**Advanced Statistical and Quantitative Genetics in the Context of Human Health**

Syllabus 2020

Instructor: Guillaume Pare

Course Objectives

Statistical genetics is a field centered around developing inferential methods while taking into account the complexity inherent to genetic data. The goal of this course is to cover the quantitative basis of these tools beyond the survey introduction to statistical genetics introduced in HRM 728. This course will cover topics in depth including heritability estimation, design and conduct of genetic association studies for both common and rare variants, secondary analysis of GWAS studies, and appropriate inference. Each week will involve a discussion of the assigned textbook reading as well as a paper relevant in the field of modern applied genetics.

Outcome Measures

Participation: 25%

> -Clearly demonstrates having done assigned reading. Comes prepared with appropriate questions.

Oral Presentation: 20%

> -Oral presentation explaining a statistical consideration with regards to inference in genetic studies.

Final Paper: 55%

> -Paper will be written describing methodologic flaws and implications of a statistical genetic method of the student's choice. Paper is expected to be at least 3000 words.

Each week a student will lead a lecture presentation supervised by Dr. Pare and another senior lab member.

Suggested Textbook:

Genetic Epidemiology: Methods and Protocols By Evangelos Evangelou

https://www.amazon.ca/Genetic-Epidemiology-Protocols-Evangelos-Evangelou/dp/1493993097

Proposed Schedule

Session 1: Basics of Population Genetics –

Video (https://www.youtube.com/watch?v=Rh8WEx5LPAk&feature=youtu.be); Slides (https://6179a24f-749f-4076-96f9-465d6cff9291.filesusr.com/ugd/2f9665_a325daa8d58e47f48aad4166f0e2c537.pdf)

**Population genetics and GWAS: A primer** (2020)

https://journals.plos.org/plosbiology/article?id=10.1371/journal.pbio.2005485

**Determinants of genetic diversity** (2016)

https://www.nature.com/articles/nrg.2016.58

Session 2: Assortative Mating

Assortative Mating: Video: (https://www.youtube.com/watch?v=OyMtbzCbzqk&feature=youtu.be); Slides: https://6179a24f-749f-4076-96f9-465d6cff9291.filesusr.com/ugd/2f9665_db0df78f8dea449d98e2502f22bca99a.pdf

Session 3: Inferring Population Structure

**Population structure in genetic studies: Confounding factors and mixed models** (2018)

https://journals.plos.org/plosgenetics/article?id=10.1371/journal.pgen.1007309

Session 4: Population Structure Cont.

**Robust Inference of Population Structure for Ancestry Prediction and Correction of Stratification in the Presence of Relatedness** (2016)

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4836868/

**Genetic Diversity and Association Studies in US Hispanic/Latino Populations: Applications in the Hispanic Community Health Study/Study of Latinos** (2016)

https://www.sciencedirect.com/science/article/pii/S0002929715004966

Session 5: Heritability estimation methods

**The heritability of human disease: estimation, uses and abuses** (2013)

https://www.nature.com/articles/nrg3377

**Assessing the Heritability of Complex Traits in Humans: Methodological Challenges and Opportunities** (2017)

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5635617/

Session 6: Genome Wide Association Studies context

**Benefits and limitations of genome-wide association studies** (2019)

https://www.nature.com/articles/s41576-019-0127-1

**Genomics of disease risk in globally diverse populations** (2019)

https://www.nature.com/articles/s41576-019-0144-0

Session 7: GWAS methods in more detail

**Meta-analysis methods for genome-wide association studies and beyond** (2013)

https://www.nature.com/articles/nrg3472#Sec7

**Dissecting the genetics of complex traits using summary association statistics** (2017)

https://www.nature.com/articles/nrg.2016.142

Session 8: GWAS Considerations

**Statistical power and significance testing in large-scale genetic studies** (2014)

https://www.nature.com/articles/nrg3706

**Using genetic data to strengthen causal inference in observational research**

https://www.nature.com/articles/s41576-018-0020-3#Sec5

Session 9: Secondary GWAS Analyses – Fine Mapping, Genetic Correlation

**From genome-wide associations to candidate causal variants by statistical fine-mapping** (2018):

https://www.nature.com/articles/s41576-018-0016-z

**Genetic correlations of polygenic disease traits: from theory to practice** (2019):

https://www.nature.com/articles/s41576-019-0137-z

**A robust method to estimate regional polygenic correlation under misspecified linkage disequilibrium structure** (2018)

https://pubmed.ncbi.nlm.nih.gov/30156736/

Session 10: Secondary GWAS Analyses – Polygenic Risk Scores

**Tutorial: a guide to performing polygenic risk score analyses**

https://www.nature.com/articles/s41596-020-0353-1

**Analysis of polygenic risk score usage and performance in diverse human populations**

https://www.nature.com/articles/s41467-019-11112-0

**Polygenic Scores:**

https://6179a24f-749f-4076-96f9-465d6cff9291.filesusr.com/ugd/2f9665_c2c96aa6f5504a3893374ef6336ae839.pdf

**Eurocentric Biases in Polygenic Risk Scores:**

https://6179a24f-749f-4076-96f9-465d6cff9291.filesusr.com/ugd/2f9665_aefbe67c2c454762b4f028aa68351eb2.pdf

Session 11: Secondary GWAS Analyses: Mendelian Randomization

**Evaluating the potential role of pleiotropy in Mendelian randomization studies** (2018)

https://academic.oup.com/hmg/article/27/R2/R195/4996734

**Recent Developments in Mendelian Randomization Studies** (2017)

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5711966/

**Detection of widespread horizontal pleiotropy in causal relationships inferred from Mendelian randomization between complex traits and diseases** (2018)

https://www.nature.com/articles/s41588-018-0099-7

Session 12: Secondary GWAS Analysis – Pathway Analysis

**Ten Years of Pathway Analysis: Current Approaches and Outstanding Challenges** (2012): https://journals.plos.org/ploscompbiol/article?id=10.1371/journal.pcbi.1002375

**Gene set analysis: a step by step guide** (2015):

https://pubmed.ncbi.nlm.nih.gov/26059482/

**The statistical properties of gene-set analysis** (2016)

https://www.nature.com/articles/nrg.2016.29

**How to Perform GSEA:**

https://www.youtube.com/watch?v=KY6SS4vRchY

Session 13: Biomarkers and Proteomics

**Emerging Affinity-Based Proteomic Technologies for Large-Scale Plasma Profiling in Cardiovascular Disease** (2017)

https://pubmed.ncbi.nlm.nih.gov/28438806/

**Genetic Architecture of the Cardiovascular Risk Proteome** (2017)

https://www.ahajournals.org/doi/full/10.1161/CIRCULATIONAHA.117.029536

**Biomarkers of cardiovascular disease: molecular basis and practical considerations** (2006)

https://pubmed.ncbi.nlm.nih.gov/16702488/

**Mendelian randomisation applied to drug development in cardiovascular disease: a review** (2015)

https://jmg.bmj.com/content/52/2/71

**Novel Drug Targets for Ischemic Stroke Identified Through Mendelian Randomization Analysis of the Blood Proteome** (2019)

https://www.ahajournals.org/doi/abs/10.1161/CIRCULATIONAHA.119.040180

**Genetic drug target validation using Mendelian randomisation** (2020) [optional]

https://www.nature.com/articles/s41467-020-16969-0

Session 14: Rare Variants and Collapsing Tests

**Watch the following lecture:**

http://faculty.washington.edu/tathornt/SISG2020/lectures/SISG2020session08.pdf

https://washington.zoom.us/rec/share/z817NJqh7DNIHNLo6E3fB7IfWa21T6a80SEZ8_AFxU1xSh8FJE2cr7fj6PA8213X?startTime=1595967611000

**Rare-variant collapsing analyses for complex traits: guidelines and applications** (2019)

https://www.nature.com/articles/s41576-019-0177-4

Session 15: Rare Variant Analysis: Kernel (Variance Component) Tests and Omnibus Tests

**Watch the following lecture:**

http://faculty.washington.edu/tathornt/SISG2020/lectures/SISG2020session09.pdf

https://washington.zoom.us/rec/play/6Jwpc-qopz83TtPHtwSDBPIoW42_Kqis0nRP-PZezUm9UCZQOlSuNLYUMbemwwh_8nPvSFS2uU4uJAOw?startTime=1596034912000&_x_zm_rtaid=ehUAaxo3RVeh-NzzjavU9g.1597947032089.f95ed0bef0c1e47c269929507dabe31f&_x_zm_rhtaid=522

Format: Reading discussion will take place during the tutorial held once weekly among the students. Dr. Pare will meet with all students once a week to discuss issues encountered during the weekly student discussion led by senior lab members. Journal club style presentation will be expected from each participant at the biweekly GMEL lab meeting on an applied or methodological paper of the student's choice. Critical appraisal will be conducted and understanding of the underlying concepts presented in the paper will be assessed by Dr. Pare and fellow lab members. Students will divide into two groups and work on one of two final papers on a topic of methodological interest. The suggested topics are:

1) Two sample Mendelian randomization in the setting of participant overlap
2) Inferential difficulties in bidirectional Mendelian randomization