



HG 542: Molecular Basis of Human Genetic Disease

Syllabus Winter 2007

Location: 5915 Buhl

This is last year's syllabus. The latest one for 2008 will be updated soon by Prof. Thomas Glover

HG 542 will emphasize the principles and methods of genetics and molecular genetics as they relate to human disease. The course covers the topics of monogenic traits, cytogenetics, non-Mendelian inheritance, cancer genetics, and complex genetic disease. In each section, principles of genetics are presented by way of illustration with human genetic diseases. Papers from the current and classic literature will supplement lecture material. HG 541 is a prerequisite for this course.

Instructor Contact Information

Date	Lecturer	Topic, Reading Assignment
1/5 F	Glaser	<p>Simple Mendelian traits: Structure, function and regulation of the beta globin complex. We will use the human genetic diseases sickle cell anemia and beta thalassemia to illustrate the following concepts: pedigrees, modes of inheritance, mutational mechanisms, aberrant mRNA splicing, haplotype analysis, founder effects, and the locus control region.</p> <ol style="list-style-type: none">1. <u>Orkin SH, Kazazian HH, Antonarakis SE, Ostrer H, Goff SC, and Sexton JP. Abnormal RNA processing due to the exon mutation of beta(E)-globin gene. Nature 300:768-769 (1982). PDF</u>2. <u>Bender MA, Bulger M, Close J, and Groudine M. Beta-globin gene switching and DNase I sensitivity of the endogenous beta-globin locus in mice do not require the locus control region. Mol. Cell 5:387-393 (2000). PDF</u>
1/8 M	Glaser	<p>Mechanisms of dominance I: Loss-of-function mutations. We will use the human genetic disease familial hypercholesterolemia to explore haploinsufficiency, contiguous gene deletion syndromes, receptor-mediated endocytosis, and the paradigm of structure/function analysis.</p> <ol style="list-style-type: none">1. <u>Wilkie AOM. The molecular basis of genetic dominance. J. Med. Genet. 31:89-98 (1995). PDF</u>2. <u>Davis CG, Lehrman MA, Russell DW, Anderson RG, Brown MS, Goldstein JL. The J.D. mutation in familial hypercholesterolemia: amino acid substitution in cytoplasmic</u>

domain impedes internalization of LDL receptors. Cell 45:15-24 (1986). [PDF](#)

1/10 W	Glaser	<p>Mechanisms of dominance II: Gain-of-function mutations. We will use the human skeletal malformations (achondroplasia, craniosynostosis, and osteogenesis imperfecta) to illustrate the concepts of constitutively active, dominant-negative and dysregulatory alleles; paternal and maternal age effects; locus (genetic) and allelic heterogeneity.</p> <ol style="list-style-type: none">1. <u>Shiang R, Thompson LM, Zhu Y-Z et al. Mutations in the transmembrane domain of FGFR3 cause the most common genetic form of dwarfism, achondroplasia. Cell 78:335-342 (1994). PDF</u>2. <u>Webster MK, and Donoghue DJ. FGFR activation in skeletal disorders: too much of a good thing. Trends Genet. 13:178-182 (1997). PDF</u>3. <u>Goriely A, McVean GA, van Pelt AM et al. Gain-of-function amino acid substitutions drive positive selection of FGFR2 mutations in human spermatogonia. Proc. Natl. Acad. Sci. 102:6051-6056 (2005). PDF</u>
-----------	--------	---

1/12 F	Glaser	<p>Gene interactions: Digenic retinitis pigmentosa - one disease arising from synergistic mutations in two genes. We will use this disease to explore synthetic phenotypes, epistasis, modifiers, enhancer/suppressor screens and conditional alleles, and introduce the concept of polygenic traits.</p> <ol style="list-style-type: none">1. <u>Kajiwara K, Berson EL, and Dryja TP. Digenic retinitis pigmentosa due to mutations at the unlinked peripherin/RDS and ROM1 loci. Science 264:1604-1608 (1994). PDF</u>2. <u>Badano, JL, and Katsanis, N. Beyond Mendel: an evolving view of human genetic disease transmission. Nature Rev. Genet. 3:779-789 (2002). PDF</u>3. <u>Nadeau, JH. Modifier genes in mice and humans. Nature Rev. Genet. 2:165-174 (2001). PDF</u>
--------	--------	---

1/15 M		No Class MLK day
-----------	--	------------------

1/17 W	Glaser	<p>Principles of maternal inheritance: Mitochondrial genetic disorders. In this lecture, we consider the unique properties and evolution of the mitochondrial genome. We will also compare transmission genetics of mtDNA and the Y-chromosome.</p> <ol style="list-style-type: none">1. <u>Shoffer JM, Lott MT, Lazza AMS et al. Myoclonic epilepsy and ragged-red fiber disease (MERRF) is associated with a mitochondrial DNA tRNA(Lys) mutation. Cell 61:931-937 (1990). PDF</u>2. <u>Trifunovic A, Wredenberg A, Falkenberg M et al. Premature ageing in mice expressing defective mitochondrial DNA polymerase. Nature 429:417-423 (2004). PDF</u>
-----------	--------	---

1/19 F	Glaser	<p>Non-mendelian perspectives: In this lecture, we will conclude our discussion of polygenic and mitochondrial inheritance, and review concepts of somatic mutation and mosaicism.</p> <ol style="list-style-type: none">1. <u>Bakker E, van Broeckhoven C, Bonten EJ et al. Germline mosaicism and Duchenne</u>
--------	--------	--

		<p><u>muscular dystrophy. Nature 329:554-556 (1987). PDF</u></p> <p>2. <u>Rossant J and Spence A. Chimeras and mosaics in mouse mutant analysis. Trends Genet. 14:358-363 (1998). PDF</u></p>
1/22 M	Chan	<p>Chromosome structure and function in mitosis and meiosis</p> <p>1. Natashe Kireeva, Margot Lakonishok, Igor Kireev, Tatsuya Hirano, and Andrew S. Belmont PDF</p> <p>2. Ana Losada and Tatsuya Hirano PDF</p> <p>Lecture Notes PDF</p>
1/24 W	Glover	<p>Aneuploidy</p> <p>1. Hassold T, Hunt P. To err (meiotically) is human: The genesis of human aneuploidy. <i>Nat Rev Genet</i> 2: 280-291, 2001. PDF</p> <p>2. Hodges CA, et al. SMC1b-deficient female mice provide evidence that cohesins are a missing link in age-related nondisjunction. <i>Nat Genet</i> 37: 1351-1355, 2005. PDF</p>
1/26 F	Glover	<p>Structural rearrangements: implications of genomic architecture.</p> <p>1. Emanuel BS, Shaikh TH. Segmental duplications: An ‘expanding’ role in genomic instability and disease. <i>Nat Rev Genet</i> 2: 791-800, 2001. PDF</p> <p>2. Shaw-Smith C, et al: Microdeletion encompassing <i>MAPT</i> at chromosome 17q21.3 is associated with developmental delay and learning disability. <i>Nat Genet</i> 38: 1032-1037, 2006. PDF</p>
1/29 M	Glover	<p>Large scale copy number variation in the human genome</p> <p>1. Sharp AJ, et al: Discovery of previously unidentified genomic disorders from the duplication architecture of the human genome. <i>Nat Genet</i> 38: 1038-1042, 2006. PDF</p> <p>2. Redon R, et al: Global variation in copy number in the human genome. <i>Nature</i> 444: 444-454, 2006. PDF</p>
1/31 W	Glover	<p>Fragile X syndrome and unstable repeat disorders</p> <p>1. Gatchel JR and Zoghbi HY. Diseases of unstable repeat expansion: Mechanisms and common principles. <i>Nat Rev Genet</i> 6: 743-755, 2005. PDF</p>
2/2 F	Glover	<p>Chromosome abnormalities in human cancer</p> <p>1. Tomlins SA, et al. Recurrent fusion of <i>TMPRSS2</i> and ETS transcription factor genes in prostate cancer. <i>Science</i> 310: 644-648, 2005. PDF</p>
2/5 M	Sekiguchi	<p>Inherited cancer predisposition syndromes</p> <p>1. Hereditary Cancer Predisposition Syndromes PDF</p> <p>2. Inactivation of the p53 pathway in retinoblastoma PDF</p>
2/7 W	Sekiguchi	<p>Genomic instability disorders</p> <p>1. Genome maintenance mechanisms for preventing cancer PDF</p> <p>2. Fanconi anemia and breast cancer susceptibility PDF</p>

2/9 F	Sekiguchi	Molecular mechanisms of oncogenesis 1. Causes of oncogenic chromosomal translocation PDF 2. Role of genomic instability and p53 in AID-induced c-myc-Igh translocations PDF
2/12 M	Moran	
2/14 W	Moran	
2/16 F	Burmeister	Complex genetics I: Gene identification in the presence of heterogeneity - example rare recessive ataxias. 1) Cayman Ataxia paper PDF 2) Jittery Paper PDF 3) Lander Schork PDF
2/19 M	Burmeister	Complex genetics II: Gene x environment interaction in behavioral genetics. Papers: Caspi et al. 2002, Caspi et al. 2003 PDF PDF PDF PDF
2/21 W	Burmeister	Pharmacogenetics 1) Natrev DD review PDF 2) Pharmacogenetics Drug Label PDF
2/23 F	EXAM	

E-mail an instructor

T.Glaser	tglaser@umich.edu
T.Glover	glover@umich.edu
J.Long	longjc@umich.edu
J. Moran	moranj@umich.edu
J. Sekiguchi	sekiguch@umich.edu

Course Director: T.Glover - glover@umich.edu

Course TA:

[Back to top](#)