BI423/523 Human Molecular Genetics (CRN 30942), SPRING '07

Alice Barkan, Instructor (abarkan@uoregon.edu)

Meeting Time: MWF 11-11:50
Meeting Place: 171 Onyx
Office Hours: Tues 3-4 pm, Thurs 2-3 pm, 280 Onyx

This course will focus on selected topics in human molecular genetics that illustrate fundamental and fascinating genetic principles. My goals for this course are to help students to increase their breadth of knowledge by exploring current topics in human molecular genetics; to develop skills associated with reading the primary research literature, evaluating data, formulating hypotheses, and devising experiments to test hypotheses; to improve their written and oral communication skills; and to enjoy discussing current topics in genetics that are directly relevant to human health.

Readings and Class Format

Background readings are assigned in a text by Strachan and Read (Human Molecular Genetics 3, ISBN 0-8153-4182-2). It is available for purchase at the U of O Bookstore and two copies have been placed on reserve in the Science Library. Each topic will be introduced in one or two lectures and will then be explored in more depth through discussion of several research articles. *PDF files of the assigned papers and of lecture handouts are available on-line through BLACKBOARD.* The lecture handouts are provided to facilitate your notetaking. Please bring printouts of the relevant lecture handouts and papers to class.

Graded Assignments

There will be six graded sets of "Discussion Questions" These questions will be posted on Blackboard, and will frame our discussions of the research articles. These assignments will help you focus on the relevant issues while reading the papers, they will prepare you to participate actively in discussions, and they will help you to refine your writing skills.

The set of questions for each topic will be divided into two components: "pre-Discussion" questions will be short answer, factual questions concerning the papers to be discussed, and will be turned in at the beginning of class on the day the discussion begins. The remainder of the questions will be more open-ended , and will concern data interpretation, implications, and future experiments. Please bring a draft of these answers to class on the day the papers are discussed. You will turn in your answers in a subsequent session (dates to be announced) so that you can incorporate what you learned during the discussion. Answers will be graded on a "check", "check-plus" or "check-minus" basis (with occasional "check-plus-plus's" awarded for exceptionally well-done assignments). *ANSWERS MUST BE TYPED! You should aim to provide concise answers that do not include extraneous information .*

In addition, there will be a final project that includes both an oral and written component. As a class, we will identify five broad subjects for the oral presentations. Students will be divided into five groups according to their preferences. Each group will be assigned a class session during which they will present an overview of their topic, identify several key unresolved issues (scientific or ethical), and discuss how one might go about resolving those issues. Each member of the group will participate in the presentation and will turn in a 2 page typed summary of their portion of the presentation, as well as printouts of their slides/overheads.

Graduate students in the class are required to develop a Research Proposal in which a scientific controversy is summarized and experimental approaches to resolve the controversy are outlined. The proposal should be between six and eight double-spaced type-written pages (not including references) and will be due at 5 pm on Tuesday of Finals Week. Graduate students are also required to take the Final Exam.

Undergraduates in the class can choose to develop a research proposal, or can take a Final Exam during Final's week.

I do not use a strict formula for calculating grades, as this is a discussion-based course. However, a rough breakdown of the weight of each assignment is as follows: Contribution to discussions- 15%; written answers to discussion questions- 35%; oral presentation 15%; Midterm exam 15%; Final exam or research proposal 20%

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(Dates are subject to change according to the flow of our discussions!)

Date		Background Reading	Papers for Discussion
4/2	The human genome: chromosomal organization gene content: predicting genes from DNA sequence	Strachan: 2.1-2.41; 8.1, 8.3.5-8.3.7 Chapter 9	Lecture
4/4	Human Genome: "non-gene" content: mobile elements microRNAs	Snyder and Gerstein (2003) Defining genes in the genomic era. Science 300: 258-260. Stein (2004) End of the beginning. Nature: 431:915-916 Kazazian (2004) Mobile Elements: Drivers of Genome Evolution. Science 303:1626-1632.	Nobrega et al (2003) Scanning human gene deserts for long-range enhancers. Science 302: 413.
4/6	Human Genome Discussion: finding genes in genome sequence		Bertone et al. (2004) Global identification of human transcribed sequences with genomic tiling arrays. Science 306: 2242-2246. Kim et al (2005) A high-resolution map of active promoters in the human genome. Nature 436: 876-880. *Don't worry about the details. Read to get a sense of the general findings.*
4/9	Human Genome Discussion cont'd: alternative splicing, retrotransposons, microRNAs	BR Graveley (2001) Alternative splicing: increasing diversity in the proteomic world. Trends in Genetics 17: 100-107.	Yang and Kazazian (2006) L1 retrotransposition is suppressed by endogenously encoded small interfering RNAs in human cultured cells. Nat. Struct. Mol. Biol. 13: 763-771.
4/11	Mouse as a model organism for human genetics	Strachan, Chapter 20 Strachan 8.4 Capecchi (2005) Gene targeting in mice: functional analysis of the mammalian genome for the 21st century. Nat Rev Gen 6: 507-512.	lecture

Date	Topic	Background Reading	Papers for Discussion
4/13	Dosage Compensation: X chromosome inactivation	Strachan 10.5.6 Chow et al (2005) Silencing of the Mammalian X Chromosome. Annu. Rev. Genomics Hum Genet. 6:69-92.	lecture
4/16	X-inact Discussion		Wutz and Jaenisch (2000) A shift from reversible to irreversible X inactivation is triggered during ES cell differentiation. Molec Cell 5: 695-705.
4/18	X-inact Discussion cont'd		Lee and Lu (1999) Targeted mutagenesis of Tsix leads to nonrandom X inactivation. Cell 99: 47-57. Shibata and Lee (2004) Tsix transcription-versus RNA-based mechanisms in Xist repression and epigenetic choice. Current Biology 14:1747-1754.
4/20	X-inact Discussion cont'd		Donohoe et al (2007) Identification of a CTCF cofactor, Yy1, for the X-chromosome binary switch. Mol. Cell 25:43-56.
4/23	Sex Determination: the Y chromosome	Strachan: p.93 Box 3.9 12.2.6-12.2.7 (pp367-371) Review: Brennan and Capel (2004) One tissue, two fates: Molecular genetic events that underlie testis versus ovary development. Nat. Rev. Genet. 5: 509-521.	lecture
4/25	Sex Determ : discussion		Koopman et al (1991) Male development of chromosomally female mice transgenic for Sry. Nature 351: 117-121. Vidal et al (2001) Sox9 induces testis development in XX transgenic mice. Nature Genetics 28: 216-217.

date	topic	background reading	papers for discussion
4/27	Sex Determ: Disc cont'd **Discuss Project Topics**		Kim et al (2006) Fgf9 and Wnt4 act as antagonistic signals to regulate mammalian sex determination. PLOS Biology 4: 1000-1009.
4/30	**Midterm Exam**		
5/2	Diseases of Unstable Repeat Expansion	Strachan: 16.6.4; pp 476-478 Gatchel and Zoghbi (2005) Diseases of unstable repeat expansion. Nat Rev Gen 6: 743- 755 Ranum LP, Day JW. (2004) Pathogenic RNA repeats: an expanding role in genetic disease. Trends Genet. 20: 506-12.	lecture
5/4	How does repeat expansion cause disease?: influence on gene expression		Charlet –B. et al (2002) Loss of the muscle-specific chloride channel in type 1 myotonic dystrophy due to misregulated alternative splicing. Molecular Cell 10: 45-53. Kanadia et al (2003) A muscleblind knockout model for myotonic dystrophy. Science 302: 1978-1980.
5/7	How does repeat expansion cause disease: the polyglutamine diseases	Gusella and MacDonald (2006) Huntington's disease: seeing the pathogenic process through a genetic lens. Trends Biochem. Sci. 31: 533-540.	Nucifora et al (2001) Interference by Huntingtin and Atrophin-1 with CBP-mediated Transcription Leading to Cellular Toxicity. Science 291: 2423-2428. Zuccato et al (2003) Huntingtin interacts with REST/NRSF to modulate the transcription of NRSE-controlled neuronal genes. Nature Genetics 35: 76-83.
5/9	Finish Repeat Expansion Discussion: does the RNAi pathway contribute to pathogenesis?		Krol et al (2007) Ribonuclease Dicer cleaves triplet repeat hairpins into shorter repeats that silence specific targets. Mol. Cell 25: 575-586.

date	topic	background reading	papers for discussion
5/11	Genetics of Cancer	Strachan Chapter 17 (pp 487-507 Hanahan and Weinberg (2000) The hallmarks of cancer. Cell 100: 57-70. Folkman and Kalluri (2004) Cancer without disease. Nature 427: 787.	Lecture
5/14	Genetics of Cancer Cont'd		Shih and Weinberg (1982) Isolation of a transforming sequence from a human bladder carcinoma cell line. Cell 29: 161-169. Hahn et al (1999) Creation of human tumor cells with defined genetic elements. Nature 400: 464-468.
5/16	Cancer Epigenetics	Feinberg et al (2006) The epigenetic progenitor origin of cancer. Nat. Rev. Genetics 7:21-33.	Croce et al (2002) Methyltransferase recruitment and DNA hypermethylation of target promoters by an oncogenic transcription factor. Science 295: 107901082. Gaudet et al (2003) Induction of Tumors in mice by genomic hypomethylation. Science 300: 489-492.
5/18	MicroRNAs and Cancer		O'Donnell et al (2005) c-myc regulated microRNAs modulate E2F1 expression. Nature 435: 839-843. Voorhoeve et al (2006) A Genetic Screen Implicates miRNA-372 and miRNA-373 As Oncogenes in Testicular Germ Cell Tumors. Cell 124: 1169-1181.

date	topic	background reading	papers for discussion
5/21	Aneuploidy: Phenotypic Consequences.	Strachan: pp 51-58; p. 480-483 (section 16.8) Review: Hassold and Hunt (2001) To Err (Meiotically) is human: the genesis of human aneuploidy. Nature Rev. Genet. 2: 280-291 Review: Zinn and Ross (1998) Turner Syndrome and haploinsufficiency. Curr Opin Genet Dev 322-327	Lecture
5/23		Roper and Reeves (2006) Understanding the Basis for Down Syndrome Phenotypes. PloS Genetics, 2:231-236.	Rao et al, (1997) Pseudoautosomal deletions encompassing a novel homeobox gene cause growth failure in idiopathic short stature and Turner syndrome. Nat Genet 16: 54-62. Arron et al (2006) NFAT dysregulation by increased dosage of *DSCR1* and *DYRK1A* on chromosome 21. Nature 441: 595-600.
5/25	Model Organisms for Human Genetics: Zebrafish	Optional reading: Ward and Lieschke (2002) The Zebrafish as a Model System for Human Disease. Frontiers in Biosci 7: 827-833	Sarah Cheesman, guest lecture
5/30, 6/1. 6/4, 6/6, 6/8	Student Presentations		
Tues 6/12	**Proposal due, 5 pm.**	Graduate students are required to turn in a Research Proposal. Undergraduates can choose to write a research proposal or to take the Final Exam.	
Wed 6/13	**Final Exam 10:15**		