Keck School
of Medicine
of USC

PM 534: Statistical Genetics:

Introduction to Medical Population Genetics

Units: 3

Term—Day—Time: Fall 2021-Tuesday/Thursday-10:30-11:50am

Location: SSB116 (Tuesdays), SSB114 (Thursdays)

Course Coordinator: Charleston Chiang, Ph.D.

Office: virtual via zoom

Office Hours: Fridays 1-2pm

Contact Info: charleston.chiang@med.usc.edu

(Preferred, please include “PM534” in subject line)

Course Description

Genetics is no longer restricted to an academic pursuit. Today, genetics permeate multiple facets of our lives, from Directed-to-consumer genetic testing and embryo selection to the use of forensic genetics to capture the Golden State Killer. It is thus becoming important for everyone to understand genetic variation in human populations, how it arises, how it evolves, and how it is related to complex human traits. This course will take an evolutionary approach to survey quantitative topics in human population genetics and its applications to medical genetics and genetic epidemiology. Topics covered will include human genome variation and genetic diversity, linkage disequilibrium, population structure and admixture, genetic drift and natural selection, genome-wide association studies from an evolutionary perspective, statistical genetic applications (phasing, imputation, and fine-mapping), genetic risk predictions, human history through ancient DNA, and race, ethnicities, and genetic ancestry. The target audience include doctoral and master students in Epidemiology and Biostatistics, or other quantitative-minded students looking for a non-specialist introduction to population genetics.

Learning Objectives

After taking this course, the student will be able to:

1. Describe the major evolutionary forces that shaped human genetic variation
2. Appreciate the progression of human genetic studies in the 21st century
3. Explain the quantitative intuition behind population genetic methods and statistical genetic machinery
4. Perform basic data analysis in population genetics and genetic epidemiology
5. Distinguish the difference between race and genetic ancestry, interpret predicted risk from directed-to-consumer genetic testing, and understand the application of genetics in forensics.

Prerequisite(s): A course that covered probability at the undergraduate level will be sufficient. Basic understanding of genetic inheritance and molecular biology will be useful, but not required.

Co-Requisite(s): None

Concurrent Enrollment: None

Foundational Knowledge needed: As prerequisite, plus a strong interest in human genetics

Course Notes

The course will be a combination of lectures, in-class exercises, and paper discussions. Lectures will be accompanied by reading assignments serving as background material that should be completed before or after the lecture. Paper discussions will be led by students in journal club style. Copies of lecture slides will be posted on Blackboard.

Communication

Please be comfortable asking questions and providing feedbacks on the course. Feel free to ask questions during the lecture, especially in situations where the question, if unanswered, will prohibit your understanding of the material and prevent you from extracting the most of the lectures. You should also feel free to ask questions during office hours or via through postings on the discussion broad on Blackboard. I will respond to questions usually within 2 working days.

Technological Proficiency and Hardware/Software Required

Access to a laptop is required for the course. There are 3 planned sessions of in-class lab exercises this semester during which will require you use your personal laptop in class. During these in-class labs, access to data analysis software R is required. Due to the pandemic, we will also hold office hours virtually through zoom. Other than these, no special hardware or software is required.

USC Technology Support Links

Zoom information for students
Blackboard help for students
Software available to USC Campus

Required Materials

Required readings are generally based on primary literature; the citation for each paper is provided below and students should download them through pubmed. For papers that may be difficult to find (such as classic papers) or book chapters relevant to the lecture, you can access them through USC Library Reserve via Blackboard.

Optional Materials

Many papers and other sources will be referenced throughout the course, and you will be able to find the references within the context they are mentioned in the lecture slides. Interested students can follow up these references through pubmed.

Description of Assessments and Alignment Grid

Assessment will be based on a midterm paper (20%), a group-based project (40%), paper discussion (journal club presentation; 20%), class attendance and participation (15%), and completing both pre- and post-semester self-assessment surveys (5%).

Midterm paper (20%). An often overlooked but essential aspect of science is the dissemination of research product to the general public. Dissemination needs to be rigorous, accurate, and accessible to the public. This means the description of the science should avoid technical jargon, avoid excessive hype often seen in press release and media, and accurately reflects the context and caveat of the science. Good examples of these include articles from science journalists such as Ed Yong, Carl Zimmer, or Sarah Zhang, or the News and Views section of some journals (e.g.

Nature Genetics, https://www.nature.com/ng/articles?type=news-and-views). For the midterm paper, you will need to identify a recent statistical genetics or population genetics paper published in 2019 or later and write a News and Views style article between 400-600 words. Your article should aim to contextualize the research finding in a manner accessible to your peers. The original research paper needs to be a primary research paper, but can be published in any major journal. **The paper needs to first receive the approval of the course instructor (via email) before the end of Week 5 of class. Your article is then due during week 8 of class (by end of day, 10/12/2021).**

You are encouraged to discuss with your peers regarding the choice and content of the research paper you would like to pursue. You are permitted to solicit feedback from your peer. However, each piece of text you write should be your own work. You cannot solicit direct edits of your writing from your peers. The course instructor cannot read your writing before your turn in the paper.

URLs:
Ed Yong (https://www.theatlantic.com/author/ed-yong/)
Carl Zimmer (https://carlzimmer.com/category/articles/)
Sarah Zhang (https://www.theatlantic.com/author/sarah-zhang/)

Group-based project (40%). In groups of 2 or 3 students, the project should result in a scientific paper in a Brief Communication format (see examples of Nature Genetics Brief Communications papers in the past. *e.g.* https://www.nature.com/articles/ng.760). Students can (1) analyze real data using existing methods or new methods proposed by the students, (2) evaluate existing methods by simulations and applications to real data, or (3) perform a comprehensive literature review on a specific topic and propose the next step. The format of the paper (note that they differ a little from Nature Genetics Brief Communication format) will include an abstract of 100-150 words, a main text of 1000-1500 words, 2-3 display items with legend, and 10-20 references. Students can elect to break the paper into sections (Introduction, Results, Discussion), but it is not required. A succinct methods section is expected as appendix, which will *not* count towards the word limit. Student(s) are welcomed to discuss with the course instructor on project topics. **Topic approval by the course instructor needs to occur by the last class before Thanksgiving (11/23/2021), at the latest. You are encouraged to obtain approval before this deadline. The final write-up is due on 12/9/2021.**

You are *required* to discuss with your partner(s) regarding the choice and content of the project. You are permitted to solicit feedback from your peers. However, each piece of text you write should be the work of you and your partner(s). All members of the team are expected to contribute towards the final product. You cannot solicit direct edits of your writing from anyone outside of your team. The course instructor cannot read your writing before your turn in the project.

Paper Discussion (20%). At least nine class sessions are designated as paper discussion sections. Each of these sessions will be led by 2 students, each leading the discussion of a research paper from literature in a journal-club format. This will involve, at minimum, preparing slides to be projected in class that introduce the background, results, conclusion and interpretation of the research paper. It is not necessary that every supplemental figure and table are presented; the student should decide on the important and relevant display items to deliver their narrative. At the same time, if there are external sources (*e.g.* the authors referenced their previous paper for a simulation framework) that will aid the understanding, those display items should be included in the presentation. Finally, the presentation should stand-alone. That is, the presentation should not just be a collage of figures and tables pasted at the last minute. Figures and tables should be accompanied with text (not excessively!) that make the presentation flow. Someone who views

the slides without being present at the journal club should get a general sense of the paper. Each student should prepare for a 25-30 min presentation (which will be adjusted based on number of students presenting in each class), with remaining time used for discussions. You can find an example of slides on Blackboard.

You cannot discuss the paper with any of your peers before the meeting; discussions will be saved for the in-class meeting. You are expected to work independently to prepare for the journal club presentation.

Participation/In-class work (15%). While each Paper Discussion meeting will be led by 2 or 3 students, the rest of the class is expected to engage in the discussion by asking questions, sharing your own experience, and contribute your own interpretation and thoughts of the paper. You are also expected to actively participate in the three in-class computer lab sessions scheduled on the syllabus. Additionally, class attendance in general is expected from all students. If you have to miss a class, arrive late to class, or leave the class early, please let the course instructor know ahead of time.

Self-assessment surveys (5%). There will be two self-assessment surveys that asks you to evaluate your aptitude and knowledge of topics covered in this course. You will be asked to complete one in the beginning of the course (by end of Week 1), and complete one at the end of the course (by end of Week 15). There is no right or wrong answer. This is merely a way for you and the course instructor to reflect on the material taught in the course, and identify components of the course that can be strengthened in the future. Your name will be tracked so you can receive credits for completing the survey. This is in addition to the course evaluation.

Grading Breakdown

Assignment	**% of Grade**
Midterm paper	20
Final group-based project	40
Paper discussion / journal club presentation	20
Participation • Attendance • Participation/Discussion • In-class lab exercises	15
Self-assessment surveys	5
Total	**100**

In general, grades will be given for a good-faith effort to complete the midterm paper, the final project, and the journal club presentation. Sloppiness, such as the result of procrastination, will lead to deduction of points. This *does not* mean the quality and rigor of the product is ignored when grading. Nevertheless, grading will take into account other factors such as the student's prior experience in the field, the amount of time they have to prepare (*e.g.* the first student to present a journal club who has little information of what journal club entails, compared to the last student to present a journal club who has sat through numerous similar presentations already), and the difficulty of the topic / task chosen to be tackled.

Grading Scale

Course final grades will be determined using the following scale.

A	92.5 - 100
A-	89.5 - 92.4
B+	84.5 - 89.4
B	82.5 - 84.4
B-	79.5 - 82.4
C+	74.5 - 79.4
C	72.5 - 74.4
C-	69.5 - 72.4
D+	64.5 - 69.4
D	62.5 - 64.4
D-	59.5 - 62.4
F	59.4 and below

The instructor reserves the right to slide the scale downward as appropriate for class performance, but the scale will not be moved upward to increase the rigor. For example, a student receiving a score of 90% will be guaranteed an A- or better, and receiving a 73% a C or better.

Course-specific Policies

Assignment Submission

Midterm paper and group-based project write-up are to be submitted via Blackboard by the aforementioned dates.

Grading Timeline

Midterm paper will be graded no later than 3 weeks from the submission deadline. Group-based project will be graded within a week of submission.

Late work

Late work will be considered on a case-by-case basis. Unexcused late work will receive an automatic 10% deduction per day it is late. Make-up for full credit due to extenuating circumstances is possible given a written explanation submitted to the course instructor, ideally in advance but otherwise as soon as possible. You may be requested to present documentation to receive an extension. Note that there is a limitation to allow make-up work as there are university deadlines for grade submissions. A grade of “IN” (incomplete), “0”, or “F” must be entered at the end of the semester.

Technology in the classroom

You are allowed to use personal electronic devices (laptops, tablets) for academic purposes directly related to the class. However, I asked that you refrain from using these or other electronic devices for purposes unrelated to the classroom activities. For example, taking phone calls, texting, and web surfing should not occur during class. If there is an emergency call you must take, please excuse yourself quietly so to not disrupt the rest of the class.

Academic integrity

A grade of zero will be applied to submitted work that does not comply with the USC standards of academic conduct. Such work may not be resubmitted for a new grade

Attendance

You are expected to attend and be on time for all class sessions. You are expected to be prepared to discuss the reading assignment. If you miss an in-class assignment due to an unexcused absence, you will not be allowed to make up those points.

Classroom norms

I believe that for the course to be successful there has to be mutual respect between instructors and students. I will make every effort to start and end class on time, treat all students with respect, and do the best to stay on track with class material and inform students in a timely manner if there needs to be any change. It is also expected that students conduct themselves professionally, which includes (but not limited to): come to class on time, refrain from being disruptive to class (*e.g.* talking with other students), and actively participate in class.

Zoom etiquette

We will be conducting office hours this semester through zoom. During virtual office hour, students are expected to keep their camera on. This is important as I can learn your names and receive visual cues on whether my explanation is sufficient. Depending on the number of individuals attending office hour, muting may not be necessary. But I do ask you to be considerate of others and mute yourself if there are excessive background noises in your surroundings.

Sharing of course materials outside of the learning environment

USC has a policy that prohibits sharing of any synchronous and asynchronous course content outside of the learning environment.

SCampus Section 11.12(B)

Distribution or use of notes or recordings based on university classes or lectures without the express permission of the instructor for purposes other than individual or group study is a violation of the USC Student Conduct Code. This includes, but is not limited to, providing materials for distribution by services publishing class notes. This restriction on unauthorized use also applies to all information, which had been distributed to students or in any way had been displayed for use in relationship to the class, whether obtained in class, via email, on the Internet or via any other media. (SeeSection C.1 Class Notes Policy).

Course evaluation

Two surveys will gather student opinions about the course: the mid-semester evaluation and the standard USC course evaluation survey at the end of the semester. Your opinion is valued and

can make a difference in how this course is conducted; please give your honest and constructive recommendations.

Course Schedule: A Weekly Breakdown

Week	Date	Topic
1	**8/24 (Chiang)**	**Lecture 01:** Introduction & Course Logistic, Historical Perspective on Human Genetics. **Reading:** a. Collins, F. S. *et al.* (2021) 'Human Molecular Genetics and Genomics — Important Advances and Exciting Possibilities', *New England Journal of Medicine*.
	8/26 (Chiang)	**Lecture 02:** Organization and Inheritance of the Human Genome **Reading:** Human Evolutionary Genetics, Chapter 2 (on Reserve) ***Self-Assessment Survey #1 Due.***
2	**8/31 (Chiang)**	**Lecture 03:** Human Genetic Variation, Mendel's Law **Reading:** a. 1000 Genomes Project, C. *et al.* (2015) 'A global reference for human genetic variation', *Nature*.
	9/2 (Chiang)	**Paper Discussion:** 1. Biddanda, A., Rice, D. P. and Novembre, J. (2020) 'A variant-centric perspective on geographic patterns of human allele frequency variation', *eLife*. 2. Lek, M. *et al.* (2016) 'Analysis of protein-coding genetic variation in 60,706 humans', *Nature*.
3	**9/7 (Chaisson)**	**Lecture 04:** Methods to Assay Genetic Variation **Reading:** a. Shendure, J. *et al.* (2017) 'DNA sequencing at 40: past, present and future', *Nature*. b. Zhao, X. *et al.* (2021) 'Expectations and blind spots for structural variation detection from long-read assemblies and short-read genome sequencing technologies', *The American Journal of Human Genetics*.
	9/9 (Chiang)	**Lecture 05:** Mutations and Recombination **Reading:** a. Ségurel, L., Wyman, M. J. and Przeworski, M. (2014) 'Determinants of Mutation Rate Variation in the Human Germline', *Annual Review of Genomics and Human Genetics*.

		b. Goldmann, J. M., Veltman, J. A. and Gilissen, C. (2019) 'De Novo Mutations Reflect Development and Aging of the Human Germline', *Trends in Genetics*.
4	**9/14 (Chiang)**	**Paper Discussion:** 3. Jonsson, H. *et al.* (2021) 'Differences between germline genomes of monozygotic twins', *Nature Genetics*. 4. Sasani, T. A. *et al.* (2019) 'Large, three-generation human families reveal post-zygotic mosaicism and variability in germline mutation accumulation', *eLife*.
	9/16 (Chiang)	**Lecture 06:** Population Structure, Demographic History Inference **Reading:** Human Evolutionary Genetics, Chapter 5 (on Reserve)
5	**9/21 (Chiang)**	**Paper Discussion:** 5. Zaidi, A. A. and Mathieson, I. (2020) 'Demographic history mediates the effect of stratification on polygenic scores', *eLife*. 6. Li, H. and Durbin, R. (2011) 'Inference of human population history from individual whole-genome sequences', *Nature*. 7. Gravel, S. *et al.* (2011) 'Demographic history and rare allele sharing among human populations', *Proc Natl Acad Sci U S A*.
	9/23 (Chiang)	**Lecture 07:** Admixture, Ancestry Inference, Admixture Mapping **Reading:** a. Mathieson, I. and Scally, A. (2020) 'What is ancestry?', *PLoS genetics*. b. Winkler, C. A., Nelson, G. W. and Smith, M. W. (2010) 'Admixture mapping comes of age', *Annual Review of Genomics and Human Genetics*. ***Midterm paper topic due.***
6	**9/28 (Chiang)**	**Paper Discussion:** 8. Ioannidis, A. G. *et al.* (2020) 'Native American gene flow into Polynesia predating Easter Island settlement', *Nature*. 9. Spear, M. L. *et al.* (2020) 'Recent shifts in the genomic ancestry of Mexican Americans may alter the genetic architecture of biomedical traits', *eLife*.
	9/30 (Gazal)	**Lecture 08:** Pedigree Analysis, Mendelian Disease and Gene Mapping, Linkage Analysis **Reading:** a. Ott, J., Wang, J. and Leal, S. M. (2015) 'Genetic linkage analysis in the age of whole-genome sequencing', *Nature Reviews. Genetics*. b. Ng, S. B. *et al.* (2010) 'Exome sequencing identifies the cause of a mendelian disorder', *Nature Genetics*.

7	**10/5 (Gazal)**	**Lecture 09:** Complex Trait Analysis, GWAS, Phasing and Imputation, Population Stratification **Reading:** a. Visscher, P. M. *et al.* (2017) '10 Years of GWAS Discovery: Biology, Function, and Translation', *Am J Hum Genet*. b. Claussnitzer, M. *et al.* (2020) 'A brief history of human disease genetics', *Nature*.
	10/7 (Gazal, Chiang)	**Paper Discussion:** 10. The Wellcome Trust Case Control Consortium (2007) 'Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls', *Nature*. 11. Schizophrenia Working Group of the Psychiatric Genomics Consortium (2014) 'Biological insights from 108 schizophrenia-associated genetic loci', *Nature*.
8	**10/12 (Chiang)**	**Lecture 10:** Natural Selection, Polygenic Adaptation **Reading:** a. Fan, S. *et al.* (2016) 'Going global by adapting local: A review of recent human adaptation', *Science*. ***Midterm paper due.***
	10/14	**FALL RECESS**
9	**10/19 (Dinh)**	**Lab:** R/Linux Tutorial, Allele Frequency Estimations
	10/21 (Dinh)	**Lab:** HGDP Population Structure Exercises
10	**10/26 (Dinh)**	**Lab:** 1000 Genomes Selection Exercises
	10/28 (Chiang)	**Paper Discussion:** 12. Berg, J. J. and Coop, G. (2014) 'A population genetic signal of polygenic adaptation', *PLoS Genet*. 13. Sohail, M. *et al.* (2019) 'Polygenic adaptation on height is overestimated due to uncorrected stratification in genome-wide association studies', *Elife*.
11	**11/2 (Young)**	**Lecture 11:** Genetic Nurture **Reading:** a. Young, A. I. *et al.* (2019) 'Deconstructing the sources of genotype-phenotype associations in humans', *Science*.

	11/4 (Edge)	**Lecture 12:** Forensic Genetics, Golden State Killer Case, and Genetic Privacy **Reading:** a. Edge, M. (Doc) and Coop, G. (2019) *How lucky was the genetic investigation in the Golden State Killer case? bioRxiv*. b. Molteni, M. 'Cops are Getting a New Tool for Family-Tree Sleuthing' Wired (on Reserve)
12	**11/9 (Mooney)**	**Lecture 13:** Race, Eugenics, and Disparity in GWAS **Reading:** Eugenic Nation by Alexandra Minna Stern (Introduction and Chapter 3, on Reserve))
	11/11 (Edge, Chiang)	**Paper Discussion:** 14. Edge, M. D. and Coop, G. (2020) 'Attacks on genetic privacy via uploads to genealogical databases', *eLife*. 15. Erlich, Y. *et al.* (2018) 'Identity inference of genomic data using long-range familial searches', *Science*.
13	**11/16 (Mooney, Chiang)**	**Paper Discussion:** 16. Martin, A. R. *et al.* (2019) 'Clinical use of current polygenic risk scores may exacerbate health disparities', *Nature Genetics*. 17. Muller, H. J. (1950) 'Our load of mutations', *American Journal of Human Genetics*.
	11/18 (Chiang)	**Lecture 14:** Genetic Testing, Genetic Prediction, Embryo Selection. **Reading:** a. Choi, S. W., Mak, T. S.-H. and O'Reilly, P. F. (2020) 'Tutorial: a guide to performing polygenic risk score analyses', *Nature Protocols*. b. Khera, A. V. *et al.* (2018) 'Genome-wide polygenic scores for common diseases identify individuals with risk equivalent to monogenic mutations', *Nat Genet*.
14	**11/23 (Chiang)**	**Paper Discussion:** 18. Harden, K. P. *et al.* (2020) 'Genetic associations with mathematics tracking and persistence in secondary school', *npj Science of Learning*. 19. Karavani, E. *et al.* (2019) 'Screening Human Embryos for Polygenic Traits Has Limited Utility', *Cell*. 20. Khera, A. V. *et al.* (2019) 'Polygenic Prediction of Weight and Obesity Trajectories from Birth to Adulthood.', *Cell*. ***Final Group Project topic approval deadline.***
	11/25	**THANKSGIVING**

15	**11/30 (Chiang)**	**Lecture 15:** (tentatively) Human Evolutionary History, Archaic Humans, Phenotypic Legacy from Archaic Admixture **Reading:** TBA
	12/2 (Chiang)	**Paper Discussion:** 17. TBA 18. TBA ***Self-Assessment Survey #2 Due.***
16	**12/7**	
	12/9	***Final Group Project Write-Up due.***

Statement on Academic Conduct and Support Systems

Academic Conduct:

[The text below should be included but always check the Syllabus template at the CET site and ensure that your syllabus has the most current text for this section.]

Plagiarism – presenting someone else's ideas as your own, either verbatim or recast in your own words – is a serious academic offense with serious consequences. Please familiarize yourself with the discussion of plagiarism in SCampus in Part B, Section 11, "Behavior Violating University Standards." Other forms of academic dishonesty are equally unacceptable. See additional information in SCampus and university policies on scientific misconduct.

Support Systems:

Counseling and Mental Health

phone number (213) 740-9355
On call 24/7
Free and confidential mental health treatment for students, including short-term psychotherapy, group counseling, stress fitness workshops, and crisis intervention.

National Suicide Prevention Lifeline

Phone number 1 (800) 273-8255
On call 24/7

Free and confidential emotional support to people in suicidal crisis or emotional distress 24 hours a day, 7 days a week.

Relationship and Sexual Violence Prevention Services (RSVP)
Phone Number (213) 740-9355(WELL), press “0” after hours
On call 24/7
Free and confidential therapy services, workshops, and training for situations related to gender-based harm.

USC Office of Equity, Equal Opportunity, and Title IX
Phone number (213) 740-5086
Title IX Office (213) 821-8298
Information about how to get help or help someone affected by harassment or discrimination, rights of protected classes, reporting options, and additional resources for students, faculty, staff, visitors, and applicants.

Reporting Incidents of Bias or Harassment

Phone number (213) 740-5086 or (213) 821-8298
Avenue to report incidents of bias, hate crimes, and microaggressions to the Office of Equity, Equal Opportunity, and Title IX for appropriate investigation, supportive measures, and response.

The Office of Disability Services and Programs

Phone number (213) 740-0776
Support and accommodations for students with disabilities. Services include assistance in providing readers/notetakers/interpreters, special accommodations for test taking needs, assistance with architectural barriers, assistive technology, and support for individual needs.

USC Campus Support and Intervention

Phone number (213) 821-4710
Assists students and families in resolving complex personal, financial, and academic issues adversely affecting their success as a student.

Diversity at USC

Phone number (213) 740-2101
Information on events, programs and training, the Provost’s Diversity and Inclusion Council, Diversity Liaisons for each academic school, chronology, participation, and various resources for students.

USC Emergency

UPC phone number (213) 740-4321
HSC phone number (323) 442-1000
On call 24/7

Emergency assistance and avenue to report a crime. Latest updates regarding safety, including ways in which instruction will be continued if an officially declared emergency makes travel to campus infeasible.

USC Department of Public Safety

UPC phone number (213) 740-6000
HSC phone number (323) 442-120
On call 24/7
Non-emergency assistance or information.