University of Pittsburgh  
Graduate School of Public Health  
Department of Human Genetics

**HuGen 2080**  
**Statistical Genetics**

Monday 1:00-2:30 PM  
Thursday 12:30-1:55 PM  
A425 Crabtree Hall  
3 Credit Hours  
Spring 2022

**Faculty**

Daniel E. Weeks, Ph.D.  
3119 Public Health  
412-624-5388  
weeks@pitt.edu  
Office Hours available upon request

John Shaffer, Ph.D.  
3120 Public Health  
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john.r.shaffer@pitt.edu  
Office hours available upon request

**Faculty Availability**

We are available to meet with you upon request - please feel free to set up an appointment.

We welcome your questions at any time. For questions about the course content, we prefer that you submit your questions via the Canvas Discussion Board, so that other students, who may have similar questions, may also benefit from the discussion. E-mail is also an excellent way to reach us. However, since we get so many e-mails, please use an informative subject line, starting with "HuGen 2080: ". And if we don't respond to your e-mail in a timely manner, please feel free to send a reminder e-mail.

**Course Description**

AN ADVANCED COURSE WHICH DISCUSSES THE PRINCIPLES AND PRACTICE OF STATISTICAL GENETICS IN THE AREA OF GENETIC EPIDEMIOLOGY OF HUMAN DISEASES AND TRAITS. THE COURSE WILL COVER STATISTICAL MODELING AND METHODOLOGY IN FAMILIAL AGGREGATION, LINKAGE ANALYSIS AND ASSOCIATION ANALYSIS; THE COURSE INCLUDES HANDS-ON EXPERIENCE WITH CURRENT COMPUTER PROGRAMS USED IN THESE RESEARCH AREAS.

The objective of this class is to introduce students to advanced topics in genetic epidemiology, specifically related to human diseases and traits, with an emphasis on statistics and the
mathematics behind the statistics. As such, the course requires familiarity with basic probability theory and statistical principles, as well as population genetics. After finishing this course, the student should understand the assumptions, strengths, and weaknesses of the various statistical tests, as well as be well prepared to undertake a statistical genetics analysis, including study design, phenotype definition and modeling, estimation of heritability, linkage analysis, and association analysis.

**Learning Objectives**

Upon completion of this course the student will be able to:

- Explain the assumptions, strengths, and weaknesses of the various statistical tests used in genetic epidemiology.
- Devise testable hypotheses in human genetics and identify appropriate study designs to test these hypotheses.
- Describe preferred methodological alternatives to commonly used statistical methods when assumptions are not met.
- Apply the statistical models presented in analyzing and interpreting real data sets.
- Apply genetic analysis programs and interpret the results.
- Read and evaluate current literature in statistical genetics.

**Course Prerequisites**

HUGEN 2022 · Human Population Genetics
BIOST 2041 · Introduction to Statistical Methods 1

or approval of the instructor

**Required Textbooks**


Full text available online: [https://ebookcentral.proquest.com/lib/pitt-ebooks/detail.action?docID=708055](https://ebookcentral.proquest.com/lib/pitt-ebooks/detail.action?docID=708055)

E-learning platform: [https://application.wiley-vch.de/books/geneticepidemiology/IMS_LO/onCampusBook/65270/index.html](https://application.wiley-vch.de/books/geneticepidemiology/IMS_LO/onCampusBook/65270/index.html)

**Supplemental Readings/Bibliography**

Henry Stewart Talks: [https://info.hsls.pitt.edu/updaterreport/?p=4167](https://info.hsls.pitt.edu/updaterreport/?p=4167)

There are multiple methods for locating the Henry Stewart Talks:

1. All talks are catalogued in PITTCat; search for Henry Stewart Talks under “Title Begins with” for an alphabetical list or to search by individual title.
2. Click on the “Videos” tab on the MolBio home page.

DOI: 10.1007/978-1-4419-7338-2
Web access: https://pitt.primo.exlibrisgroup.com/permalink/01PITT_INST/e8h8hp/alma9998511583406236

Statistical Human Genetics
Methods and Protocols
Editor: Robert C. Elston
Web access: https://pitt.primo.exlibrisgroup.com/permalink/01PITT_INST/i25aoe/cdi_springer_books_10_1007_978_1_4939_7274_6

Handbook on Analyzing Human Genetic Data
Computational Approaches and Software
2010
Web access: https://pitt.primo.exlibrisgroup.com/permalink/01PITT_INST/i25aoe/cdi_springer_books_10_1007_978_3_540_69264_5

DOI: 10.1002/0471142905
Web access: https://pitt.primo.exlibrisgroup.com/permalink/01PITT_INST/1sjtb5p/alma9998843113206236

Stram, Daniel O (2014) Design, analysis, and interpretation of genome-wide association scans

Electronic Supplementary Material:
Canvas and GitHub Classroom Instruction
This course will extensively use the University’s Canvas site (canvas.pitt.edu). To login, you must have a Pitt account. Your login ID is the same as your login ID for your Pitt account and your password is the same as for your Pitt account. This will be augmented with GitHub Classroom.

*We strongly recommend that you set up your notifications in Canvas so that any announcements will be sent to your preferred e-mail address.*

Each lecture will be accompanied by supporting material and further reading, all of which will be made available around the time of the lecture. It is the student’s responsibility to check for, and read, this material.

Discussion topics related to the course may also be posted on Canvas, and, for the purpose of determining a student’s grade, participation in these discussions will be considered as equivalent to participation in-class discussion.

The instructors will use the Canvas site and GitHub Classroom as the primary means of communicating with the students, who are expected to check these sites on a regular basis throughout the semester.

Accessibility
Ensuring an accessible and pleasant experience to all users, regardless of disability, is a key focus of Canvas. The Canvas platform was built using the most modern HTML and CSS technologies, and is committed to W3C’s Web Accessibility Initiative and §508 guidelines. GitHub Classroom’s compliance with §508 guidelines can be found at government.github.com/accessibility/.

Health and Safety
During this pandemic, it is extremely important that you abide by the [public health regulations](#), the University of Pittsburgh’s [health standards and guidelines](#), and [Pitt’s Health Rules](#). These rules have been developed to protect the health and safety of all of us. Universal [face covering](#) is required in all classrooms and in every building on campus, without exceptions, regardless of vaccination status. This means you must wear a face covering that properly covers your nose and mouth when you are in the classroom. If you do not comply, you will be asked to leave class. It is your responsibility have the required face covering when entering a university building or
classroom. For the most up-to-date information and guidance, please visit coronavirus.pitt.edu and check your Pitt email for updates before each class.

If you are required to isolate or quarantine, become sick, or are unable to come to class, contact us as soon as possible to discuss arrangements.

**Class Expectations/ Behavior and Ground Rules**
Attendance and active participation are expected.

Please be on time and turn off your cell phone. While laptops may be used to complete computer exercises or to take notes, please do not use them during class time for non-class purposes. It is expected that you will have read all the assigned readings prior to class. To facilitate our use of the readings, please bring an interesting discussion question from the readings to class with you. If you will miss a class, please let us know in advance.

**Statement on Classroom Recording**
To ensure the free and open discussion of ideas, students may not record classroom lectures, discussion and/or activities without the advance written permission of the instructor, and any such recording properly approved in advance can be used solely for the student’s own private use.

**Grading Scale**

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<td>D+</td>
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Student Performance Evaluation (Assessments and Weights)
Evaluation will be based on the following components:

Attendance and Participation
Attendance and active participation are expected.

Homework (50% of final grade)
The homework assignments will comprise problems that extend the in-class activities and complement the lectures.

Students will read the weekly assigned scientific paper and summarize their understanding of the main points of the assigned paper.

A least one of the homework assignments will consist of reviewing a preprint. After the reviews are completed, students will be divided into two groups, and each group will consolidate their set of reviews into one combined polished review, which will then be submitted to AcademicKarma as a formal review.

Paper Presentation (10% of final grade)
All students will give a 30 minute presentation on an assigned paper in statistical genetics.

Mid-term exam (20% of final grade)
A written in-class mid-term exam will be given.

Final exam (20% of final grade)
A written in-class final exam will be given.

Schedule of Sessions and Assignments
The detailed schedule is provided at the end of this document.
Accommodation for Students with Disabilities

If you have a disability for which you are or may be requesting an accommodation, you are encouraged to contact both your instructor and Disability Resources and Services, 140 William Pitt Union, 412-648-7890 as early as possible in the term.

Academic Integrity Statement

All students are expected to adhere to the school’s standards of academic honesty. Cheating/plagiarism will not be tolerated. The Graduate School of Public Health’s policy on academic integrity, which is based on the University policy, is available online in the Pitt Public Health Academic Handbook [www.publichealth.pitt.edu/home/academics/academic-requirements](http://www.publichealth.pitt.edu/home/academics/academic-requirements). The policy includes obligations for faculty and students, procedures for adjudicating violations, and other critical information. Please take the time to read this policy.

Plagiarism

Integrity of the academic process requires that credit be given where credit is due. Accordingly, it is unethical to present as one's own work the ideas, representations, words of another, or to permit another to present one's own work without customary and proper acknowledgement of sources.

A student has an obligation to exhibit honesty and to respect the ethical standards of the profession in carrying out his or her academic assignments. Without limiting the application of this principle, a student may be found to have violated this obligation if he or she:

1. Presents as one's own, for academic evaluation, the ideas, representations, or words of another person or persons without customary and proper acknowledgment of sources.

2. Submits the work of another person in a manner which represents the work to be one's own.

See: [http://www.bc.pitt.edu/policies/policy/02/02-03-02.html](http://www.bc.pitt.edu/policies/policy/02/02-03-02.html)

To avoid plagiarism, you must give “customary and proper acknowledgment of sources” by appropriately and clearly identifying which thoughts are yours and which are others, and appropriately citing your sources.

Sophisticated plagiarism detection software will be used in this course. If plagiarism is detected, you will automatically receive a grade of zero for that assignment and the incident will be reported, as required, to your Dean.
Sexual Misconduct, Required Reporting and Title IX Statement

The University is committed to combatting sexual misconduct. As a result, you should know that University faculty and staff members are required to report any instances of sexual misconduct, including harassment and sexual violence, to the University’s Title IX office so that the victim may be provided appropriate resources and support options. What this means is that as your professor, I am required to report any incidents of sexual misconduct that are directly reported to me, or of which I am somehow made aware.

There are two important exceptions to this requirement about which you should be aware:

A list of the designated University employees who, as counselors and medical professionals, do not have this reporting responsibility and can maintain confidentiality, can be found here: https://www.diversity.pitt.edu/civil-rights-title-ix/make-report/report-form

An important exception to the reporting requirement exists for academic work. Disclosures about sexual misconduct that are shared as part of an academic project, classroom discussion, or course assignment, are not required to be disclosed to the University’s Title IX office.

If you are the victim of sexual misconduct, Pitt encourages you to reach out to these resources:

Title IX Office: 412-648-7860
SHARE @ the University Counseling Center: 412-648-7930 (8:30 A.M. TO 5 P.M. M-F) and 412-648-7856 (AFTER BUSINESS HOURS)

If you have a safety concern, please contact the University of Pittsburgh Police, 412-624-2121.

Other reporting information is available here: https://www.diversity.pitt.edu/civil-rights-title-ix-compliance/make-report

Diversity Statement

Pitt Public Health Diversity Statement | Effective Academic Year 2021–22

The University of Pittsburgh Graduate School of Public Health considers the diversity of its students, faculty, and staff to be a strength and critical to its educational mission. Pitt PublicHealth is committed to creating and fostering inclusive learning environments that value human dignity and equity and promote social justice. Every member of our community is expected to be respectful of the individual perspectives, experiences, behaviors, worldviews, and backgrounds of others. While intellectual disagreement may be constructive, no derogatory statements, or demeaning or discriminatory behavior will be permitted.

If you feel uncomfortable or would like to discuss a situation, please contact any of the following:
• the course director or course instructor;
• the Pitt Public Health Associate Dean responsible for diversity and inclusion;
• the University’s Office of Diversity and Inclusion at 412-648-7860 or
  (anonymous reporting form)

Copyright Notice
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101, et seq., in addition to University policy and procedures, prohibit unauthorized duplication
or retransmission of course materials. See Library of Congress Copyright Office and the
University Copyright Policy.

Schedule of Sessions and Assignments
Note: This schedule is, of course, subject to change and will be updated as we proceed through the course.

Background reading:
Ziegler and König - Chapter 1: Molecular Genetics
Ziegler and König - Chapter 2: Formal Genetics

Henry Stewart Talk:
Genotyping algorithms for genome wide association studies/ Dr. Vincent Plagnol

1/10/2022 - Lecture 01: Models, Maps, and Markers
Lecturer: Dan Weeks
Active Learning: Intro to Unix & PLINK

Required Reading:
Ziegler and König - Chapter 3: Genetic Markers
Ziegler and König - Chapter 5: Genetic Map Distances

Henry Stewart Talk:
Introductory genetics for statisticians/ Robert C. Elston.
Supplementary reading:


Assignment:
Homework 1

Learning objectives:
To review basic genetic models
To learn about genetic markers

1/13/2022 - Lecture 02: Study Design Overview
Lecturer: Dan Weeks

Henry Stewart Talk:
Designing a genome-wide association study/ Dr. Chris Spencer

Learning objectives:
To learn the basic principles of study design for genetic studies
To understand the vital importance of phenotype definition
To understand the best sample selection strategies

1/17/2022: No class - Martin Luther King Day

1/20/2022 - Lecture 03: Familial Aggregation: Recurrence Risk Ratios, Heritability
Lecturer: Dan Weeks
Active Learning: Student Presentation

Required Reading:
Ziegler and König - Chapter 6: Familiality, Heritability, and Segregation Analysis

Henry Stewart Talk:
Heritability and its uses/ Doug Speed.
Inferring relatedness/ Prof. Emmanuelle Génin
Supplementary reading:

Assignment:
Homework 2

Learning objectives:
To learn aggregation analysis
To learn how to estimate recurrence risk ratios
To review the concept of heritability

1/24/2022 - Lecture 04: **Familial Aggregation: Segregation Analysis, Ascertainment**
Lecturer: Dan Weeks
Active Learning: SOLAR heritability computer lab

Required Reading:
Ziegler and König - Chapter 6: Familiality, Heritability, and Segregation Analysis

Learning objectives:
To learn about segregation analysis
To understand how to take ascertainment into account in the segregation models
To formulate testable hypotheses about genetic models

1/27/2022 - Lecture 05: **LOD scores: Model-based Linkage Analysis**
Lecturer: Dan Weeks
Active Learning: Student Presentation

Required Reading:
Ziegler and König - Chapter 7: Model-based Linkage Analysis

Henry Stewart Talk:
Linkage and sequence analysis in families/ Christopher Amos.

Supplementary reading:

Assignment:
Homework 3
Learning objectives:
To learn how to compute LOD scores
To learn about different map functions, and the distinction between genetic and physical maps
To formulate testable hypotheses about linkage

1/31/2022 - Lecture 06: **Non-parametric methods**
Lecturer: Dan Weeks
Active Learning: Merlin computer lab

Required Reading:
Ziegler and König - Chapter 8: Model-free Linkage Analysis for Dichotomous Traits

Supplementary reading:

Learning objectives:
To learn how to carry out non-parametric linkage analyses
To understand the motivation behind non-parametric linkage analysis approaches

2/3/2022 - Lecture 07: **Association: Case/Control & Quantitative Traits**
Lecturer: Dan Weeks
Active Learning: Student Presentation

Required Reading:
Ziegler and König - Chapter 10: Fundamental Concepts of Association Analysis
Ziegler and König - Chapter 11: Association Analysis with Unrelated Individuals

Henry Stewart Talk:
Introduction to genetic association analysis/ Jenny Barrett.

Statistical tests for association/ Dr. Andrew Morris
Supplementary reading:


Assignment:
Homework 4

Learning objectives:
To formulate testable hypotheses about association
To understand and apply various case/control association tests
To understand allele-based and genotype-based association tests, and trend tests.

2/7/2022 - Lecture 08: Association: Family-based and Haplotype-based
Lecturer: Dan Weeks
Active Learning: PLINK computer lab

Required Reading:
Ziegler and König - Chapter 12: Association Analysis in Families

Supplementary reading:


Learning objectives:
To learn how to analyze family data for association
To learn how to test haplotypes for association
To understand sparsity issues involved in haplotyped-based tests

2/10/2022 - Lecture 09: Multiple testing
Lecturer: Dan Weeks
Active Learning: Student Presentation

Required Reading:
Ziegler and König - Chapter 14, Section 14.4: Multiple Testing
Henry Stewart Talk:
Assessing significance in genome-wide studies/ Dr. David Evans

Supplementary reading:

Assignment:
Homework 5

Learning objectives:
To understand how to adjust for multiple testing

2/14/2022 - Lecture 10: Power to detect Association: Linkage vs. Association
Lecturer: Dan Weeks

Supplementary reading:

Learning objectives:
To learn how to compute power for detecting association
To compare and contrast linkage and association
To understand the relative strengths and weaknesses of linkage and association tests

2/17/2022 - Lecture 11: Rare variants
Lecturer: Dan Weeks
Active Learning: Student Presentation

Supplementary reading:


Assignment:
Homework 6
Learning objectives:
To learn how to test rare variants for association
To learn about burden tests, collapsing or grouping tests, weighted sum tests, and variable threshold tests.

2/21/2022 - Lecture 12:  **Methods for correlated data: LME, GEE, Score**
Lecturer: Dan Weeks
Active Learning: Student Presentation

Learning objectives:
To learn about linear mixed effects models, generalized estimating equations, and score tests
To learn how to properly model relatedness while testing genetic hypotheses

2/24/2022 - Lecture 13:  **Bayesian Methods in Human Genetics**
Lecturer: Dan Weeks
Active Learning: Student Presentation

Assignment:
Homework 7

Learning objectives:
To learn about Bayesian methods in human genetics
To understand Bayesian principles

2/28/2022 - Lecture 14:  **Review for Mid-term exam**

3/3/2022 - Lecture 15:  **Mid-term exam**
Assignment:
Mid-term Exam

3/7/2022:  **Spring Recess**

3/10/2022:  **Spring Recess**
3/14/2022 - Lecture 16: Gene x Gene interaction, vQTLs

Lecturer: John Shaffer

Supplementary reading:


Learning objectives:
- To learn how to test for gene x gene interaction
- To formulate testable hypotheses about gene x gene interaction

3/17/2022 - Lecture 17: Gene x Environment interaction

Lecturer: John Shaffer

Active Learning: Student Presentation

Henry Stewart Talk:
Statistical issues in epidemiologic studies of gene-environment interaction/ Peter Kraft, Donna Spiegelman.

GxE interactions in genome-wide association studies/ David V. Conti.

Supplementary reading:


Learning objectives:
- To learn how to test for gene x environment interaction
- To formulate testable hypotheses about gene x environment interaction
3/21/2022 - Lecture 18: Meta analysis
Lecturer: John Shaffer

Required Reading:
Ziegler and König - Chapter 14, Section 14.5: Accumulating Data from Genome-wide Association Studies

Henry Stewart Talk:
Winner’s curse, replication and meta-analysis/ Frank Dudbridge.

Meta-analysis in genome-wide association studies: application to type 2 diabetes/ Dr. Eleftheria Zeggini

Assignment:
Homework 8

Learning objectives:
To learn about the different types of meta analysis.
To understand the assumptions made by meta analysis.

3/24/2022 - Lecture 19: Fine mapping
Lecturer: Dan Weeks

Active Learning: Student Presentation

Learning objectives:
To learn how to carry out fine mapping
To understand and apply conditional tests of association

3/28/2022 - Lecture 20: Methods for multivariate phenotypes
Lecturer: John Shaffer

Assignment:
Homework 9

Learning objectives:
To learn about methods for analyzing multivariate phenotypes
To learn how to properly account for correlation among phenotypes
3/31/2022 - Lecture 21: **Special Topic Lecture**
**Lecturer:** To be determined

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4/4/2022 - Lecture 22: **Heritability from GWAS**
**Lecturer:** John Shaffer
**Active Learning:** Student Presentation

**Henry Stewart Talk:**
Heritability and its uses/ Doug Speed.

**Assignment:**
Homework 10

**Learning objectives:**
To learn how to estimate heritability using unrelated samples.
To understand polygenicity.

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4/7/2022 - Lecture 23: **Special Topic Lecture**
**Lecturer:** To be determined

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4/11/2022 - Lecture 24: **LDscore regression**
**Lecturer:** John Shaffer
**Active Learning:** Student Presentation

**Assignment:**
Homework 11

**Learning objectives:**
To understand the principles of LDscore regression
To understand polygenicity.

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4/14/2022 - Lecture 25: **Special Topic Lecture**
**Lecturer:** To be determined
4/18/2022 - Lecture 26: Mendelian Randomization
Lecturer: John Shaffer
Active Learning: Student Presentation

Henry Stewart Talk:

Assignment:
Homework 12

Learning objectives:
To understand the basic principles of Mendelian Randomization.
To formulate testable hypotheses about causation using Mendelian Randomization approaches.

4/21/2022 - Lecture 27: Special Topic Lecture
Lecturer: To be determined

Lecturer: John Shaffer
Active Learning: Student Presentation

Learning objectives:
To understand how to construct and use genetic risk scores.
To understand the limits of genomic predication.

4/28/2022 - Lecture 29: Final exam
Assignment:
Final Exam

4/30/2022: Spring Term ends.