Human Genetics 542 Winter 2019 Syllabus

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

Course Director: Tony Antonellis

Jan 9th 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, 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.

Jan 11th Fri "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.

Jan 14th 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 functional assays.

Jan 16th Wed "Loss- vs. gain-of-function effects" (Antonellis): This lecture will cover the molecular mechanisms of diseases caused by a loss or gain of gene function. First, we will extend our CMT examples by discussing how gene amplification causes demyelinating peripheral neuropathy. Second, we will extend our aminoacyl-tRNA synthetase examples by discussing unpublished data on how loss-of-function cysteinyl-tRNA synthetase (*CARS*) variants cause a multi-syndrome recessive disease that includes peripheral neuropathy.

Jan 18th Fri Paper Discussion I (Antonellis)

Jan 21st Mon No Class - MLK Day

Jan 23rd Wed Paper Discussion II (Antonellis)

Jan 25th Fri "Role of DNA methylation and histone post-translational modifications in human disease" (Kalantry): Epigenetic dysregulation is increasingly thought to contribute to human disease etiology. Methylation of DNA and covalent modifications of histone proteins in chromatin are believed to play a critical role in epigenetic inheritance. In this lecture, we will explore how dysregulation of the cellular chromatin modification machinery contributes to human disease.

Jan 28th 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.

Jan 30th Wed Paper Discussion III (Kalantry)

Feb 1st Fri "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.

Feb 4th Mon "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.

Feb 6th Wed Review session for Exam I

Feb 8th Fri Exam I – 8 to 10 a.m.

Feb 11th Mon "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.

Feb 13th Wed "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.

Feb 15th Fri Paper Discussion IV (Moran)

Feb 18th Mon "Genomics for the study of complex traits" (Gagliano): An overview of the hypotheses underlying genome-wide association studies, as well as study design. We will discuss population stratification and how to account for it, quality control and filtering of genetic data, and rare variant burden tests. We will introduce the concept of heritability and discuss how to measure it in various study designs.

Feb 20th Wed "Genomics for the study of complex traits- part 2" (Gagliano): We will continue the discussion of genome-wide association studies, including the basics of genotype imputation, how to increase power for these studies to increase the proportion of trait variance explained and how to develop more a complete understanding of the genetic basis of complex traits. We will discuss why we focus on coding variation, and efforts to discover the functional gene after identifying statistical association.

Feb 22nd Fri "Gene by environment interaction" (Gagliano): We will discuss gene by environment interactions with examples such as from the Science paper Caspi 2003 showing gene by environment interaction for risk of depression, as well as the entanglement of genes and environment and how it can be resolved.

Feb 25th Mon Paper Discussion IV (Gagliano)

Feb 27th Wed "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..

Mar 1st Fri "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).

Mar 4th Mon No Class - Spring Break

Mar 6th Wed No Class - Spring Break

Mar 8th Fri No Class - Spring Break

Mar 11th Mon Paper Discussion VI (Parker)

Mar 13th Wed Review session for Exam II

Mar 15th Fri Exam II – 8 to 10 a.m.

Mar 18th Mon "Classic chromosome abnormalities in humans" (Glover): This lecture will cover the origins, mechanisms and consequences of aneuploidy and gross chromosome rearrangements in humans and their major role in genetic disorders.

Mar 20th Wed "Microdeletions and copy number variants" (Glover): We will cover the events leading to the discovery of the surprisingly large amount of normal submicroscopic genomic structural variation, its role in evolution and phenotypic variation and the evolution of tools used to detect these changes. We will discuss the genetic principles learned from microdeletion syndromes and the importance of CNVs as a major class of mutation in human disease and how their mechanistic origins dictate genetic risks.

Mar 22nd Fri "Somatic mutations in genetic disease" (Glover): It is becoming increasingly clear that the contribution of somatic mosaicism to human disorders is greater than has been commonly appreciated. Disorders caused by both somatic CNVs and SNVs will illustrate how parental and gonadal mosaicism can lead to recurrence of genetic disorders and how postzygotic somatic mutations can occur at any stage of development and lead a wide array of genetic disorders. In addition, we will discuss the progress and challenges of identifying somatic mutations and for this field.

Mar 25th 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.

Mar 27th Wed Paper Discussion VII (Glover)

Mar 29th 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.

Apr 1st 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.

Apr 3rd **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.

Apr 5th **Fri** **Paper Discussion VIII (Yashar)**

Apr 8th **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 10th **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 12th **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 15th **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 17th **Wed** **Paper Discussion I (Sekiguchi)**

Apr 19th **Fri** **Review session for Exam III**

Apr 22nd **Mon** **Exam III – 8 to 10 a.m.**