HG544 : Basic Concepts in Population and Statistical Genetics

Syllabus for Fall 2008

Description: The concepts and analytic methods for studying variation in human populations are the subject matter of this course. The topics covered include the distribution of genetic variation, major forces of genetic stasis and change, quantitative traits, linkage analysis, association tests, and the role of the environment. We take a problem solving approach and present 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.

Starting Date: September 3, 2008
Time: MWF 3:10 – 4:00 pm
Location: 5915 Buhl Bldg*
Credits: 3 hrs.

* Class will be held in room 2901 of Taubman Medical Library on **September 19** (Friday), **September 29** (Monday), and **December 1** (Monday) and the North Lecture Hall of Med Sci II on **October 15** (Wednesday) and **November 12** (Wednesday).

Instructor:	Julie Douglas, PhD	Jeffrey Long, PhD	Michele Gornick (TA)
Hours:	By appt.	By appt.	T 3-4 pm & Th 5-6 pm
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Grades: Each midterm will contribute 25% to your grade and a final comprehensive exam will contribute 40% to your grade. All exams are given in class and must be completed in class. Participation in the discussions of the readings and problem sets will contribute 10% to your grade.

Assigned Problems: Mastering the assigned problems at the end of the lecture notes is a crucial step in preparing for the exams. Do NOT neglect the assigned problems.

Lectures:

9/3 (W) Probability in Genetics Long

Concepts of probability, conditional probability, independence, Bayes' theorem.

Readings:
1. Lecture Notes & Problems

9/5 (F) Probability in Genetics cont. Douglas

Random variables, discrete and continuous distributions, expectations.

Readings:
1. Lecture Notes & Problems

9/8 (M) Mendelian Populations Long

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

Readings:
1. Lecture Notes & Problems
2. Waples RS, Gaggiotti O. 2006. What is a population? An empirical evaluation of some genetic methods for identifying the number of gene pools and their degree of connectivity. Mol Ecol 15: 1419-39

9/10 (W) Random Mating Populations (One Locus): Douglas

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

Readings:
1. Lecture Notes & Problems

9/12 (F) Discussion of Problem Sets

9/15 (M) Inbreeding, Kinship, and Allele Sharing Douglas

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

Readings:
1. Lecture Notes & Problems
2. Weir BS, Anderson AD, Hepler AB (2006) Genetic relatedness analysis: modern data and new challenges. *Nat Rev Genet* 7: 772-780.

9/17 (W) Random Mating Populations (Two or More Loci) Douglas

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

Readings:
1. Lecture Notes & Problems
2. The International HapMap Consortium (2007) A second generation human haplotype map of over 3.1 million SNPs. *Nature* 449: 851-862.

9/19 (F) Discussion of Readings and Problem Sets

9/22 (M) Statistical Estimation and Testing in Genetics Douglas

Likelihoods, maximum likelihood estimation, EM algorithm

Readings:
1. Lecture Notes & Problems

9/24 (W) Linkage I Douglas

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 & Problems
2. Hall et al. (1990) Linkage of early-onset familial breast cancer to chromosome 17q21. *Science* 250:1684-1689

9/26 (F) Discussion of Readings and Problem Sets

9/29 (M) Natural Selection Long

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

Readings:

1. Lecture Notes & Problems
2. Haldane JBS. 1937. The effect of variation on fitness. *American Naturalist* 71: 337-349

10/1 (W) Natural Selection cont. Long

Readings:

1. Lecture Notes & Problems

10/3 (F) EXAM I

10/6 (M) Finite Populations: Long

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

Readings:

1. Lecture Notes & Problems
2. Puffenberger, EG (2003) Genetic Heritage of the Old Order Mennonites of Southeastern Pennsylvania. Am J of Med Genet Part C (Semin. Med. Genet.) 121C:18–31

10/8 (W) Finite Populations cont. Long

10/10 (F) Discussion of Readings and Problem Sets

10/13 (M) No class

10/15 (W) Quantitative Traits Douglas

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

Readings:

1. Lecture Notes & Problems
2. Weedon et al. (2007) A common variant in HMGA2 is associated with adult and childhood height in the general population. *Nat Genet* 39: 1245-1250.

10/17 (F) Quantitative Traits cont. Douglas

10/20 (M) No class – Fall Break

10/22 (W) Discussion of Readings and Problem Sets

10/24 (F) Correlations Between Relatives Douglas

The correlation between relatives on the supposition of Mendelian inheritance with contributions from polygenes and environment.

Readings:

1. Lecture Notes & Problems
2. Visscher et al. (2008) Heritability in the genomics era – concepts and misconceptions. *Nat Rev Genetics* 9:255-266

10/27 (M) Correlations Between Relatives cont. Douglas

10/29 (W) Genes and Environment Long

Readings:
1. Lecture Notes & Problems
2. Ordovas JM, Corella D, Demissie S, Cupples LA, Couture P, et al. 2002. Dietary fat intake determines the effect of a common polymorphism in the hepatic lipase gene promoter on high-density lipoprotein metabolism: evidence of a strong dose effect in this gene-nutrient interaction in the Framingham Study. *Circulation* 106: 2315-21

10/31 (F) Discussion of Readings and Problem Sets

11/3 (M) Coalescence Long

Time back to a common ancestral DNA sequence. Differences in DNA sequence between randomly chosen copies of a locus. The origin of linkage disequilibrium. Testing the neutral evolution model.

Readings:
1. Lecture Notes & Problems
2. Hudson RR. 1983. Testing The Constant-Rate Neutral Allele Model With Protein-Sequence Data. *Evolution* 37: 203-17

11/5 (W) Coalescence cont. Long

11/7 (F) EXAM II

11/10 (M) DNA Sequence Analysis Long

Comparison between two or more DNA sequences that have descended from a common ancestor.

Readings:
1. Lecture Notes & Problems
2. Parmley JL, Chamary JV, Hurst LD. 2006. Evidence for purifying selection against synonymous mutations in mammalian exonic splicing enhancers. Mol Biol Evol 23: 301-9

11/12 (W) Phylogenetics Long

Readings:
1. Lecture Notes & Problems
2. Benton MJ, Donoghue PC. 2007. Paleontological evidence to date the tree of life. Mol Biol Evol 24: 26-53

11/14 (F) Discussion of Readings and Problem Sets

11/17 (M) Linkage II – Model Free Douglas
Model-free linkage analysis of complex, qualitative traits using the affected sibling pair design with known allele sharing.

Readings:
1. Lecture Notes & Problems
2. Larson et al. (2005) Genetic linkage of prostate cancer risk to the chromosome 3 region bearing *FHIT*. *Cancer Res* 65:805-814

11/19 (W) Genetic and Physical Maps Douglas

Map distances and mapping functions. Interference.

Readings:

1. Lecture Notes & Problems
2. Kong et al. (2002) A high-resolution recombination map of the human genome. *Nat Genet* 31:241-247

11/21 (F) Discussion of Readings and Problem Sets

11/24 (M) Population Subdivision Long

Local subpopulations, the Wahlund effect, Migration

Readings:
1. Lecture Notes & Problems
2. Rosenberg NA, Pritchard JK, Weber JL, Cann HM, Kidd KK, et al. 2002. Genetic structure of human populations. *Science* 298: 2381-5

11/26 (W) Population Subdivision cont. Long

11/28 (F) No Class – Thanksgiving Break

12/1 (M) Association and Transmission Disequilibrium: Douglas

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

Readings:
1. Lecture Notes & Problems
2. Graham et al. (2008) Polymorphism at the TNF superfamily gene TNFSF4 confers susceptibility to systemic lupus erythematosus. *Nat Genet* 40:83-89

12/3 (W) Association and Transmission Disequilibrium cont. Douglas

12/5 (F) Discussion of Readings and Problem Sets

12/8 (M) Mutation, Polymorphism, and Disease Long

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

Readings:
1. Lecture Notes & Problems
2. Cohen JC, Kiss RS, Pertsemlidis A, Marcel YL, McPherson R, Hobbs HH. 2004. Multiple rare alleles contribute to low plasma levels of HDL cholesterol. *Science* 305: 869-72

12/17 (W) FINAL EXAM