GENE4500/6500 – Human genetics – Spring 2017
Syllabus – Jan 5, 2017

The course syllabus is a general plan for the course; deviations announced to the class by the instructor may be necessary.

Instructor: Dr. Mary Bedell C110 Davison Life Sciences
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Class time and location: 9:30 – 10:45 TR, 145 Science Learning Center.

Prerequisite: GENE3200. Knowledge of the basic principles of classical, molecular, and population genetics is expected. Although these topics will be reviewed, you are expected to know these principles and apply them in your readings of the research papers.

Course objectives: Students will gain an understanding of the following concepts relating to human genetics: the human genome; patterns of inheritance and pedigree analysis; mapping and identification of disease genes; molecular, biochemical, and cellular mechanisms of genetic disease; animal models of human genetic disorders; genetic basis for phenotypic variation, and ethical issues. Students will gain on understanding of methods and experimental approaches used to dissect molecular processes involved in human disease and phenotypic variation. Successful students will have developed a strong foundation for continued medical studies and/or research in biomedical sciences at the graduate level.

Course material: A textbook is not required but reference textbooks are available from the instructor. In addition, links to general information will be provided for some topics.

- All assigned readings (book chapter, primary research papers, and research review articles) as well as optional (supplemental) papers, will be available on eLC. Lecture slides, which will contain both background information and specific information that relates to the assigned readings, and study guides will be available on eLC.

Class format: The assigned review articles contain important background information for the primary research paper. For each assigned primary research paper, you will be expected to understand the overarching theme of the research, the hypothesis (or hypotheses) being tested, the experimental approach(es), and the main conclusions of the research. In addition, you should be able to interpret and critically evaluate the experimental results, and formulate additional hypotheses/questions that need to be addressed.

Attendance and class participation: Attendance at each class will be recorded and will count toward your grade (see next page). Students are expected to read the assigned papers before class and should be prepared to answer questions from the instructor. You are NOT expected to understand all aspects of the papers on your own. Class times (lecture and discussions) are designed to help you understand the concepts and experimental approaches. In addition, there will be multiple in-class activities where students will work in small groups to critically assess and discuss the research papers.

- In-class, students will be asked questions on basic concepts, the rationale and experimental approach, and interpretation of results and conclusions in the papers. You are not expected to know all the answers! The questions are designed to encourage critical thinking and to help you apply concepts, not to embarrass you. Don't be shy during class or embarrassed that you don't know something!

Quizzes: There will be 10 quizzes that will be given either in class or at home through eLC. These quizzes are designed to encourage you to read the assigned papers before class, as well as to develop your critical thinking skills and improve understanding of key concepts and experimental approaches. The **top 8 quiz scores** will be used to calculate your grade (see next page).

Exams: There will be **three 100-pt exams** that will be based on material in assigned readings (book chapters, research, and review papers) and lecture slides. Although the exams will be non-cumulative and will test primarily on topics since the preceding exam, much of the knowledge needed for these exams is cumulative.

- If a student has an excused absence, a make-up exam will be given at a day and time to be arranged and within one week of the original exam. Questions and problems on the make-up exam will NOT be the same as the original test. Requests for an excused absence will be considered on a case-by-case basis by Dr. Bedell. In order to obtain an excused absence, you will have to provide written documentation for your absence. **If you don't obtain an excused absence, you will not be allowed to take a make-up exam and the missed exam will be scored as a zero.**

Grades. The total course score will be calculated based on the following distribution:

Three exams	300 pts
Top 8 quizzes	80 pts
Class participation and quizzes	20 pts
Course/instructor evaluations	2 bonus pts

Scores will be totaled and then divided by 400 pts to calculate course percentage

GENE4500H students: In addition to exams, quizzes, etc (see above), a term paper (8-to-10 pages) that provides a review and critique of a recent research paper is required for GENE4500H credit. The first part of the term paper should be written in a style like a "Preview" or "News and Views" or "Perspective". For the second part of the term paper, you will propose a hypothesis and experimental approach to follow up on experiments in the published research paper. The research paper will be chosen in consultation with Dr. Bedell and should relate to a topic in human genetics that we've discussed in this course. More details about the research proposal will be provided.

- Your choice of research paper must be approved by Dr. Bedell by **Friday April 14**.
- Your term paper must be uploaded to eLC by **5:00 pm on Friday April 28**.
- In addition to the scores above, the term paper will count 100 pts out of a total of 500 pts.

Tentative grading scale. The course percentages shown below should be used a rough guide, actual grades will be curved relative to the performance of the entire class.

Grade	Course percentage
A	93 - 100
A-	90 – 92.9
B+	87 – 89.9
B	83 – 86.9
B-	80 – 82.9
C+	77 – 79.9
C	70 – 76.9
D	60 – 69.9
F	< 60

Academic honesty: As a University of Georgia student, you have agreed to abide by the University's academic honesty policy, "A Culture of Honesty," and the Student Honor Code. All academic work must meet the standards described in "A Culture of Honesty" found at: https://ovpi.uga.edu/academic-honesty/academic-honesty-policy. Lack of knowledge of the academic honesty policy is not a reasonable explanation for a violation. Questions related to course assignments and the academic honesty policy should be directed to the Dr. Bedell.

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Class schedule, assigned readings, lecture slides, and study guides

This is a tentative schedule for assigned readings and lecture topics. Changes in assigned readings will be announced in class and posted on eLC. However, it is very unlikely that the dates for the three exams will be changed.

All assigned readings and supplemental material are available on eLC. Lectures slides will be posted AFTER each lecture.

Date	Topic	Assigned reading/viewing	Supplemental reading or viewing
1/5	The human genome	Gibson, G. (2015). A primer of human genetics (Sinauer Associates). Chapter 2 – The human genome.	Trask, B. J. (2002) Human cytogenetics: 46 chromosomes, 46 years and counting. Nat Rev Genet 3: 768 (Review)
1/10	Human genomics	Green, E. (2016) The genomic landscape circa 2016. (video)	
1/12	Functional organization of the nuclear genome	Bickmore, W. A. (2013) The spatial organization of the human genome. Annu Rev Genomics Hum Genet 14: 67. (Review)	
1/17	Gametogenesis, meiosis, and fertilization	Carlson, B. M. (2014) Human Embryology and Developmental Biology, 5th ed. (Elsevier Saunders): Chapter 1, p. 2-14 Clift, D. and M. Schuh (2013) Restarting life: fertilization and the transition from meiosis to mitosis. Nat Rev Mol Cell Biol 14: 549 (Review)	
1/19, 1/24	Meiotic nondisjunction and meiotic recombination	Nagaoka, S. I. et al (2012) Human aneuploidy: mechanisms and new insights into an age-old problem. Nat Rev Genet 13: 493. (Review) Baudat, F. (2013) Meiotic recombination in mammals: localization and regulation. Nat Rev Genet 14: 794 (Review)	Handel, M. A. and J. C. Schimenti (2010) Genetics of mammalian meiosis: regulation dynamics and impact on fertility. Nat Rev Genet. 11: 124
1/26	The early embryo: cleavage stages,	Schoenwolf, G. C. et al (2015) Larsen's Human Embryology, 5th ed. (Churchill Livingstone). Intro, p. 1-12	Schoenwolf, G. C. et al (2015) Larsen's Human Embryology, 5th ed. (Churchill Livingstone). Chapter 3, p. 57-71.

	implantation, and gastrulation	Niakan, K. K. et al (2012) Human pre-implantation embryo development. Development 139: 829-841 (Review) Carlson, B. M. (2014) Human Embryology and Developmental Biology, 5th ed. (Elsevier Saunders): Chapter 3 Schoenwolf, G. C. et al (2015) Larsen's Human Embryology, 5th ed. (Churchill Livingstone). Chapter 1, p. 35-42	
1/31 and 2/2 classes cancelled because of illness			
2/7	The first lineage decision in the early embryo	Cockburn, K. and J. Rossant (2010) Making the blastocyst: lessons from the mouse. J Clin Invest 120: 995	Frum, T. and A. Ralston (2015) Cell signaling and transcription factors regulating cell fate during formation of the mouse blastocyst. Trends Genet 31: 402.
2/9	Introduction to pluripotent stem cells	Jaenisch, R. and R. Young (2008) Stem cells, the molecular circuitry of pluripotency and nuclear reprogramming. Cell 132: 567	Spagnoli, F. M. and A. Hemmati-Brivanlou (2006) Guiding embryonic stem cells towards differentiation: lessons from molecular embryology. Curr Opin Genet Dev 16: 469
2/14	**Exam 1**		
2/16, 2/21	Molecular mechanisms in differentiation of pluripotent stem cells - epigenetic regulation	Lee, T. I. et al (2006) Control of developmental regulators by polycomb in human embryonic stem cells. Cell 125: 301 Part I of video of introduction to this paper - you should watch this before class on 2/16 (approx 19 min) Part II of video of introduction to this paper - you should watch this before class on 2/16 (approx 30 min)	Keenen, B. and I. L. De La Serna (2008) Chromatin remodeling in embryonic stem cells: Regulating the balance between pluripotency and differentiation. J Cell Physiol 219 :1-7.
2/23, 2/28	Molecular mechanisms in differentiation of pluripotent stem cells - alternative splicing	Gabut, M. et al (2011) An alternative splicing switch regulates embryonic stem cell pluripotency and reprogramming. Cell 147: 132 Gravely, B. R. (2011) Splicing up pluripotency. Cell 147: 22 (Preview of Gabut et al)	Fu, X.-D. and M. Ares. (2014) Context-dependent control of alternative splicing by RNA-binding proteins. Nat Rev Genet. 15: 689. Jangi, M. and P.A. Sharp (2014) Building robust transcriptomes with master splicing factors. Cell 159: 487.

		Part I of video of introduction to this paper - you should watch this before class on 2/23 (approx 30 min) Part II of video of introduction to this paper - you should watch this before class on 2/23 (approx 30 min)	
3/2	Introduction to induced pluripotent stem cells (iPSCs) and genome editing	Musunuru, K (2013) Genome editing of human induced pluripotent stem cells to generate human cellular disease models. Dis Models Mech 6: 896. (Review) Note that the paper by Musunuru includes a nice summary of the paper by Reinhardt et al (2013) - see below Shi, Y. et al (2017) Induced pluripotent stem cell technology: a decade of progress. Nat Rev Drug Discov 16: 115 (Review) (note that you should read the parts marked in red)	Apostolou, E. and K Hochedlinger (2013) Chromatin dynamics during cellular reprogramming. Nature 502: 462
	Review of mutations and modes of inheritance, genetic mapping	Video will be posted online - the video represents two days of lecture **The video is in three parts -** Part I – Mutations and modes of inheritance (posted 3/13) Part II – Mendelian traits (posted 3/19) Part III – Complex traits (posted 3/19)	Alkuraya, F. S. (2013) The application of next-generation sequencing in the autoygosity mapping of human recessive diseases. Hum Genet. 132: 1197 Bamshad, M.J. et al (2011) Exome sequencing as tool for Mendelian disease gene discovery. Nat Rev Genet 12: 745 (*Review*)
3/6 - 3/10	**Spring Break**		
3/14	Using induced pluripotent stem cells to model genetic disorders	Reinhardt, P. et al (2013) Genetic correction of a LRRK2 mutation in human iPSCs links Parkinsonian neurodegeneration to ERK-dependent changes in gene expression. Cell Stem Cell 12: 354	Schiesling, C. et al (2008) Review: Familial Parkinsons' disease - genetics, clinical phenotype and neuropathology in relation to the common sporadic form of the disease. Neuropath Appl Neuro 34: 255.
3/16	Using induced pluripotent stem cells to	Young, C. S. et al (2016) A single CRISPR-Cas9 deletion strategy that targets the majority of DMD patients restores	Guiraud, S. et al (2015) The pathogenesis and therapy of muscular dystrophies. Annu Rev Genomics Hum Genet 16: 281.

	model genetic disorders (cont)	dystrophin function in hiPSC-derived muscle cells. Cell Stem Cell 18: 533. Breitbart, A. and C. E. Murry (2016) Imprecision medicine: A one-size-fits-many approach for muscle dystrophy. Cell Stem Cell 18: 423 (Preview of the paper by Young et al)	
3/21	Review for exam 2	None!	
3/23	**Exam 2**		
3/28	Id of mendelian trait - autozygosity mapping	Attanasio, M. et al (2007) Loss of GLIS2 causes nephronophthisis in humans and mice by increased apoptosis and fibrosis. Nat Genet 39: 1018	Vasyutina, E. and M. Treier (2010) Molecular mechanisms in renal degenerative disease. Sem Cell Devel Biol 21: 831.
3/30	Functional validation of SNPs identified through GWAS	Musunuru, K. et al (2010) From noncoding variant to phenotype via SORT1 at the 1p13 cholesterol locus. Nature 466: 714	Strong, A. and D. J Rader (2012) Sortilin as a regulator of lipoprotein metabolism Curr Atheroscler Rep 12: 211 Holdt, L.M. and D. Teupser (2013) From genotype to phenotype in human atherosclerosis - recent findings. Curr Opin Lipidol 24: 410
4/4, 4/6	Functional validation of SNPs identified through GWAS (cont)	Sankaran, V. G. et al (2008) Human fetal hemoglobin expression is regulated by the developmental stage-specific repressor BCL11A. Science 322: 1839 Michelson, A. M. (2008) From genetic association to genetic switch. Science 322: 1803. (Perspective on Sankaran et al)	Stamatoyannopoulos, G. (2005) Control of globin gene expression during development and erythroid differentiation. Exp Hematol. 33:259 Sankaran, V. G. et al (2010) Advances in the understanind of haemoglobin switching. Br J Haematol 149: 181 - 194 (through the section on KLF1 on p. 186)
4/11	Long-range transcriptional regulation	Xu, J. et al (2010) Transcriptional silencing of gamma-globin by BCL11A involves long-range interactions and cooperation with SOX6. Genes Dev 24: 783	Kim, A. and A. Dean (2012) Chromatin loop formation in the b-globin locus and its role in globin gene transcription. Mol Cells 34: 1
4/13	Human evolution	Gibson, G. (2015). A primer of human genetics (Sinauer Associates).Chapter 3 – Human evolution.	Paabo, S (2014) The human condition - A molecular approach. Cell 157: 216

			Fan, S. et al (2016) Going global by adapting local: a review of recent human adaptation. Science 354: 54
4/18	Structural variation in the human genome	Eichler, E. (2011) Evolution of human duplications: genomic instability and new genes **You should watch this video before class** youtu.be/wV8fYgjV7Ek?t=50s Lecture slides 16 - 25 have images from the video that are higher resolution than in the video	
4/20	Creation of a human-specific gene by segmental duplication	Dennis, M. Y. et al (2012) Evolution of human-specific neural SRGAP2 genes by incomplete segmental duplication. Cell 149: 912 Geschwind, D. H. and G. Konopka (2012) Genes and human brain evolution. Nature 486: 481 (News and Views of Dennis et al) Tyler-Smith, C. and Y. Xue (2012) Sibling rivalry among paralogs promotes evolution of the human brain. Cell 149: 737. (Preview of Dennis et al)	O'Bleness, M. et al (2012) Evolution of genetic and genomic features unique to the human lineage. Nat Rev Genet. 13: 853. (Review) **2 supplemental papers added 4/16/17** Dennis, M.Y. and E. E. Eichler (2016) Human adaptation and evolution by segmental duplication. Curr Opin Genet Devel 41:44 Charrier, C. et al (2012) Inhibition of SRGAP2 function by its human-specific paralogs induces neoteny during spine maturation. Cell 149: 923.
4/25	Genomic disorders	Ballif, B. C. et al (2007) Discovery of a previously unrecognized microdeletion syndrome of 16p11.2-p12.2. Nat Genet. 39:1071 (very short!) Shinawi, M. et al (2010) Recurrent reciprocal 16p11.2 rearrangements associated with global developmental delay, behavioral problems, dysmorphism, epilepsy, and abnormal head size. J. Med. Genet. 47:332. Horev, G. et al (2011) Dosage-dependent phenotypes in models of 16p11.2 lesions found in autism. Proc. Natl. Acad. Sci. 108:17076	Malhotra, D. and J. Sebat (2012) CNVs: Harbingers of a rare variant revolution in psychiatric genetics. Cell 148: 1223 Golzio, C. and N. Katsanis. (2013) Genetic architecture of reciprocal CNVs. Curr Opin Genet Dev 23:240
5/2	**Exam 3, 9:00am - 11:00am**		