. Recessive metabolic disorders. Phenylketonuria. Lactic acidosis.

Topic 16. Polygenic and multi-factor inheritance

Concept of complex and multi-factor disorder. Determining the genetic basis in multi-factor inheritance. Polygenic theory of quantitative characteristics. Polygenic theory of discontinuous characteristics. Threshold. Empirical risk: concept and uses. Search for susceptibility loci. Association studies. Analysis of sibling pairs. Transmission disequilibrium test (TDT). Name, frequency and examples of multi-factor disorders. Non-familial senile Alzheimer's disease.

Topic 17. Cancer

Oncogenes and tumour suppressor genes. Mechanisms of oncogene activation: amplification, point mutation, translocation and the formation of chimeric genes. Translocation t(9;22) and chronic myeloid leukaemia. Suppressor genes. Retinoblastoma. Familial cancers. Loss of heterozygosity. Methylation. Control of the cell cycle. DNA repair defects. Control of genome integrity. Microsatellite instability. Telomerase activity. Colorectal cancer. Breast cancer.

Topic 18. The genetics of certain physiological processes

Expression of globin genes in the embryo, foetal and post-natal stages. Thalassemia. Genetics of pigmentation: melanocytes and melanosomes. Pro-opiomelanocortin. Albinism. Waardenburg's syndrome. Adipose tissue. Regulation of body weight. Obesity. Changes of gene expression through exercise. Muscular hypertrophy. Duchenne's muscular dystrophy. Genetics of ageing. Progeria.

Topic 19. Prevention of genetic-based disorders; genetic counselling

Detecting high-risk families and individuals. Population screening. Pre-symptomatic diagnosis. Pre-test and post-test risks. Prenatal and neonatal diagnosis: general aspects, description and indications. Genetic counselling.

Topic 20. Treatment of inherited diseases

Current state of treatment of inherited diseases. Possible treatment strategies. Organ transplants. Gene therapy. Pharmacological modification of gene expression. Protein replacement. Metabolic intervention: dietary restrictions, supplements, inhibition and elimination. Surgical correction. Assisted reproduction techniques. ICSI. Ethical and legal aspects of gene therapy and new treatment techniques.

Practical classes

1. Obtaining and interpreting the karyotype

Methodology for obtaining metaphases. Nomenclature of chromosomes and chromosome bands. Normal karyotype. Identifying the most common karyotype alterations (45,X; 47,XXY; 47,XX, +21; translocation 13:14)

2. Amplification by PCR, digestion, PCR and interpretation of genotyped results obtained via PCR-RFLP and PCR-SSCP

Methods available for detecting mutations and polymorphisms. Interpreting the results of PCR, PCR-RFLP and PCR-SSCP analyses. APOE alleles, polymorphism. Insertion/Deletion of the ECA gene, C282Y and H63D alleles of the HFE gene.

3. Obtaining and interpreting the results of DNA sequencing

Methodology of DNA sequencing. Automatic sequencers. Interpreting electropherograms in the identification of mutations or polymorphisms. Identifying polymorphisms. Insertion/Deletion of the ECA gene.

4. Drawing up a family tree. The clinical history in human genetics

Obtaining a family tree. The family interview in human genetics. Methods of physical examination. Requesting complementary tests. Using internet to search for laboratories that conduct molecular tests.

5. Interpreting the clinical history in medical genetics

Reading the clinical history in a chronological and structured way. Action to be taken at the different stages of the clinical assessment and genetic counselling process. Information search.