CHL5430: Fundamentals of Genetic Epidemiology

24 August 2010

CHL5430
FUNDAMENTALS OF GENETIC EPIDEMIOLOGY

SYLLABUS

When: Fall 2010; Thursdays 16:00-18:30. Lectures start Sept. 23 Note: The lectures for this course start later than most courses. This is to give you time to review background materials as needed. It is expected that you will attend the first lecture having reviewed some pre-requisite materials as needed (see below Block A “Additional reading materials”).

Where: Room: 618

Course coordinator and lead instructor
France Gagnon
HSB Room 662
416-978-0130
france.gagnon@utoronto.ca
http://www.phs.utoronto.ca/faculty_template_new.asp?GetFile=GFrance

Office hours: by appointment (out of town/office the following Thursdays: Oct 14, Nov. 4 & 25)

Lecturers
Steven Narod
steven.narod@wchospital.ca

Lyle Palmer
lyle.palmer@oicr.on.ca

Course description
This introductory course provides an overview of central concepts and topical issues in genetic epidemiology, providing an overall framework for investigating the role of genetic factors in the etiology of common complex disorders. This course integrates human genetics, biostatistics and epidemiology. The main course objective is to provide the common terminology and fundamental concepts underlying the design and conduct of genetic epidemiologic studies. Advanced and novel genetic epidemiology study designs and methods will not generally be discussed as this goes beyond the scope of the course. The students are expected to be active participants in their learning experience. Critical appraisal and presentation of selected scientific articles in the field will be a major component of the course, as well as in-class exercises.
Target audience & Prerequisites

Students with a strong interest in learning basic elements of genetic epidemiologic studies but with minimal or no formal training in the field. This is a required course for trainees of the CIHR STAGE (Strategic Training for Advanced Genetic Epidemiology) program. Aiming for a group size of 8 students. Prerequisites: Introduction to Epidemiology (CHL 5401), Biostatistics (CHL 5201), or equivalent. Students who have not taken these courses must discuss their eligibility with the course coordinator.

Specific goals

1. The students will have basic understanding of the fundamental principles and concepts underlying the main study designs and methods used in genetic epidemiologic research, and their specific objectives

2. The students will have some level of critical appraisal skills for the interpretation of scientific articles in the field of genetic epidemiology

Required readings: Articles listed for each blocks. Note that some weeks will require more reading than others. Be prepared. Additional and/or more advanced reading materials also included.

A few useful – but not required - textbooks


DETAILED COURSE OUTLINE

Block A – Introduction and overview of study design types in genetic epidemiology
What are the main goals in genetic epidemiologic studies? What are the main steps in genetic epidemiologic studies? What is the basic vocabulary used in genetic epidemiology?

September 23 (France Gagnon)
- Presentation of the course syllabus and dialogue re. learning outcomes, students & instructors’ expectation
- Fundamental genetic terminology/biology; Complex phenotypes/traits
- Introduction to genetic epidemiologic research objectives and tools

Required reading materials
1. Burton PR, Tobin MD, Hopper JL (2005) Key concepts in genetic epidemiology. Lancet 366: 941-951. (First article from a series of 7 on Genetic Epidemiology; The whole series is a nice overview of basic concepts in the field of genetic epidemiology)

Additional reading materials as needed
1) A genetic textbook (or other reliable tools such as chapter 1 of Ziegler A and König IR (2006) to answer questions such as:
   a. Where is the genetic information located?
   b. What does the genetic information mean?
   c. How is the genetic information translated?
   d. How is genetic information transmitted from generation to generation?
   e. How do individuals differ with regard to their genetic information?
   f. How can individual differences be detected?
2) Biostatistics and epidemiology textbooks to review the following concepts:
   a. Population and sample
   b. Parameters and statistics
   c. Descriptive statistics
   d. Measurement scale
   e. Random variables
   f. Probability distribution
   g. Hypothesis testing
   h. Type I error
   i. Power
   j. Sample size
   k. Estimation of a population parameter
   l. Modeling
   m. Case-control & cohort designs
   n. Risk factors/determinants of health
o. Measure of disease frequency and association
p. Bias
q. Confounders
r. Effect modifier/interaction

Website with a comprehensive list of pedagogical references in genetic epidemiology
M. Tevfik DORAK website: http://www.dorak.info/epi/genetepi.html
Block B – Segregation studies

September 30 (Steven Narod)
& October 7 (France Gagnon)

Segregation studies: What is the nature of the genetic determinants involved in the disease/trait?

- Simple segregation analysis & Family ascertainment (Narod)
- Complex segregation analysis (Gagnon)

- Weekly critical appraisal of an article (Journal Club format – presentation & discussion/critical appraisal led by a student): Segregation analysis studies

Required reading materials


Additional & Advanced reading materials


Block C – Linkage studies

October 14 (Steven Narod) & 21 (France Gagnon)

Linkage studies: Where are these genetic determinants located on the genome?

- Model-based (Parametric) linkage analysis (Narod)
- Model-free (Non-parametric) linkage analysis (Gagnon)

- Weekly critical appraisal of an article (Journal Club format – presentation & discussion/critical appraisal led by a student): Linkage analysis studies

Required reading materials


Additional & Advanced reading materials


3. Gagnon F, Jarvik GP, Badzioch MD, Motulsky AG, Brunzell JD, Wijsman EM (2005) Genome scan for quantitative trait loci influencing HDL levels: evidence for multilocus inheritance in familial combined hyperlipidemia. Hum Genet 117:494-505. (Joint oligogenic linkage and segregation analysis - Just for the fun of knowing a bit more about what else is out there!)

Block D - Observational Epidemiology studies

October 28 & November 4 (Lyle Palmer)

Observational Epidemiology studies: Do genetic determinants play a role in the disease expression?

- Population level
  - Migrant studies
  - Admixture studies
  - Inbreeding studies
- Family level
  - Family studies
  - Twin studies
  - Adoption studies
- Individual level (e.g. candidate gene studies)

- Weekly critical appraisal of an article (Journal Club format – presentation & discussion/critical appraisal led by a student): Observational epidemiology studies

Required reading materials


Additional and Advanced reading materials
**Block E – Genetic Association studies**

**November 11 & 18 (Lyle Palmer)**

What are the causal variants?
- Association studies in unrelated individuals, including GWAS
- Family-based association studies
- Critical appraisal of one article (Journal Club format – presentation & discussion led by a student): Association studies

**Required reading materials**


4. Gordon D and Finch SJ (2005) Factors affecting statistical power in the detection of genetic association. JCI 115: 1408-1418. (*Nice and easy review paper on statistical power; also includes a glossary of terms used in genetic epidemiology and statistical genetics*)

5. Palmer LJ, Cardon LR (2005) Shaking the tree: mapping complex disease genes with linkage disequilibrium. Lancet 366:1223-1234. (*4th article of the 2005 Lancet series on Genetic Epidemiology; Linkage disequilibrium is an important concept in genome-wide association studies*)


(Simultaneous publication in Annals of Internal Medicine, PLOS Medicine, Genetic Epidemiology, European Journal of Epidemiology, Journal of Clinical Epidemiology, European Journal of Clinical Investigation, Human Genetics. (Useful tool for critical appraisals & writing manuscripts on genetic association studies of various designs)

Additional and Advanced reading materials


Block F – Clinical genetics studies & Public Health Genetics

November 25 (Steven Narod)

- Clinical genetics

Required reading materials


Additional and Advance reading materials
Block G – Topic of your choice and course evaluation

December 2 (France Gagnon)
Advanced topic and wrap-up
  • Topic of your choice: e.g. CNVs, epigenetics, etc
  • Discussion on Assignment 4
  • Course evaluation

Required reading materials
None

Additional and Advance reading materials

Evaluation

1. **Assignment 1: (500-1000 words paper)**
   - 20%
   - Due September 30 at 9:00 AM.
   - Marks will be deducted at the rate of 15%/day (-5% before noon; -10% before 18:00; -15% after 18:00; including weekend days) to a maximum of 100%.

2. **Assignment 2: (two journal club presentations and discussion)**
   - 30% (15% + 15%)
   - Presentation dates and assignment of papers will be done on September 23.
   - Each student from the team will be individually marked i.e., based on their response to questions, etc.

3. **Assignment 3: (take-home exam)**
   - 40%
   - Due November 25 at 9:00 AM.
   - Marks will be deducted at the rate of 15%/day (-5% before noon; -10% before 18:00; -15% after 18:00; including weekend days) to a maximum of 100%.

4. **Assignment 4: (500-1000 words paper)**
   - 10%
   - Due December 9 at 9:00 AM.
   - Marks will be deducted at the rate of 15%/day (-5% before noon; -10% before 18:00; -15% after 18:00; including weekend days) to a maximum of 100%.
Assignment 1

Assignment 1 is to develop your personal learning outcomes and major goal for the course, and propose ways of how you plan to achieve it. This is an individual assignment. It should be electronically submitted as a Word document (other formats will not be accepted), and typed single-spaced, 1" margins, 12 pt. (10 pt. in the table) Times New Roman. The length should be of **500-1000 words**, including the table but excluding title page and references if any: “Be precise! Be concise! – Points may be taken off for verbosity (the write everything you think you know about the subject in hopes that some of it will be correct phenomenon).” I borrowed this quote from my colleagues teaching Biostatistics II – but the same applies here!

Your assignment should follow the guidelines below.

1. A title page that includes:
   - Project Title
   - Your name and U of T student number
   - Course name and number
   - Date

2. Personal learning outcomes/objectives: Guidelines for developing learning outcomes have been developed by the University of Toronto Office of Teaching Advancement (OTA) and are summarized by the acronym “SMART(TT)”. The acronym “SMART(TT)” characterizes the qualities of good learning outcomes. This acronym has been borrowed from goal-setting strategies from the management literature and has been adapted for teaching purposes. Here, I slightly revised SMART(TTT) to become a self-assessment tool not only for me, the instructor, but also for each of my students. I re-labeled the student version of the instrument “SMART 4 YOU”. Your main goal will guide the development of your learning outcomes.

   When writing your learning outcomes, keep in mind that they should be **SMART 4 YOU**:

   ![SMART 4 YOU Table]

   *Refers to new elements specific to SMART 4 YOU; $ max. marks allocated; In addition, marks will be allocated for the clarity, the organization, and the precision of the language used $ /2
To help you writing your learning outcomes, prepare a table such as the one below. The table is also part of the assignment.

<table>
<thead>
<tr>
<th>Unit of instruction</th>
<th>Objective</th>
<th>Outcome</th>
<th>How do you know?</th>
<th>Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>e.g. literature review, exercise, additional activity outside the class (provide a specific example)</td>
<td>e.g. What specific content or skills in this unit of instruction?</td>
<td>What should you know or be able to do as a result of this unit of instruction?</td>
<td>How will you be able to tell that you have achieved this outcome?</td>
<td>What kind of work can you produce to demonstrate this?</td>
</tr>
</tbody>
</table>

In the preparation of this assignment, I recommended that you read the document entitled “Developing learning outcomes” prepared by the OTA. When reading the document, simply replace the words “the students” by “you”. When writing your learning objectives, replace “the students” by “I”. There are several examples in the document, as well as useful appendices.

With respect to the “units of instruction”, use some of the tools that I proposed in the context of the course (e.g. oral presentation, written critical appraisal, regular or specific journal clubs), as well as some activities that you will be doing outside the class. If you feel adventurous, you are welcome to propose an exercise to be done in the context of one of our regular classes.

**Hoping that “SMART 4 YOU” will become an exercise that you can use for personal development in future courses and endeavors!**
Assignment 2

For assignment 2, you and a fellow student will lead two journal club sessions in the field of genetic epidemiology i.e., critical appraisal of a scientific article. For each, you will be responsible for preparing a 15-20 minutes presentation on a pre-determined scientific article, and leading the discussion for the remaining 40-45 minutes. It is expected that you will prepare questions for your audience about the study design choices, as well as challenges you encountered while reading the paper. Please, electronically send your Power Point presentation to France before or right after your presentation. Each presentation is worth 15% (total of 30% for both presentations). Each student is marked separately based on their level of preparedness and quality of their answers to questions.

Your assignment should follow the guidelines below.

1. Brief introduction of the topic – including some biological background.

2. Why is this study important? What gap in the literature does it fill (or what the authors claim it does?)

3. Present the method section with a focus on the study design and analytic strategies.

4. What are the most important results?

5. Significance – Is the study important? Why/why not? What’s next?

6. Be prepared with questions for your audience – even some for which you do not have answers!

7. Additional points: Pay attention to the quality of your slides. Here, I do not refer to “how pretty” these can be but rather how “readable” they are e.g., not too much information per slide, font that can be read by the audience. Make sure that each slide has a purpose. The text on the slide should be concise i.e., present the most relevant information but be ready to discuss the details during the discussion if necessary. The presentation should not last more than 20 minutes (excluding interruption time for questions); 15-20 slides should be sufficient.

A journal club presentation is a bit like a critical appraisal with the exception that you are not expected to be an expert on the topic that you are presenting. This means that you are not only allowed to ask questions to your audience about what you did not understand, but you are encouraged to do so!

The STREGA checklist is a tool for critical appraisal of a genetic association study of any observational study designs. There are a number of “review” and “guidelines” articles on “How” to conduct and report genetic studies; some have been listed in your reading materials. These can be useful as well. With respect to linkage studies, the Teare and Barrett’s paper should be helpful.

Now, have fun preparing it!
Assignment 2 - Marking scheme

8. Brief introduction of the topic – including some biological background.
   /3

9. Why is this study important? What gap in the literature does it fill (or what the authors claim it does?)
   /3

10. Present the method section with a focus on the study design and analytic strategies.
    /3

11. What are the most important results?
    /3

12. Significance – Is the study important? Why/why not? What’s next?
    /4

13. Be prepared with questions for your audience – even some for which you do not have answers!
    /4

14. Additional points: Pay attention to the quality of your slides.
    /2

15. Leading class discussion
    /3
Assignment 3 (Take home exam)

Assignment 3 is a take home exam. This is an individual assignment. It should be electronically submitted as a *Word* document, and typed single-spaced, 1” margins, 12 pt. Times New Roman. Again, “Be precise! Be concise! – Points may be taken off for verbosity”.

Your assignment should follow the guidelines below.

1. A title page that includes:
   - Project Title
   - Your name and U of T student number
   - Course name and number
   - Date

3. Short answers to the take home exam questions. The take home exam will include materials that covers the entire term, including the last lecture as your class reading and preparation should always be done prior to the class.

We are now toward the end of the course and we expect that you will be more of an expert than you were at the beginning of the course!
Assignment 4

Assignment 4 is for you to critically evaluate if you have reached your personal learning outcomes and course goal, and summarize your auto-evaluation in 500-1000 words. The assignment should be handed in electronically. It should be a Word document, typed single-spaced with 1” margins, 12 pt. (10 pt. in the table) Times New Roman. The length should be of 500-1000 words, including tables if any, but excluding title page and references if any. Again, “Be precise! Be concise!” …as I will stop reading after 1000 words!

Your assignment should follow the guidelines below.

1. A title page that includes:
   - Project Title
   - Your name and U of T student number
   - Course name and number
   - Date

2. Auto-evaluation: Evaluate your progress during this course against the set of personal outcomes that you developed for yourself in the context of assignment 1. Marks will be distributed as follows:

<table>
<thead>
<tr>
<th>Items to cover</th>
<th>Marks allocated</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Overall assessment (~ 1 paragraph)</td>
<td>5</td>
</tr>
<tr>
<td>2. Based on the learning outcomes that you previously set for yourself, what did you learn? (be specific; you can use point form as the example below) e.g. I can distinguish the main goal of common study design types in genetic epidemiologic studies</td>
<td>4</td>
</tr>
<tr>
<td>3. Based on the learning outcomes that you previously set for yourself, what remains to be learned? (be specific; you can use point form as the example below) e.g. To interpret the results of gene-gene interaction studies</td>
<td>4</td>
</tr>
<tr>
<td>4. Aspects that contributed to achieving your learning outcomes</td>
<td>5</td>
</tr>
<tr>
<td>5. Aspects that held you back from achieving your learning outcomes</td>
<td>5</td>
</tr>
</tbody>
</table>

Clarity and organization

2