A TOUR IN GENETIC EPIDEMIOLOGY

(GBIO0015-1)

Prof. Dr. Dr. K. Van Steen

(February 2010)

CHAPTER 1: SETTING THE PACE

1 Course Responsible

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1 Course Responsible

Kristel Van Steen, PhD[2]

Home
List of Publications
Curriculum Vitae Short
Curriculum Vitae Long
NEW: Consultancy Charter

Links to affiliations

- ULg homepage
- Institut Montefiore
- Center for Medical Genetics Ghent (at UG)
- Center for Statistics (at UHasselt)
- Center for Human Genetics (at K.U.Leuven)
- Global Allergy and Asthma European Network
- StepGen, cvba

Teaching 2009-2010

- GBIO0015-1: Genetic Epidemiology for Engineering / Stats
- EPID0754-1: Genetic Epidemiology for Public Health
- GBIO0009-1: Bioinformatique

Teaching 2008-2009

Contact Information

Dépt / Unité : Dép. d'électric., électron. et informat. (Inst.Montefiore) / Bioinformatique

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Belgium

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Research Interests

Statistical Genetics / Biostatistics

- (Genomewide) genetic association screening methodology
- Disovery of gene-gene interactions
- Multiple testing
- Missing data
- Multicollinearity
- Coarsened data
- Complex data analysis (Multivariate / Longitudinal / Family)
- Quality of Life data

Statistical Genetics Research Club

Mathematics

- Finite geometry
- Affine and Euclidean buildings

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

Course website

Teaching 2009-2010

GBIO0015-1 : A tour in genetic epidemiology

SOME PRACTICAL ARRANGEMENTS:

- When does the first class take place?
  - Friday February 12.
  - 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 (will be on February 11 !!!)

- Where do the classes take place?
  - room 1.123 (B28)
- 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

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

INFORMATION BY CLASS:

12 February 2010 : 2pm-4pm

Updated (February 11)

Course organization

Engagement pédagogique de la déclinaison de cours
GBIO0015-1

GBIO0015-1	A tour in genetic epidemiology [english version]
Durée :	15h Th, 15h Pr
Crédits/ECTS :	Master en ingénieur civil biomédical, à finalité approfondie, 2e année 3 Master en bioinformatique et modélisation, à finalité approfondie, 2e année 3 Master en statistiques, orientation générale, à finalité spécialisée, 2e année 3
Titulaire(s) :	Kristel VAN STEEN
Aperçu général :	Le cours constitue une première introduction à l'épidémiologie génétique. Afin d'en illustrer les différentes facettes, le cours couvre plusieurs facettes qui sont adressées par l'épidémiologie génétique, incluant: 1. introduction à la génétique, 2. les différents visages de l'épidémiologie génétique, 3. génétiques de population , 4. linkage disequilibrium, 5. approches statistiques de la génétique, 6. l'association génétique, basée sur la population, 7. l'association génétique, basée sur les familles
Objectif du cours :	Familiariser les étudiants avec les différentes facettes de l'épidémiologie génétique, avec une emphase à la génétique statistique.
Pré-requis :	Connaissances de base de concepts statistiques. Les termes génétiques seront représentés.
Travaux pratiques :	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: http://www.montefiore.ulg.ac.be/~kvansteen/TeachingGE20092010.html Par exemple (années précédentes):

Course outline

CHAPTER 2: INTRODUCTION TO GENETICS

1 Basics of molecular genetics

2 Overview of human genetics

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: 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	
1.123-B28	12 February	14-16		CH1: Setting the Pace + CH2: Basics of genetics		
1.123-B28	19 February	14-16		CH4: Basic Population Genetics: HWE and LD / intro R	HW1 due 26 February	data extraction/exploration
1.123-B28	26 February	14-16		CH5: Population-Based Association Studies	HW2 due 19 March	population genetics analysis
1.123-B28	19 March	14-16		Population-based association studies using R	HW3 due 2 April	population association analysis
1.123-B28	26 March	14-16		CH6: Family-Based Association Studies		
1.123-B28	2 April	14-16		Family-based association studies using R	HW4 due 23 April	family-based association analysis
1.123-B28	23 April	14-16		CH7: A World of Interactions		
1.123-B28	30 April	14-16		Multi-locus analysis and multi-factor dimensionality reduction	HW5 due May 14	interactions using machine learning
1.123-B28	7 May	14-16	exam project (*)	Recapitulation Class		

(*) exam project:

On May 14, 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)

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

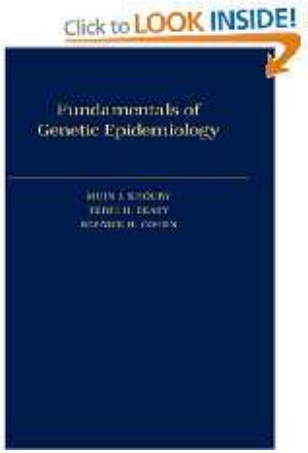
Master en ingénieur civil biomédical, à finalité approfondie, 2e année

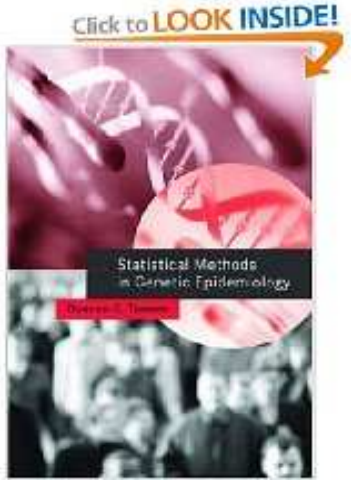
20 T / 20 P

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 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.

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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.

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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.

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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.