

HG544 : Basic Concepts in Population and Statistical Genetics

Syllabus 2007

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: March 5, 2007

Time: MWF 10:10 – 11:00

Location: 4917 Buhl Bldg*

Credits: 2 hrs.

*Class will be held in room 2901 of Taubman Medical Library on Friday, March 9.

Instructor:	Julie Douglas, PhD	Jeffrey Long, PhD	Marie-Hélène Roy-Gagnon, PhD
Hours:	11 am–noon MW	9–10 am TTh	5–6 pm M and 11 am–noon F
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Grades: A midterm and a final exam will each contribute 50% to your grade. The midterm is a take home exam due on the next day. The allotted time is ample if you have studied in advance; it is inadequate if you have not. The final exam is given on the last day of class. It must be completed in class.

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

Background reading: Crow JF (1986) Appendix, Basic Concepts in Population, Quantitative, and Evolutionary Genetics. WH Freeman Co. San Francisco, CA.

Lectures:

3/5 (M) Population Concepts: Douglas

Population and gene pool, genotype and allele frequencies, measures of diversity.

Readings:

1. Lecture Notes & Problems
2. Clark AG, Hubisz MJ, Bustamante CD, Williamson SH, Nielsen R. 2005. Ascertainment bias in studies of human genome-wide polymorphism. *Genome Res* 15: 1496-502

3/7 (W) Random Mating Populations (One Locus): Douglas

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

Readings:

1. Lecture Notes & Problems
2. Hardy GH (1908) Mendelian proportions in a mixed population. *Science* 28:49-50

3/9 (F) 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

3/12 (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

3/14 (W) 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

3/16 (F) 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.

3/19 (M) 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. Kim U-K, Jorgenson E, Coon H, Leppert M, Risch N, Drayna D (2003) Positional Cloning of the Human Quantitative Trait Locus Underlying Taste Sensitivity to Phenylthiocarbamide. *Science* 299: 1221-1225.

3/21 (W) 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. Boyd et al. (2002) Heritability of mamographic density, a risk factor for breast cancer. *N Engl J Med* 347:886-894

3/23 (F) 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

3/26 (M) Random Mating Populations (Two or More Loci) Long

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

Readings:

1. Lecture Notes & Problems
2. The International HapMap Consortium (2005). A haplotype map of the human genome. *Nature* 437: 1299-1320.

3/28 (W) Linkage I – Model Based: 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

MIDTERM EXAM will be handed out. *It must be returned to Janet Miller (Room 4924, Buhl Building) by noon on Thursday, 3/29.*

3/30 (F) 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. Hugot et al. (1996) Mapping a susceptibility locus for Crohn's disease on chromosome 16. *Nature* 379:821-823

4/2 (M) 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

4/4 (W) Population Subdivision: Douglas

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

- 4/6 (F) Association and Transmission Disequilibrium: Long
- Basic measures and tests of association. Introduction to the transmission disequilibrium concept.
- Readings:
1. Lecture Notes & Problems
 2. Duerr RH, et al. 2006. A genome-wide association study identifies IL23R as an inflammatory bowel disease gene. *Science* 314: 1461-3
- 4/9 (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. Louie E, Ott J, Majewski J (2003) Nucleotide frequency variation across human genes. *Genome Research* 13:2594-2601
- 4/11 (W) 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
- 4/13 (F) Common Disease Common Variant Hypothesis: Long
- 4/16 (M) FINAL EXAM