**Human Genetics 544: Basic Concepts in Population and Statistical Genetics**
**Fall 2017 Syllabus**

**Description**: The concepts and analytic methods for studying variation in natural populations are the subject matter of this course. The topics covered include the distribution of genetic variation, major forces of genetic stasis and change, molecular population genetics, quantitative genetics, and human population genetics. We introduce the basic models of population, quantitative, and statistical genetics at a mathematical level appropriate to students in the life sciences. Our focus is on current human genetics research. However, most of what we present is broadly useful and applies to natural populations of other species.

**Course objectives:**

1) Develop an understanding of basic concepts in population and statistical genetics.
2) Apply that knowledge to real-world situations and problem-solving contexts.

**Recommended textbook:** A Primer of Population Genetics (3rd edition) by Daniel L. Hartl.
To access a copy, see the instructors or Bev Yashar.

**Starting Date**: September 6, 2017
**Time**: 2:10 – 3:30 pm (M-W)
**Location**: Buhl Building, Room 5915
**Credits**: 3 hrs.

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| **Instructor:** | Jun Li, PhD | Jeff Kidd, PhD | David Burke, PhD | Sarah Gagliano, PhD |
| **Hours:** | By appt | By appt | By appt | By appt |
| **Office:** | 5940 Buhl | 3726 Med Sci II | 4945 Buhl | Location TBD |
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**Conflict of interest:** The instructors, Jun Li, Jeff Kidd, David Burke, and Sarah Gagliano, have no industry relationships.

**Grading:** Your final grade will be based on a combination of exams, quizzes, and writing assignments (see distribution below).

**Exams:** Two interim exams will each contribute 20% to your grade, and a final comprehensive exam will contribute 30%. All exams will be given in class and must be completed in class.

**Quizzes:** Brief, in-class quizzes will contribute 15% to your grade. To prepare, it is crucial that you read the lecture notes and complete the exercises. You may drop two quiz scores, including missed quizzes and/or lowest scores.

**Writing assignments:** Informal writing assignments will contribute 15% to your grade. With guidance from the instructors, you and your classmates will discuss non-review papers from the literature during the Discussion sessions (see Readings below). To prepare, you are required to write a brief response to specific questions for each assigned paper. Questions will be posted by the instructors prior to each Discussion session (see CANVAS). Your responses should be typewritten in your own words using complete sentences. Responses are due by noon on the day of the Discussion session. For each reading assignment, please post a copy of your written responses on CANVAS under Assignments and bring an extra copy with you on the day of the discussion. Your responses

will be graded informally, meaning you will receive full credit as long as you answer all questions completely and thoughtfully.

**Lectures**:

9/6 (W) Mendelian Populations — Burke

Population and gene pool concepts, genotype and allele frequencies, variation.

Readings:

1. Lecture notes and exercises
2. Crow JF (1986) Appendix, Basic Concepts in Population, Quantitative, and Evolutionary Genetics. WH Freeman Co. San Francisco, CA (review)

9/11 (M) Random Mating Populations (One Locus) — Kidd

Hardy-Weinberg Law, genetic equilibrium, X-linked loci, departure from equilibrium.

Readings:

1. Lecture notes and exercises
2. Salanti I et al. (2005) Hardy-Weinberg equilibrium in genetic association studies: an empirical evaluation of reporting, deviations, and power. *European Journal of Human Genetics* 65:1956-58
3. Edwards AWF (2008) G.H. Hardy (1908) and Hardy-Weinberg equilibrium. *Genetics* 179:1143-50 (perspective)

9/13 (W) Random Mating Populations (Two or More Loci) — Li

Haplotypes, recombination, linkage disequilibrium (LD), measuring LD.

Readings:

1. Lecture notes and exercises
2. Hinds DA et al. (2005) Whole-genome patterns of common DNA variation in three human populations. *Science* 307:1072-79
3. Pritchard JK, Przeworski M (2001) Linkage disequilibrium in humans: models and data. *Am J Hum Genet* 69:1-14 (review)

9/18 (M) Discussion — Li/Kidd

9/20 (W) Inbreeding — Gagliano

Genotype distributions in inbred individuals, calculation of inbreeding coefficients, the concept of genetic kinship, allelic identity states.

Readings:

1. Lecture notes and exercises
2. Calboli et al. (2008) Population structure and inbreeding from pedigree analysis of purebred dogs. *Genetics* 179:593-601
3. Weir BS et al. (2006) Genetic relatedness analysis: modern data and new challenges. *Nat Rev Genetics* 7:771-80 (review)

9/25 (M) Quantitative Traits Gagliano

Genetic model for quantitative phenotypes, allelic and genotypic effects, partitioning phenotypic variance into genetic and environmental components.

Readings:

1. Lecture notes and exercises
2. Weedon MN, Lettre G, Freathy RM, Lindgren CM, Voight BM, et al. (2007) A common variant in HMGA2 is associated with adult and childhood height in the general population. *Nat Genet* 39: 1245-1250
3. Mackay TF et al. (2009) The genetics of quantitative traits: challenges and prospects. *Nat Rev Genetics* 10:565-77(review)

9/27 (W) Discussion Gagliano

10/2 (M) Finite Populations Li

Genetic sampling and loss of variation. Balance between mutation and drift. Effective population size. Genetically isolated populations.

Readings:

1. Lecture notes and exercises
2. Jakkula E et al. (2008) The genome-wide patterns of variation expose significant substructure in a founder population. *Am J Hum Genet* 312:1614-20
3. Charlesworth B (2009) Effective population size and patterns of molecular evolution and variation. *Nat Rev Genetics* 10:195-205 (review)

10/4 (W) Natural Selection Li

The concept of fitness and a simple model for the increase, removal, or maintenance of allelic variation by natural selection.

Readings:

1. Lecture notes and exercises
2. Lamason RL et al. (2005) SLC24A5, a putative cation exchanger, affects pigmentation in zebrafish and humans. *Science* 310:1782-86

3. Hurst LD (2009) Genetics and the understanding of selection. *Nat Rev Genetics* 10:83-93 (review)

10/9 (M) Mutation, Polymorphism, and Disease Li

The level of variation under the balance between mutation and selection.

Readings:
1. Lecture notes and exercises
2. Cohen JC et al. (2004) Multiple rare alleles contribute to low plasma levels of HDL cholesterol. *Science* 305: 869-72

10/11 (M) Discussion Li

10/16 (M) NO CLASS – Fall Study Break

10/18 (W) EXAM I

10/23 (M) Correlations between Relatives Gagliano

The correlation between relatives and the contributions from polygenes.

Readings:
1. Lecture notes and exercises
2. Yang J et al. (2010) Common SNPs explain a large proportion of the heritability for human height. *Nat Genet* 42:565-69
3. Visscher PM et al. (2008) Heritability in the genomics era – concepts and misconceptions. *Nat Rev Genetics* 9:255-266 (review)

10/25 (W) Genes and Environment Gagliano

The role of the environment in the relationship between genotype and phenotype. Gene-environment interaction and covariance. Norms of reaction.

Readings:
1. Lecture notes and exercises
2. King MC et al. (2003) Breast and ovarian cancer risks due to inherited mutations in BRCA1 and BRCA2. *Science* 302:643-646
3. Hunter DJ (2005) Gene-environment interactions in human diseases. *Nat Rev Genetics* 6:287-98 (review)

10/30 (M) Discussion Gagliano

11/1 (W) Population Subdivision Li

Local subpopulations, the Wahlund effect, and migration.

Readings:

1. Lecture notes and exercises
2. Rosenberg NA, Pritchard JK, Weber JL, Cann HM, Kidd KK, et al. (2002) Genetic structure of human populations. *Science* 298: 2381-5

11/6 (M) Association and Transmission Disequilibrium Li

Basic measures and tests of association. Introduction to the transmission disequilibrium concept.

Readings:

1. Lecture notes and exercises
2. Graham DSC et al. (2008) Polymorphism at the TNF superfamily gene TNFSF4 confers susceptibility to systemic lupus erythematosus. *Nat Genet* 40:83-89

11/8 (W) Discussion Li

11/13 (M) Linkage Burke

Model-based linkage analysis of classical Mendelian traits. Introduction to the statistical concept of likelihood and LOD scores, including specification of genetic parameters.

Readings:

1. Lecture notes and exercises
2. Hall JM et al. (1990) Linkage of early-onset familial breast cancer to chromosome 17q21. *Science* 250:1684-1689
3. Bailey-Wilson JE, Wilson AF (2011) Linkage analysis in the next-generation sequencing era. *Hum Hered* 72:228-236 (review)

11/15 (W) Genetic and Physical Maps Burke

Map distances and mapping functions. Interference.

Readings:

1. Lecture notes and exercises
2. Botstein et al. (1980) Construction of a genetic linkage map in man using restriction fragment length polymorphisms. Am J Hum Genet 32:314-331

3. Crow JF (1990) Mapping functions. *Genetics* 125:669-71 (perspective)

11/20 (M) Discussion Burke

11/22 (W) EXAM II

11/27 (M) Coalescence Kidd

Time back to a common ancestral DNA sequence. Difference in DNA sequence between two randomly chosen copies of a locus.

Readings:

1. Lecture notes and exercises
2. Rodrigo AG et al. (1999) Coalescent estimates of HIV-1 generation time in vivo. *Proc Natl Acad Sci* 96:2187-91
3. Rosenberg NA and Nordburg M (2002) Genealogical trees, coalescent theory and the analysis of genetic polymorphisms. *Nat Rev Genetics* 3:380-90 (review)

11/29 (W) DNA Sequence Evolution Kidd

Sequence mutations and distance metrics, Jukes Cantor, dN/dS, evolution of protein coding regions, gene duplication, and the evolution of new gene functions.

Readings:

1. Lecture notes and exercises
2. Gonzalez-Candelas et al. (2013) Molecular evolution in court: analysis of a large hepatitis C virus outbreak from an evolving source. *BMC Biology* 11:76

12/4 (M) Discussion Kidd

12/6 (W) Molecular Phylogenetics Kidd

Gene trees versus species trees, UPGMA algorithm for making trees, incomplete lineage sorting and background selection during human/primate evolution.

Readings:

1. Lecture notes and exercises
2. Cooper GM et al. (2010) Single-nucleotide evolutionary constraint scores highlight disease-causing mutations. *Nat Methods* 7:250-1

12/11 (M) Discussion. Review, Q&A

12/19 (T) FINAL EXAM (Room 5915 of the Buhl Building from 1:30 to 3:30 pm)