INTRODUCTION TO GENETIC EPIDEMIOLOGY

(EPID0754)

Prof. Dr. Dr. K. Van Steen

(February 2012)

CHAPTER 1: SETTING THE PACE

1 Course Responsible

Contact details

2 Administrative Issues

Course details and examination methods

3 Exploring the Scene

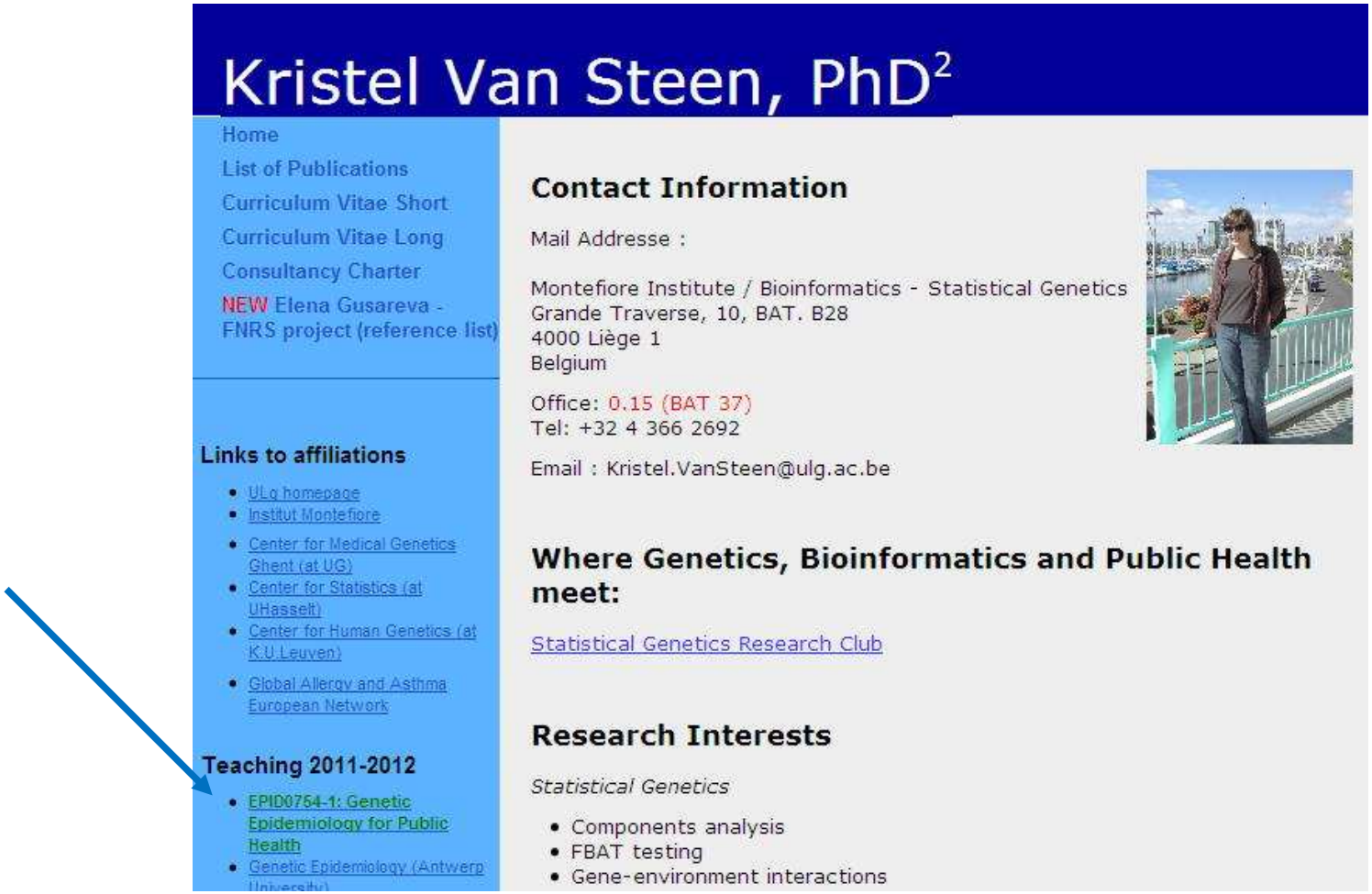
Expectations

4 Medical Genomics

Recent evolutions in medical genomics

5 “First-class” discussion document

1 Course Responsible



Contact details via

www.montefiore.ulg.ac.be/~kvansteen

Questions or remarks via e-mail

kristel.vansteen@ulg.ac.be

Use “genetic epi” in header when sending a mail to ask questions or to make a face-to-face appointment for a meeting

2 Administrative Issues

Learning outcomes

Acquis d'apprentissage (objectifs d'apprentissage) du cours	Learning outcomes of the course
Familiariser les étudiants avec les différentes facettes de l'épidémiologie génétique, avec une emphase à la génétique statistique.	To familiarise students with the different facets of genetic epidemiology, with an emphasis on statistical genetics.
Prérequis et corequis / Modules de cours optionnels recommandés	**Prerequisites and co-requisites/ Recommended optional programme components**
Connaissance de base de concepts de statistiques. Les termes génétiques seront répresentés.	Basic knowledge of statistical concepts. Genetic terms will be re-introduced.
Activités d'apprentissage prévues et méthodes d'enseignement	**Planned learning activities and teaching methods**
Travail personnel par l'intermédiaire des tâches de lecture, homeworks et plus grands projets, à l'aide principalement des outils de Bioconductor dans le logiciel libre R. Les informations seront disponibles sur la page www.montefiore.ulg.ac.be/~kvansteen/	Personal work through tasks set during lectures, homework and larger projects, with the help primarily of Bioconductor tools using the 'R' open source software. Further information is available at www.montefiore.ulg.ac.be/~kvansteen/
Mode d'enseignement (présentiel ; enseignement à distance)	**Mode of delivery (face-to-face ; distance-learning)**
2eme semestre. Le cours sera interactif dans anglais/français. Slides en anglais. Devoirs peut être en français. Les examens ont organisés en français. Toutes les modalités pratiques du cours seront disponibles sur la page www.montefiore.ulg.ac.be/~kvansteen/	2nd semester. The course will be interactive in English/French. All course notes are in English. Homeworks can be handed in in French. Examination will be in French. All practical details about the course will be available at www.montefiore.ulg.ac.be/~kvansteen/
Lectures recommandées ou obligatoires et notes de cours	**Recommended or required readings**
Slides en anglais (www.montefiore.ulg.ac.be/~kvansteen/)	English-language slides via www.montefiore.ulg.ac.be/~kvansteen/

Course website

Teaching 2011-2012

EPID0754-1 : Introduction à l'épidémiologie génétique

SOME PRACTICAL ARRANGEMENTS:

- When does the first class take place?
  - Wednesday February 8.
  - If you have a laptop, please bring it to the class.
  - No other material is necessary. This will be a class to discuss the set-up of the future classes, to discover the background knowledge, to talk about your expectations and wishlist for these classes, and to start with a gentle introduction on some concepts and terms

- When do the next classes take place?
  - Click here for an updated course schedule

    Updated (21 February !!!)

- Where do the classes take place?
  - room 11 (B23 RDC)

- What about homeworks?
  - Click here for some guidelines

- What if I have additional questions?
  - Consult Kristel Van Steen (kristel.vansteen@ulg.ac.be) before or after class or by e-mail. In order for the mail not to get lost, please mention "epidemiology course" in the header

Course website

FOR FUTURE CLASS MATERIAL DOWNLOADS (use 7-Zip to unpack zipped files):

INFORMATION BY CLASS:

8 February 2012 - CLASS 1 : 1pm-3pm

- Course notes: Chapter 1
  - Downloading instructions R and Bioconductor: Follow this link
- In class reading:
  - Paper: Genetic epidemiology and public health
  - Assignment on Mendelian randomization
    Updated (7 February !!!)

8 February 2011 - CLASS 2 : 1pm-3pm

Please bring your laptop to the class

- Course notes: Chapter 2
  - Downloading instructions R and Bioconductor: Follow this link
  - Information on using R:
    - Part 1: R manuals
    - Part 2: Basic Commands !!!
    - Part 3: An introduction to R
    - Part 4: Advanced
- Background reading (series 1):
  - Paper 1: Genetic link to ageing
  - Paper 2: Genetics of telomere length
  - Paper 3: The epigenetic regulation of mammalian telomeres
- Background reading (series 2):

Course organization

	HW1	HW2	HW3	HW4	Participation	Written /Oral Exam	Total
Max	**10**	**10**	**10**	**10**	**10**	**10/40**	**100**

Written = exam project, combining HW1-4

Oral = starting from written exam project and "themes"

(questions are based on "in-class reading" questions)

Course outline

CHAPTER 2: INTRODUCTION TO GENETICS

1 Basics of molecular genetics

2 Overview of human genetics

CHAPTER 3: DIFFERENT FACES OF GENETIC EPIDEMIOLOGY

1 Basic epidemiology

2 Genetic epidemiology

3 Phenotypic aggregation within families

4 Segregation analysis

5 Genetic epidemiology and public health

CHAPTER 4: BASIC POPULATION GENETICS

1 What is means and doesn't mean

2 How does evolution take place?

3 Distributions of genotypes in human populations

4 Natural selection revisited

5 Inbreeding

6 Fitness

CHAPTER 5: POPULATION BASED ASSOCIATION STUDIES

CHAPTER 6: FAMILY-BASED GENETIC ASSOCIATION STUDIES

1 Setting the scene

2 Families versus cases/controls

3 From complex phenomena to models

4 Family-based screening strategies

5 Validation

CHAPTER 7: TRAVELLING THE WORLD OF INTERACTIONS

1 Beyond main effects

2 Multifactor dimensionality reduction

3 Future challenges

Course schedule

Theory	Date	In class time	In class time2 (optional)	Topic of the Day	Practicals:	Due Date and Description
Salle 11 (B23 RDC)	8-févr	13-15		CH1: Setting the Pace		
Salle 11 (B23 RDC)	8-févr	15-17		CH2: Introduction to Genetics; Introduction to R		
Salle 11 (B23 RDC)	15-févr	13-15		CH3: Different Faces of Genetic Epidemiology	HW1 due 29/2	data extraction/exploration
Salle 11 (B23 RDC)	22-févr	13-15		CH4: Basic Population Genetics: HWE and LD	HW2 due 28/3	population genetics analysis
Salle 11 (B23 RDC)	29-févr	13-15		CH5: Population-Based Association Studies Population-based association studies using R	HW3 due 28/4	population association analysis
Salle 11 (B23 RDC)	7-mars	13-15	Time for practical	Common good practice in genetic association studies Mapping complex disease genes with linkage disequilibrium		
Salle 11 (B23 RDC)	28-mars	13-15		CH6: Family-Based Association Studies Family-based association studies using fbat	HW4 due 2/5	family-based association analysis
Salle 11 (B23 RDC) Salle 11 (B23 RDC)	18-avr	13-17	 Time for practical	CH7: A world of interactions Multi-locus analysis using fbat	 Exam project (*)	
Salle 11 (B23 RDC)	25-avr	13-15		The epidemiology side of gene-gene and gene-environment interactions		
Salle 11 (B23 RDC)	2-mai	13-15		Miscellaneous / loose ends		
?	?	?	exam project (*) / recap			

(*) exam project:

On May 15, I will communicate what the causal SNPs and interacting loci in the data are.
Based on this knowledge, you will now be able to better interprete the findings of the homeworks
The reflection of your summary conclusions and understanding of the analysis results, needs to be written down in a brief report (written exam)
You will have the opportunity to motivate these reflections in person as well (oral exam)

HOMEWORKS COUNT FOR 40% OF MARKS

History on different student populations for the course

15 T / 15 P

Master en bioinformatique et modélisation, à finalité approfondie, 2e année

Master en statistiques, orientation générale, à finalité spécialisée, 2e année

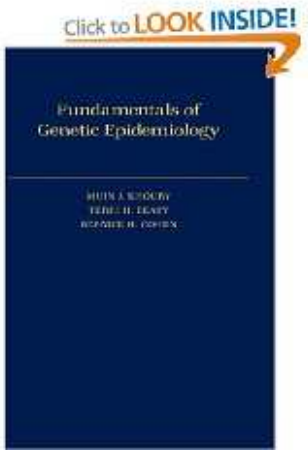
Master en ingénieur civil biomédical, à finalité approfondie, 2e année

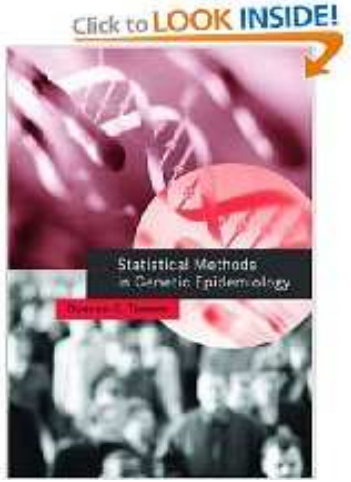
20 T / 20 P

Master en sciences de la santé publique, à finalité spécialisée en épidémiologie et économie de la santé, 2e année

Course material

- Check out course website for slides and assignments
- These slides are comprehensive enough for the subset of material that will be covered in class
- For those who are interested, key references are provided as well.





3 Exploring the Scene

Round-Table Discussion

Q1: What is your background? What is your thesis about? What do you want to achieve in your professional life?

Q2: Have you analyzed data before? How? Which tools have you used? What was the most difficult part? Data manipulation? Interpretation? Implementation?

Q3: What is epidemiology?

Q4: What do you think genetic epidemiology includes? Personalized medicine?

Q5: What are your expectations of this course? What would you really like to do in this course?

4 Medical Genomics

Genomics Primer from Mayo Clinic Proceedings

Mayo staff have authored several articles that will be useful for anyone developing a thorough understanding of medical genomics. These articles have been published as a series in the Mayo Clinic Proceedings journal. The following sections have been copied from their website:

http://mayoresearch.mayo.edu/mayo/research/grc/proceedings.cfm

Part I: History of Genetics and Sequencing of the Human Genome

Cindy Pham Lorentz, MS; Eric D. Wieben, PhD; Ayalew Tefferi, MD; David A. H. Whiteman, MD; and Gordon W. DeWald, PhD

The first part of this overview gives an account of the history of genetics that spans from humankind's first attempts at understanding and influencing heredity, to the early scientific work in the field of genetics, and then to the advancements in modern genetics. The second part summarizes the Human Genome Project (HGP) from inception to the publishing of the "first draft" of the human genome sequence.

Part II: Background Principles and Methods in Molecular Genetics

Ayalew Tefferi, MD; Eric D. Wieben, PhD; Gordon W. DeWald, PhD; David A. H. Whiteman, MD; Matthew E. Bernard, MD; and Thomas C. Spelsberg, PhD

In this second part of an educational series in medical genomics, selected principles and methods in molecular biology are recapped, with the intent to prepare the reader for forthcoming articles with a more direct focus on aspects of the subject matter

Part III: Microarray Experiments and Data Analysis

Ayalew Tefferi, MD; Mark E. Bolander, MD; Stephen M. Ansell, MD, PhD; Eric D. Wieben, PhD; and Thomas C. Spelsberg, PhD

Genomics has been defined as the comprehensive study of whole sets of genes, gen products, and their interactions as opposed to the study of single genes or proteins. Microarray technology is one of many novel tools that are allowing global and high-throughput analysis of genes and gene products. In addition to an introduction on underlying principles, the current review focuses on the use of microarrays in gene expression analysis. … The current review should serve as an introduction to the subject for clinician investigators, physicians and medical scientists in training, practicing clinicians, and other students of medicine.

Part IV: Expression Proteomics

Animesh Pardanani, MD, PhD; Eric D. Wieben, MD; Thomas C. Spelsberg, PhD; and Ayalew Tefferi, MD

Proteomics, simply defined is the study of proteomes. The three broad areas are expression proteomics, which catalogues the relative abundance of proteins; cell-mapping or cellular proteomics, which delineates functional protein-protein interactions and organelle-specific protein distribution; and structural proteomics, which characterizes the 3-dimensional structure of proteins. This articles reviews the area of expression proteomics.

Part V: Bioinformatics

Peter L Elkin, MD

Bioinformatics is the discipline that develops and applies informatics to the field of molecular biology. Although a comprehensive review of the entire field of bioinformatics is beyond the scope of this article, I review the basic tenets of the field and provide a topical sampling of the popular technologies available to clinicians and researchers. These technologies include tools and methods for sequence analysis (nucleotide and protein sequences), rendering of secondary and tertiary structures for these molecules, and protein fold prediction that can lead to rational drug design. I then discuss signaling pathways, new standards for data representation of genes and proteins, and finally the promise of merging these molecular data with the clinical world (the new science of phenomics).

Part VI: Genomics and Molecular Genetics in Clinical Practice

Stephen M. Ansell, MD, PhD; Michael J. Ackerman, MD, PhD; John L. Black, MD; Lewis R. Roberts, MD, PhD; and Ayalew Tefferi, MD

An important milestone in medical science is the recent completion of a "working draft" of the human genome sequence. The identification of all human genes and their regulatory regions provides the framework to expedite our understanding of the molecular basis of disease. This advance has also formed the foundation for a broad range of genomic tools that can be applied to medical science. These developments in global gene and gene product analysis as well as targeted molecular genetic testing are destined to change the practice of modern medicine.

…

Despite these exciting advances, many practicing clinicians perceive that the role of molecular genetics, especially that of genomics, is confined primarily to the research arena with little current clinical applicability. The aim of the article is to highlight advances in DNA/RNA-based methods of susceptibility screening, disease diagnosis and prognostication, and prediction of treatment outcome in regard to both drug toxicity and response as they apply to various areas of clinical medicine.

Part VII: The Evolving Concept of the Gene

Eric D. Wieben, PhD

The draft sequence of the human genome was reported 2 years ago, and the task of filling gaps and polishing the sequence is nearing completion. However, despite this remarkable achievement, there is still no definitie assessment of the number of genes contained in the human genome. In part, this uncertainty reflects our growing understanding of the complexity and diversity of gene structure. Examples of complex gene structure are considered in the context of the discussion about the evolution of our understanding of gene structure and function.

Part VIII: Essentials of Medical Genetics for the Practicing Physician

Regina E. Ensenauer, MD; Shanda S. Reinke; Michael J. Ackerman, MD, PhD; David J. Tester; David A. H. Whiteman, MD; and Ayalew Tefferi, MD

After the mapping and sequencing of the human genome, medical professionals from essentially all specialties turned their attention to investigating the role genes play in health and disease. Until recently, medical genetics was considered a specialty of minor practical relevance. This view has changed with the development of new diagnostic and therapeutic possibilities. It is now realized that genetic disease represents an important part of medical practice. Achievements in cancer genetics, in the field of prenatal diagnostics (including carrier testing for common recessive disorders), and in newborn screening for treatable metabolic disorders reinforce the rapidly expanding role of genetics in medicine.

…

Diagnosing a genetic disorder not only allows for disease-specific management options but also has implications for the affected individual's entire family. A working understanding of the underlying concepts of genetic disease with regard to chromosome, single gene, mitochondrial, and multifactorial disorders is necessary for today's practicing physician. Routine clinical practice in virtually all medical specialties will soon require integration of these fundamental concepts for use in accurate diagnosis and ensuring appropriate referrals for patients with genetic disease and their families.

Part IX: Scientific and Clinical Applications of DNA Microarrays -- Multiple Myeloma as a Disease Model

John Shaughnessy, Jr., PhD

Multiple myeloma (MM) is a poorly understood and uniformly fatal malignancy of antibody-secreting plasma cells. …

This review discusses progress made in the development of molecular-based diagnostics and prognostics for MM through the dissection of the transcriptome of plasma cells from healthy individuals and patients with MM and other plasma cell dyscrasias.

Part X: Gene Therapy

Stephen J. Russell, MD, PhD; and Kah-Whye Peng, PhD

Gene therapy is defined as any therapeutic procedure in which genes are intentionally introduced into human somatic cells. Both preclinical and clinical gene therapy research have been progressing rapidly during the past 15 years; gene therapy is now a highly promising new modality for the treatment of numerous human disorders. Since the first clinical test of gene therapy in 1989, more than 600 gene therapy protocols have been approved, and more than 3000 patients have received gene therapy. However, at the time of writing this article, no gene therapy products have been approved for clinical use.

…

This article explains the potential clinical scope of gene therapy and the underlying pharmacological principles, describes some of the major gene transfer systems (or vectors) that are used to deliver genes to their target sites, and discusses the various strategies for controlling expression of therapeutic transgenes. Safety issues regarding clinical use of gene therapy are explored, and the most important technical challenges facing this field of research are highlighted. This review should serve as an introduction to the subject of gene therapy for clinician investigators, physicians and medical scientists in training, practicing clinicians, and other students of medicine.

5 "First-class" discussion document

- Marieke C.J. Dekker & Cornelia M. van Duijn (2003) Prospects of genetic epidemiology in the 21st century. European Journal of Epidemiology 18: 607–616

Review paper handling:

→ Genetic transmission of disease

→ Molecular basis of disease

→ Methods in genetic epidemiology

→ Genetic–epidemiologic research in families

→ Population-based studies

→ New developments

FYI: Last class discussion document

- Smith et al 2005. Genetic Epidemiology 7: Genetic epidemiology and public health: hope, hype, and future prospects. *The Lancet*, 366: 1484–98