PERMANENT EDUCATION COURSE IN HUMAN GENETICS

UNIVERSITY CERTIFICATE

Permanent Education with University Certificate in Human Genetics

Rationale

Human genetics is a relatively young medical discipline which originated in the sixties with the demonstration of chromosomal anomalies in constitutional and acquired disorders. The discipline experienced a rapid growth with the development of DNA analytical methods which enabled the identification of several genetic, mainly monogenic, disorders. At present, human genetics experiences another growth spurt due to the development of genome-wide analysis tools, high capacity mutation detection methods leading towards complete human genome sequencing. This evolution leads to an ever increasing relevance within all medical disciplines. The current technologies not only enable to identify inherited Mendelian disorders, but also increase our understanding of complex diseases. Human genetics not only enables diagnosis, but is leading more and more to improved guidance and treatment.

From this ever increasing importance and complexity, the Belgian Society of Human Genetics identified the need for a course which provides a theoretical basis for human genetics at a postdoctoral level. The members of the society represent the eight Belgian human genetics centers as well as scientists and professionals involved in human genetics.

The postgraduate course in human genetics intends to fulfill the need of a growing number of professions in which a full theoretical basis of all aspects of human genetics is useful or required. In the industry, health care, diagnostics as well as in certain areas of research, such knowledge is wanted. Within the Belgian genetics centers, the course will provide a uniform and adequate theoretical basis for all those taking up responsibilities in human genetics-related activities.

Aims

This permanent education in human genetics aims to

- Cover all aspects of human genetics
    - Clinical genetics
    - Molecular genetics
    - Cytogenetics
    - Biochemical genetics
- Bring an up-to-date program embedded within the current practices
- Deliver a certificate acknowledging a robust knowledge basis in human genetics

Target students

The course is aimed at

- Everyone taking up a responsible function in a genetic center
- Professionals in industry involved in or with human genetics
- Pharmaceutical industry involved in human genetics
- Postdocs/PhD students with interest in human genetics
- MDs involved in human genetics

Prerequisites

Participants hold

- A masters/licentiaats/license degree, or MD degree
- Some knowledge of molecular biology

Organisation

The course outline is based on the book Genetics in Medicine (Thompson & Thompson, Seventh edition). The course chapters will be tought by representatives of the 8 human genetic centers in Belgium, localized at or associated with 8 different universities. The courses will take place on the first or second Saturday of each month. A final examination will take place on a 9th Saturday. Each center for human genetics is responsible for the organization of the course at its University.

Evaluation and certificate

To obtain the certificate in human genetics the candidate will take an examination at the end of the course program. This written test will cover the different topics presented during the course. The POC is made up of eight members, representing each Belgian University. The POC consists of a working group of the Belgian Society of Human genetics. The certificate will be approved by the BeSHG and will be delivered by the University at which the student registered.

Credit points (ECTS)

The course entails 60 contact hours + exercises in human genetics. The total course sums up to **10 ECTS (credit points)**

REGISTRATION

Registration is finalized following: entering registration details at the BeSHG website. Paying the registration cost of the course is **200 Euro.** Registrations are open in each university / human genetics center, from 15/9/08 to 01/10/08.
200 Euros can be deposited at :

"**BeSHG – Course**", account No: **001-5643252-62** (Fortis Bank).
Communication: **Last name, First name, University or Center** (e.g.: DELVAUX André ULB)
!! those details in the payment's "communication" are mandatory for the registration to be efficient !!

The registrants will subsequently be registered at the University they entered when paying.

Registration Contacts:

- ULB : mwernaers@ulb.ac.be, 02 5554145
- VUB :

- ULg :
- UGent :
- KUleuven : rita.logist@med.kuleuven.be, KUL
- UCL : liliana.niculescu@uclouvain.be, 02-764 7490IPG :
- UA :

For practical reasons we can only accept 50 students.
Registration will be effective when payment is received.

Course overview

DAY 1 : 04 October 2008, KULeuven
Location: U.Z.Gasthuisberg, O&N2, Room BMW3

9:30-11:00 ***The human genome and the chromosomal basis of heredity***

Basic concepts (Thierry Voet)

Introduction: The chromosome
The 3D nucleus
Mitosis
Meiosis

11:00-13.00 Human genome: gene structure and function (Gert Matthijs)
Gene structure and function
Gene regulation and activity

14:30-17:30 ***Tools of human molecular genetics***

Mutational analysis (Harry Cuppens)
Sequencing (Harry Cuppens)
Molecular cytogenetics tools (Joris Vermeesch)
Bioinformatic tools: Human genome browsers & its applications to clinical genetics (Joris Vermeesch)

DAY 2 08 November 2008 ULB,
Aud F.2-104, Campus Erasme, 808 Lennik St, 1070 Brussels

9:30-11:00 ***Patterns of single gene inheritance***
(Marc Abramowicz)
Monofactorial genetic diseases. Penetrance, expressivity. Dominant, recessive, and X-linked inheritance, and why these models are approximations. Incidence and prevalence. Pseudoautosomal inheritance. Lyonisation (partly). Mitochondrial inheritance (partly). Anticipation. New mutations. Germ-line and soma. Somatic mosaics, germ-line mosaics. Pedigrees. Intrafamilial and interfamilial variation. Genetic background.

Consanguinity, chances of homozygosity by descent. Consanguinity as common traditional practice. Inbred communities. Pseudodominance. Founder effect, overdominance. Uniparental disomy.

Genetic variation in individuals and populations: mutation and polymorphism
(Marc Abramowicz)
The life and death of a highly penetrant mutation (hemophilia). Wild type alleles, mutated alleles. The concept of neutral polymorphisms and minor mutations. Blood groups as an example of polymorphism. SNPs. CNVs. Hardy-Weinberg equilibrium, and factors that disturb it. Metapopulation. Mutations and diversity by change. Meiosis and diversity by assembly. Biological fitness. Positive and negative selection. Divergence and diversity.

The history of DF508. Most recent common ancestors. Coalescence. A schematic overview of the ascent of man. Gene tree, species tree. Trans-species polymorphisms. The "common disease, common variant" hypothesis. Haplotype blocks. HapMap. Effective population size. The special case of the Y chromosome.

Epigenetics (François Fuks)

1. Chromatin structure

1.a. Notions of chromatin structure.
1.b. Post-translational modifications of histones
1.c. DNA methylation: definition
1.d. Biological significations of epigenetics

2. Epigenetics : mechanistic insights

2.a. Crosstalks between histones modifications et DNA methylation: the histone code hypothesis
2.b. Targeting and regulation of DNA methylation

3. Epigenetics and human diseases

3.a. DNA methylation and cancer
3.b. DNA methylation and neurodevelopmental syndromes (Rett and ICF)
3.c. Deacetylase and DNA methyltransferases inhibitors as anti-cancer epigenetic drugs

Last session = 16:30-17:30

DAY 3: 06 December 2008, Ugent

Human gene mapping and disease gene identification

Mapping of human genes: principles and applications (Paul Coucke, Jan Hellemans and Andy Willaert)

Practical exercises with lod score calculations (Paul Coucke, Jan Hellemans and Andy Willaert)

The molecular, biochemical and cellular basis of genetic disease

General introduction (Geert Mortier)

Examples of monogenic diseases caused by mutations in different classes of proteins:

Inborn errors of metabolism (Jules Leroy)

Mutations in developmental genes (Elfride De Baere)

Mutations in extracellular matrix proteins (Fransiska Malfait, Anne De Paepe)

Mutations in signaling pathways (Bart Loeys)

DAY 4: 10 January 2009, IPG

Clinical cytogenetics: disorders of the autosomes and the sex chromosomes (I. Maystadt and Ch. Verellen- Dumoulin)

Sex chromosomes and their abnormalities:

Cytogenetics and molecular cytogenetics of X and Y chromosomes (K. Rack and B. Grisart)
Molecular diagnosis of X and Y chromosomes (P. Hilbert)

The treatment of genetic disease

The treatment of genetic disease (I. Maystadt, P. Ribaï, D. Roland, Ch. Verellen-Dumoulin)

DAY 5: 07 Febr 2009 (UCL)

Auditoire central E, UCL-Cliniques universitaires St-Luc, Avenue Mounier, 51, B-1200 Brussels
(by metro: line 1B towards Stockel, ALMA station)

9:30-17:30
Cancer genetics and genomics

Hereditary cancers

Introduction (Dr. Catherine Sibille)

Breast/ovarian cancers (Dr. Catherine Sibille)

Pediatric cancers (Dr. Catherine Sibille)

Colon cancers (Dr. Karin Dahan)

Acquired cancers

Introduction (Dr. Hélène Antoine-Poirel)

Hematological malignancies (Dr. Hélène Antoine-Poirel)

Brain tumors:(Prof. Catherine Godfraind)

Developmental genetic

Genetic aspects of development

Nephrological disorders (Prof. Olivier Devyust & Dr Karin Dahan)

Vascular anomalie (Prof. Miikka Vikkula)

Cleft lip and palate (Prof. Miikka Vikkula)

Ethical issues in medical genetics

Genetics and society glossary

Introduction (Dr. Karin Dahan & Catherine Sibille)

Round table with 3 invited speakers (to be confirmed):
Prof. Gert Matthijs (pattent of human genes, KUL)
Prof. Geneviève Schamps (medical and bioethical law, UCL LLN)
Prof. Marie-Luce Delfosse (bioethical guidelines, FNDP Namur)

DAY 6/ 07 March 2009, UA: "Promotiezaal" (Building Q)

Genetics of common disorders with complex inheritance

Elementary concepts (Bettina Blaumeiser)

Qualitative traits: Familiality (λ_s), case-control studies, carter effect, twin studies

Quantitative traits: Normal distribution, heritability
Examples of multifactorial disorders
Alopecia areata, neural tube defects, cleft lip-cleft palate

State-of-the-art approaches and technologies to study complex diseases (Wim Van Hul, Guy Van Camp)

Linkage analysis for complex diseases

Association studies: From candidate gene to whole genome association, linkage disequilibrium, HAPMAP

Statistical issues: Multiple testing, stratification, confounding factors, Hardy-Weinberg equilibrium, interactions

Technology: SNP genotyping, high density microarrays, resequencing platforms, copy number variants

Examples of successful research

Animal models

Frank Kooy

1) Why animal models
2) Which animal models are available
3) What is a laboratory mouse; concept of a strain
4) Principles of Strain nomenclature
5) The mouse genome; karyotype but emphasis on molecular genome architechture
6) Standard strains, inbred, outbred, wild mice; differences among those
7) Types of mouse crosses, F1, N2, backcross intercross, advanced intercross, , etc; what is the relevance of each cross and when to use each of those.
8) Coisogenics, congenics, recombinant imbred, collaborative cross and other specialized strains
9) Mouse gene nomenclature, genetic marker nomenclature
10) Types of knockouts, conditional knockouts and transgenics?

11) Chemical mutagenisis and repositories (incl. Jackson), gene-specific mutagenesis databases.
12) Mouse genome projects

The aims of this part are to introduce the audience to the concept of a laboratory mouse and its genetics with emphasis on the genome composition ("genetic background") and mutants. Strain and gene nomenclature will be introduced. The importance of strain selection for the experimental setup will be discussed. Types of crosses with examples how these have been used in biomedical reseach are mentioned. Types of knockouts and transgenics will be shown.

Course based on:

Lee M. Silver, Mouse genetics, concepts and applications. Oxford Univ press, 1995
&
James G. Fox *et al.*, The mouse in biomedical research, 2nd ed., part 1, History, wild mice and genetics. Academic press, 2007.

Alternative: mouse model less detailed and expand to Drosophila/zebrafish

Bioinformatics

Practical course in computer class (Wim Wuyts)

1) Demonstration starting from ENSEMBL genome browser with various input data (gene name, genomic region, …). Illustration of various links (OMIM, Gene, Genbank,…..)

2) Analysis of unknown variants (dbSNP, SIFT, POLYPHEN, HGMD, splice prediction programs, ESE finder

3) HAPMAP

4) Practical excercises (limited number of excercises from which participants can choose).
   - analysis of nucleotide substitutions in a gene (pathogenic or not?)
   - defining TAG SNPS for a gene
   - Evaluation of a genomic region (gene fishing)

DAY 7: 4 April 2009, ULg

Pharmacogenetics and pharmacogenomics

Pharmacogenetics (Vincent Bours)
course will be based on 2 updated papers :

Inheritance and Drug Response by Richard Weinshilboum. New England Journal of Medicine, 2003.

Pharmacogenomics - Drug Disposition, Drug Targets, and Side Effects by WE. Evans, and HL. McLeod, New England Journal of Medicine, 2003.

- metabolic enzymes and polymorphisms.
- Polymorphisms and drug transporters and targets.
- Genetic conditions generating unexpected side effects.
- Ethnic differences and clinical consequences.

Birth defects (Lionel Van Maldergem).

Clinical aspects and nosography (Pr L Van Maldergem 30')

Illustration of genotype-phenotype relationships and a way from the birth defects to pathophysiologic mechanisms

1 - helicase-deficient syndromes (lvm 45')

2 - example of two dermatological conditions : lipodystrophies and cutis laxa syndromes (lvm 45')

The immune system

Immune genetics (Prof M. Moutschen, Vincent Bours, Hélène Poirel (UCL))

The HLA complex .

inherited immune defects.

Gene therapy in relation with immune defect.

acquired alterations of IGH and TCR loci in lymphoproliferative disorders.

DAY 8: 09 May 2009, VUB

Prenatal diagnosis

Non-invasive testing

Ultrasound (Prof W Foulon)

Biochemistry (Dr E Ankaert)

Invasive testing

Indications (Dr K. Keymolen)

Methods (Prof W Foulon)

Laboratory investigations

Cytogenetics (Dr Sci C. Staessen)

DNA (Dr Sci W. Lissens)

Biochemistry (Dr Sci W. Lissens)

Preimplantation genetic diagnosis (Prof K. Sermon, Prof I.Liebaers)

Genetic counseling and risk assessment

Indications for genetic counselling (Prof I. Liebaers)

Genetic counselling providers (Prof I. Liebaers)

Determining recurrence risks (Prof M. Bonduelle)
- Mendelian conditions
- Conditional probability
- Empirical recurrence risks

Molecular tools in determining recurrence risks (Dr Sci S. Seneca)

Managing the risk of recurrence in families (M Vanhorenbeeck, Nekkebroeck)

ADDITONAL WORK

Critical reading with written report and oral presentation, and/or Exercises on: Genetic risk calculation; segregation analysis; LOD scores; Genome-wide p-values; the use of online genetic databases; genetic counseling; sequence comparison; chromosomal aberrations; other topics. Each to be performed at University / Center of registration.

FINAL EXAMINATION

June 6th: ***(KUL)***