Human Genetics 542 Winter 2018 Syllabus

Monday, Wednesday, and Friday
9 – 10 a.m.
5915 Buhl

Course Director: Tony Antonellis

Jan 3rd Wed "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, the type of mutations that can be found, and the predicted effect of mutation classes on gene function. We will also cover a number of factors that complicate these studies, and approaches that can be used to circumvent them.

Jan 5th Fri "Mapping disease genes II: identifying disease-associated variants" (Antonellis): The second lecture will include a practical application of linkage analysis using current methods. As an example we will use the mapping of a gene responsible for Charcot-Marie-Tooth disease and will discuss the issues that arise when studying a clinically, genetically, and allelically heterogeneous disease. Finally, we will cover experimental approaches for identifying disease-associated variants in the absence of protein-coding sequence differences.

Jan 8th Mon "Functional characterization of disease-associated mutations" (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 specific functional assays.

Jan 10th Wed "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.

Jan 12th Fri "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.

Jan 15th Mon No Class - MLK Day

Jan 17th Wed "Mitochondria and Modifiers: windows into more complex issues" (Antonellis): The first half of this lecture will cover a brief review of mitochondrial function and the molecular mechanisms of mitochondrial diseases caused by nuclear and mitochondrial genome mutations. The second half will cover factors that make Mendelian diseases complicated (small pedigrees, sporadic cases, incomplete penetrance, variable expression, phenotype modifiers, pleiotropy, dominance modification, etc.) and specific examples of how to map genes that modify Mendelian phenotypes.

Jan 19th Fri Discussion – (Antonellis)

Jan 22nd Mon "Genetic and environmental interactions in Mendelian disease I" (Kohrman): These lectures 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 and environmental effects to alter genotype-phenotype correlations.

Jan 24th Wed "Genetic and environmental interactions in Mendelian disease II" (Kohrman): These lectures 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 and environmental effects to alter genotype-phenotype correlations.

Jan 26th Fri "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.

Jan 29th Mon "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.

Jan 31st Wed Discussion – (Moran and Kohrman)

Feb 2nd Fri Exam I – 8 to 10 a.m.

Feb 5th Mon "Meiosis gone wrong: Aneuploidy" (Glover): This lecture will cover the basic principles of chromosome structure and mechanisms of meiosis and meiotic recombination and how these mechanisms and maternal age influence the origin of aneuploidy in humans.

Feb 7th Wed "Zooming in on Structural rearrangements " (Glover): This lecture will cover the causes and consequences of structural rearrangements from translocations and other gross rearrangements to microdeletions and copy number variants. We will discuss how our understanding of the mechanisms causing these aberrations has changed over the past few years and how this relates to parental origin and genetic risks.

Feb 9th Fri "Copy number variants in the human genome" (Glover): We will cover the events leading to the discovery of the surprisingly large amount of normal chromosomal structural variation, its role in evolution and phenotypic variation and the tools used to detect these changes. We will discuss the importance of CNVs as a major class of mutation in human disease, the different types of structural variants and the molecular mechanisms by which they arise, and how these mechanistic origins dictate genetic risks.

Feb 12th Mon "Fragile X syndrome and trinucleotide repeat disorders " (Glover): The trinucleotide 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.

Feb 14th Wed Discussion – (Glover)

Feb 16th Fri "Genomics for the study of complex diseases" (Willer): An overview of the hypotheses underlying genome-wide association studies, as well as the basics of imputation from HapMap, and other study design issues such as joint analysis vs replication. We will discuss the overlap of genes identified from study of rare Mendelian forms of complex disease and complex diseases in large populations. We will also

discuss population stratification and how to account for it. The genetic study of type 2 diabetes and obesity will be provided as examples.

Feb 19th Mon "Genomics and cardiovascular disease" (Willer): We will continue discussion of genomic studies, including how to increase power for these studies, to increase the proportion of trait variance explained and, more importantly, how to develop more complete understanding of the genetic basis of these phenotypes. We will discuss the utility of quantitative traits, why we focus on coding variation, and efforts to discover the functional gene after identifying statistical association. We will use cardiovascular disease and related quantitative traits as an example.

Feb 21st Wed "Next-generation sequencing for Mendelian diseases" (Willer): We will discuss analysis of whole genome and whole exome sequencing studies and attempts to uncover novel genes and variants associated with Mendelian diseases. We will discuss methods for identifying causal variants from sequence data. Disease examples include Miller Syndrome and Kabuki Syndrome.

Feb 23rd Fri "Next-generation sequencing for complex diseases" (Willer): We will continue to discuss analysis of whole genome sequencing and whole exome sequencing studies and focus in this lecture on recent attempts to uncover novel genes and variants associated with complex genetic diseases. We will discuss issues related to study design, quality control and filtering of sequence data, rare variant burden tests, and findings for complex diseases. Disease examples include type 2 diabetes, hypertriglyceridemia and cardiovascular disease.

Feb 26th Mon No Class - Spring Break

Feb 28th Wed No Class - Spring Break

Mar 2nd Fri No Class - Spring Break

Mar 5th Mon "Gene x environment interaction in behavior" (Willer): We will discuss two Science papers by Caspi 2002 and Caspi 2003 showing gene x environment interaction for aggressive-impulsive-criminal behavior, and for risk for depression, as well as the entanglement of genes and environment and how it can be resolved.

Mar 7th Wed "Pharmacogenetics" (Willer): Genetic variants affect how drugs are metabolized, and how drugs act on their target. This results in differences in efficacy and side effect profiles. Drugs can also interact with each other in the same pathways, and with nutrition. Many of these genetic variants show large allele frequency differences, resulting in different susceptibilities in different ethnic groups. In some cases, genetic tests are now recommended or required before starting a drug

Mar 9th Fri Discussion – (Willer)

Mar 12th Mon Exam II – 8 to 10 a.m.

Mar 14th Wed "Epigenetic inheritance of chromatin states / Role of DNA methylation in human disease" (Kalantry): Epigenetic dysregulation is increasingly thought to contribute to human disease etiology. Epigenetic mechanisms ensure transmission of gene expression states through cell division and do not involve permanent changes in the DNA sequence. In this first lecture, we will survey various modes of epigenetic inheritance and focus on the contribution of DNA methylation to human disease.

Mar 16th Fri "Role of histone post-translational modifications in disease" (Kalantry): In addition to DNA methylation, covalent modifications of histone proteins in chromatin are known to play a critical role in

epigenetic inheritance. In this lecture, we will discuss instances where dysregulation of the histone modification machinery is believed to be a component of human disease.

Mar 19th Mon "Transgenerational epigenetic inheritance" (Kalantry): A class of genes, referred to as imprinted, is preferentially expressed either from the paternal or the maternal allele. The two alleles of an imprinted gene must therefore be differentially epigenetically marked in the parental germline. Thus, imprinted genes provide an example of meiotic, *i.e.*, transgenerational, epigenetic gene regulation. We will delve into disease syndromes that arise due to abnormal imprinted gene expression. The study of these disorders provides insights into how transgenerational epigenetic inheritance is executed.

Mar 21st Wed Discussion – (Kalantry)

Mar 23rd Fri "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.

Mar 26th Mon "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.

Mar 28th Wed "From Bench to Bedside and Beyond" (Yashar): How is a discovery translated into clinical practice and what happens when genetic testing technology moves outside of the medical system? When a genetic explanation for a disease is identified, what happens next in the translational pipeline? We will consider how federal regulations and professional society guidelines intersect with personal ethics and responsibilities.

Mar 30th Fri Discussion – (Yashar)

Apr 2nd Mon "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.

Apr 4th Wed "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.

Apr 6th Fri "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.

Apr 9th Mon "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.

Apr 11th Wed "Evolving topics in cancer genetics" (Sekiguchi): We will discuss current topics in the rapidly moving field of cancer genetics.

Apr 13th	**Fri**	**Discussion – (Sekiguchi)**
Apr 16th	**Mon**	**Exam III – 8 to 10 a.m.**