Human Genetics 542
Molecular Basis of Human Genetic Disease
Winter 2022 Syllabus

Monday, Wednesday, and Friday
9 – 10 a.m.
Med Sci II South Lecture Hall (unless otherwise noted)
Zoom link: https://umich.zoom.us/s/94267208037
Course Director: Tony Antonellis

Course Description: How do researchers study families or populations of individuals with a genetic disease to identify the disease-associated mutations? How are disease-associated variants transmitted through families and populations? How does a mutation in the human genome lead to a specific disease phenotype? How can this genetic information be used to benefit patient populations? What do genetic diseases tell us about human biology? These are just a few of the questions that Human Genetics 542 (HG542) "Molecular Basis of Human Genetic Disease" addresses using examples from the current and classic literature. HG542 emphasizes concepts including, but not limited to: (***i***) the nature of human genomic variation; (***ii***) strategies for mapping disease-associated genetic variation; (***iii***) the role of the environment in inherited disease phenotypes; (***iv***) the design and interpretation of experiments to characterize the molecular pathology of implicated mutations; and (***v***) how these discoveries are moved into the clinic. HG542 is an essential course for anyone interested in molecular genetics and human variation as it relates to human disease.

Course learning objectives:
1. Learn how pathogenic alleles are transmitted in families and populations
2. Learn approaches for disease gene discovery
3. Learn approaches for defining the molecular mechanisms of disease
4. Learn how disease gene discoveries apply in a clinical setting
5. Learn to design experiments that advance knowledge in genetic disease

Lecture Format for Winter 2022: Lectures will be held in person, in South Lecture Hall in Med Sci II with one exception: Monday February 21st will be held in North Lecture Hall in Med Sci II. The lectures will also be transmitted and recorded via Zoom at the link above. Instructors may choose to provide a previously recorded version of the lecture for review before and after the in-person lecture. In addition, the seven student-presented paper discussions will be held in-person during class time (these will be recorded), the three exam review sessions will be in person during class time, and three exams will be in person from 8am to 10am.

Grading: Final grades for HG542 will be based on the three exams (25% each; 75% total), seven problem sets (10% total), and one group presentation (15% total).

Exams: Each exam will cover all course materials (lectures, paper discussions, problem sets) since the previous exam; the exams will not be cumulative. Experimental design will be emphasized on the exams, but some questions may require students to define specific concepts or terms. At 8am on the exam day, exams will be distributed on paper in the lecture hall. The exam should be completed individually (please write clearly) and handed in before 10am.

Problem Sets: This class will include seven paper discussion sessions. For each discussion session, the instructor directing the session will assign one paper and a brief three-question problem set that assesses a general understanding of the paper. All students must read the paper prior to the discussion and submit a completed problem before the beginning of class on the day of the discussion. Problem sets should be emailed directly to the relevant instructor (see below).

Student-led Presentations: This class will include seven paper discussion sessions. At the beginning of the semester, groups of ~5 students will be formed by the course director; groups will be designed to include members of diverse training programs (see groupings on HG542 Canvas site). For each discussion session, one paper will be assigned by the instructor(s) and one student group will be responsible for presenting the paper and for leading a discussion of the paper with the other student groups. The group responsible for leading the discussion should carefully read the paper and prepare a 'journal club'-style presentation that includes: background and key questions being addressed; methods used to address the questions; and key findings and interpretations. The group should also prepare three discussion points that do

not overlap with the problem set (see above). Each discussion session is scheduled for 50 minutes (9:00am to 9:50am). The first 30 minutes should be spent presenting the paper and the last 20 minutes should be spent presenting discussion points to the class followed by small-group discussions where each group briefly reports the summary of their discussion to the class. Importantly, the presenting group should divide the work evenly among group members. Finally, each presenting group should meet with the relevant instructor the week prior to their presentation to go over how they will direct the discussion including a review of their slides and the three discussion points; a 30-minute meeting should be sufficient.

Academic Honor Code: It is required that the seven problem sets and the three exams reflect an individual effort by each student; of course, students are required to work as a group for the paper presentation. Any deviation from this expectation will be handled on a case-by-case basis. The Department of Human Genetics holds all members of its community to high standards of scholarship and integrity. It is the responsibility of all students to become knowledgeable about the definitions of academic integrity and ethical standards for the University of Michigan and Rackham Graduate School. Academic dishonesty or misconduct may be understood as actions or attempted actions to create an unfair academic advantage for oneself. Examples of violations of academic integrity include, though are not limited to, cheating, plagiarism, using resources for exams and/or assignments without explicit approval of an instructor, and discussing or sharing information about exam and/or assignment questions without explicit approval of an instructor. The Department will not tolerate violations of academic integrity and will take disciplinary action, if warranted. By upholding these standards, we ensure a scholarly educational environment for developing future leaders in research and academia.

Expectations of Students: Students are expected to: attend lectures, discussions, and student presentations; engage in class and group discussions; read papers and *independently* complete problem sets prior to the paper discussions; and *independently* complete all assignments and exams.

Expectations of Instructors: Instructors are expected to: begin lectures and/or discussions promptly at 9am and end by 9:50am; clearly present lecture material; answer student questions during the lecture or after the lecture if time is an issue; make themselves available for help and questions via scheduled appointments; and return problem sets and exams within two weeks of the date of completion.

Sensitivities to Topic Areas: The goal of this class is to discuss important topics related to human inherited phenotypes. Throughout the course we will be discussing an array of human phenotypes including, but not limited to, single-gene disorders in small families, complex diseases in large populations, developmental diseases, cancers, and sex reversal (where the genotypic and phenotypic sex of an individual are discordant). The instructors and the students are expected to conduct these conversations in a science-centric, positive, and constructive manner. Please note that some of the historical literature used in this class may use terms that, while scientifically acceptable at the time, could now be viewed by some as insensitive. Please direct any concerns in this area to the course director.

HG542 Instructor Contact Information:

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Human Genetics 542
Class Descriptions

Wednesday, January 5, 2022 Antonellis
"Mapping disease genes I: inheritance patterns and linkage analysis" (Antonellis): This lecture will cover the basic concepts of mapping disease genes using pedigrees. This includes the modes of Mendelian inheritance, mapping a Mendelian disease using linkage analysis, fine-mapping a disease locus, and logical assessments of candidate genes. As an example we will use the mapping of a gene responsible for Charcot-Marie-Tooth (CMT) disease and will discuss issues that arise when studying a clinically, genetically, and allelically heterogeneous disease. We will also cover a number of factors that complicate disease gene mapping studies, and approaches that can be used to circumvent them.

Friday, January 7, 2022 Antonellis
"Mapping disease genes II: identifying disease-associated variants" (Antonellis): This lecture will include a practical application of disease gene mapping using current methods that demonstrate the process of identifying a single-gene disorder starting at the genome level. We will also cover approaches for identifying disease-associated variants in the absence of protein-coding sequence differences.

Monday, January 10, 2022 Prasov
"Mendelian gene discovery and validation: lessons from eye disease": This presentation will cover gene discovery efforts and functional studies to determine the molecular pathology of human inherited eye disease. While it is not required, students may want to read this paper from Dr. Prasov's lab: https://www.ncbi.nlm.nih.gov/pubmed/31048900.

Wednesday, January 12, 2022 Antonellis
"Functional characterization of disease-associated mutations I" (Antonellis): This lecture will cover approaches for validating disease-associated mutations, the classes of molecular pathology, and a battery of functional studies to tease out the consequences of mutations on gene function. An emphasis will be placed on assessing the resolution of functional assays.

Friday, January 14, 2022 Antonellis
"Functional characterization of disease-associated mutations II" (Antonellis): In this lecture we will continue our discussion of functional studies employed to discover how a single mutation in protein-coding or non-coding genomic sequences affect gene function to lead to Mendelian disease phenotypes.

Monday, January 17, 2022 **No Class**
Martin Luther King Jr. Day

Wednesday, January 19, 2022 Antonellis
Paper discussion I (Antonellis); problem set due at beginning of class.

Friday, January 21, 2022 Antonellis
Paper discussion II (Antonellis); problem set due at beginning of class.

Monday, January 24, 2022 Antonellis
"Diseases associated with a loss-of-function effect" (Antonellis): This lecture will cover the molecular mechanisms of diseases caused by a loss (or decrease) of gene function, including hemoglobinopathies, cystic fibrosis, and Waardenburg-Shah syndrome. We will also discuss experimental approaches to discern between haploinsufficiency and dominant-negative effects.

Wednesday, January 26, 2022 Antonellis
"Diseases associated with a gain-of-function effect" (Antonellis): This lecture will cover the molecular mechanisms of human phenotypes caused by a gain of gene function, including *PMP22* gene duplications in Charcot-Marie-Tooth disease and *FGFR3* mutations in achondroplasia.

Friday, January 28, 2022 Antonellis

"Mitochondria, Modifiers, and Blended Mendelian Phenotypes: windows into more complex issues" (Antonellis): This lecture will build upon our discussions of single-gene disorders to consider some more complicated scenarios moving toward complex phenotypes. First, we will briefly review mitochondrial function and the molecular mechanisms of diseases caused by mitochondrial genome mutations. Second, we will introduce the recently conceived idea of 'blended phenotypes', where individual patients have multiple, independent Mendelian disease phenotypes. Finally, we will discuss how genetic modifiers impact the penetrance of Mendelian disease phenotypes and how investigators map such modifier genes.

Monday, January 31, 2022 Antonellis
"Mapping complex diseases: single-marker and genome-wide approaches" (Antonellis): We will discuss the principles of genetic association studies in large patient populations in the context of disease allele transmission. We will discuss basic principles and single-marker analyses using examples of case-control studies and transmission disequilibrium tests.

Wednesday, February 2, 2022 Antonellis
Paper discussion III (Antonellis); problem set due at beginning of class.

Friday, February 4, 2022 Antonellis
Review session for Exam I

Monday, February 7, 2022 Antonellis
Exam I – 8 to 10 a.m.

Wednesday, February 9, 2022 Moran
"Sex determination" (Moran): What happens when fundamental "rules" about sex determination in model organisms differ from those used in mammals? We will discuss how human and mouse genetics were used to elucidate the general rules of mammalian sex determination. This lecture provides illustrative examples of Bateson's seminal concept "Treasure your exceptions!" It also highlights the basic principles of "necessity" and "sufficiency" in genetic studies.

Friday, February 11, 2022 Moran
"Prion diseases" (Moran): What happens when your data do not fit established paradigms and/or models? Prion diseases provide an illustrative example of how a union of biochemical and genetic approaches can be used to solve a perplexing scientific problem. This lecture will highlight the concepts of "empiricism" and the "courage of your convictions." The lecture also will build upon our discussion regarding the principles of "necessity" and "sufficiency" in genetic studies.

Monday, February 14, 2022 Ganesh
"**Genome-wide association approaches to study complex diseases**" (Ganesh): We will review case-control and population-based approaches to identify disease-associated genetic loci, including phenotype considerations, study designs, association testing for rare and common genetic variation, and possible confounders. We will discuss how to interpret association study results, and potential extensions into risk prediction using polygenic risk scores and biologic insight by functional analysis.

Wednesday, February 16, 2022 Ganesh
"Genomics and cardiovascular disease" (Ganesh): We will discuss genomic studies of cardiovascular diseases, many of which are highly prevalent and have a complex genetic basis. We will review statistical power for association studies, advantages and disadvantages of studying dichotomous and continuous traits, and recent developments from large-scale gene discovery efforts. We will continue to discuss how specific genes can be prioritized for further functional analysis.

Friday, February 18, 2022 Kohrman
"Genetic and environmental interactions in Mendelian disease I" (Kohrman): This lecture will cover the concepts of genetic complementation, digenic, and tri-allelic inheritance, using examples from auditory and retinal disease. We will also discuss the role of genetic 'background' and the ability of modifier genes to alter genotype-phenotype correlations.

Monday, February 21, 2022 Kohrman *This session will be in Med Sci II North Lecture Hall
"Genetic and environmental interactions in Mendelian disease II" (Kohrman): This lecture will continue discussion of genetic interactions involved in disease and also touch on the role of gene X environment interactions.

Wednesday, February 23, 2022 Yashar
"General Principles in Genetic Testing" (Yashar): What are the types of genetic tests that are currently available to patients? This lecture will help students understand critical factors in evaluating the actual test, the potential utility of results to patients and their families and the decision making process utilized by clinicians.

Friday, February 25, 2022 Yashar
"Genetic Testing across the Lifespan" (Yashar): This lecture will evaluate genetic testing across the life span (prenatal, pediatrics and adult) and identify issues specific to each patient population/category. Exploration and evaluation will rely on molecular, clinical and ethical perspectives.

Monday, February 28, 2022 **No Class**
Spring Break

Wednesday, March 2, 2022 **No Class**
Spring Break

Friday, March 4, 2022 **No Class**
Spring Break

Monday, March 7, 2022 Yashar
Paper discussion IV (Yashar); problem set due at beginning of class.

Wednesday, March 9, 2022 Antonellis and Yashar
"Community engagement in genetic disease research" (Antonellis and Yashar): This class session will be dedicated to a discussion on issues pertaining to diversity, equity, and inclusion that directly apply to inherited disease research. Topics will be selected annually to reflect current issues, which may include—but will not be limited to—those that arise when using patient materials for genetic disease research. Content and reading materials for this session will be provided to the class at least two weeks prior to the discussion, which will be held during the normal lecture time. For Winter 2021, no pre-recorded lecture will be provided for this session.

Friday, March 11, 2022 Moran, Kohrman, Yashar
Review session for Exam II

Monday, March 14, 2022 Antonellis
Exam II – 8 to 10 a.m.

Wednesday, March 16, 2022 Sekiguchi
"Introduction to cancer genetics" (Sekiguchi): This lecture will cover the principles of cancer as a genetic disease. We will go over the concepts of the multiple hit hypothesis and discuss the types of mutations that are acquired during the course of tumorigenesis.

Friday, March 18, 2022 Sekiguchi
"Inherited cancer predisposition syndromes" (Sekiguchi): We will discuss the molecular mechanisms underlying cancer predisposition caused by inherited mutations in tumor suppressor genes, oncogenes and genome stability genes. The concept of inherited susceptibility to cancer will also be covered.

Monday, March 21, 2022 Sekiguchi
"Genome instability and oncogenic mutations" (Sekiguchi): This lecture will cover the mechanisms by which somatic cells acquire oncogenic mutations. We will discuss the evolving hypothesis of the molecular basis of the anti-cancer barrier. The concepts of mutation rate and selection will also be covered.

Wednesday, March 23, 2022 Sekiguchi
"Chromosomal anomalies in cancer" (Sekiguchi): This lecture will cover the types of chromosomal anomalies that arise in cancer, and we will discuss the molecular mechanisms by which these oncogenic events occur. We will discuss what is currently understood about how recurrent translocations are generated and the mechanisms by which chromosomal instability in cancer cells can arise.

Friday, March 25, 2022 Sekiguchi
Paper discussion V (Sekiguchi); problem set due at beginning of class.

Monday, March 28, 2022 Glover
"Classic chromosome abnormalities I: Anuploidy" (Glover): This lecture will cover the origins, mechanisms and consequences of germline and somatic aneuploidy in humans and its major role in genetic disorders.

Wednesday, March 30, 2022 Glover
"Classic chromosome abnormalities II: Gross rearrangements and microdeletion syndromes" (Glover): This lecture will cover the causes and consequences of gross structural rearrangements from translocations and other gross rearrangements to the microdeletions found in the microdeletion syndromes. We will discuss how our understanding of the mechanisms causing these aberrations relates to parental origin and genetic risk.

Friday, April 1, 2022 Glover
"Submicroscopic chromosome rearrangements" (Glover): We will discuss the events leading to the discovery of the surprisingly large amount of submicroscopic chromosomal structural variation and its role in evolution and phenotypic variation. We will focus on the importance of CNVs as a major class of mutation in human disease and the molecular mechanisms by which they arise.

Monday, April 4, 2022 Glover
"Fragile X syndrome and nucleotide repeat disorders" (Glover): The nucleotide repeat disorders illustrate a number of principles in human genetics including dynamic mutation, anticipation, allelic heterogeneity, protein and RNA-mediated pathogenesis. The different classes of nucleotide repeat disorders will be discussed with a focus on fragile X syndrome.

Wednesday, April 6, 2022 Glover
Paper discussion VI (Glover); problem set due at beginning of class.

Friday, April 8, 2022 Parker
"GWAS signal to mechanism: identifying relevant tissues and causal regulatory variants" (Parker): The majority of GWAS loci occur in non-coding regions, which strongly implicates regulatory element biology as a driver of genetic risk and evokes important corollary questions like: what are the relevant tissues, of all the SNPs in LD which subset may be the causal set, what are the target genes, and what direction of effect does the risk allele have on the target gene? In this lecture we will discuss methods to identify relevant tissues and nominate causal regulatory variants.

Monday, April 11, 2022 Parker
"GWAS signal to mechanism: nominating target genes using expression and chromatin QTL" (Parker): This second GWAS functional follow-up lecture will introduce the idea of building statistical association maps of genotypes with molecular features (gene expression or chromatin accessibility) to identify expression quantitative trait loci (eQTL) and chromatinQTL. We will then discuss how these e/chromatinQTL signals are compared to GWAS signals using colocalization techniques, including important caveats to consider when using such methods. Collectively, these approaches can nominate target genes and identify the risk allele directional effect (over- or under-expression of the target gene).

Wednesday, April 13, 2022 Parker
Paper discussion VII (Parker); problem set due at beginning of class.

Friday, April 15, 2022 Glover, Sekiguchi, Parker

Review session for Exam III

Monday, April 18, 2022 Antonellis

Exam III – 8 to 10 a.m.