

ANG 6532 (1203)/ ANT 4531 (12H7) MOLECULAR GENETICS OF DISEASE

Prof. Connie J. Mulligan

Class meets in 2333 Turlington

Class time: Wednesday, periods 5-7, 11:45-2:45, with a 15 min break

Contact information:

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Course summary: This course will examine the molecular genetics of disease in humans. The completion of the human genome sequence, the availability of high-throughput, 'next-generation' sequencing platforms, and public databases of genetic variants have greatly accelerated the discovery of genes involved in disease, leading to breakthroughs in diagnosis and treatment. We will discuss a range of genetic disorders from single-gene recessive defects (e.g. myotonic dystrophy and alpha 1-antitrypsin deficiency) to complex diseases (e.g. diabetes and Alzheimer's). We will discuss the methods used to isolate genes involved in disease (e.g. whole genome scans and linkage disequilibrium) as well as genetic testing and types of diagnosis and treatment (e.g. microarrays and gene therapy). Other topics such as pharmacogenomics and epigenetics will be discussed. We will also discuss the ethical, legal and social issues associated with genetic investigation of human health and disease.

Course design: This course is intended for advanced undergraduate and graduate students who have an interest in the molecular genetics of disease. Most human genetics courses spend only 1-2 weeks/semester discussing the genetics of disease, whereas this course focuses on disease for the entire semester. We will discuss the basics of the human genome and the basis of simple and complex diseases, including cause, inheritance, diagnosis, and treatment. We will discuss a number of diseases in detail, with the specifics determined by the state of research for a particular disease, i.e. certain eye diseases are now being treated by gene therapy so we will focus on gene therapies for that day, but will focus on the use of microarrays to diagnose different brain tumors on another day. Throughout the semester, guest lecturers (mainly from the medical school) will speak about their research on the diseases that we discuss in detail in class.

The course is intended for students from all colleges and departments – in the past, I have had students from anthropology, chemistry, English, molecular genetics and microbiology, pharmacology and zoology to name a few. A diverse audience makes for a more interesting class since everyone has different backgrounds, different perspectives and different interests to contribute to class discussions. Active participation is one of the strengths of the class in this regard. It also helps to have a class with undergraduate and graduate students together. Contrary to what one might think, undergrads are often as well prepared and as insightful as graduate students. I keep separate sets of grades for the undergraduate and graduate classes so that each set of students is only compared to his/her cohort.

Course objectives and student goals: All students are expected to gain knowledge on the molecular genetic basis of simple and complex diseases in general and the specific genetic basis for a number of particular human diseases. The class is fairly intense and demanding because knowledge across a broad range of fields is fundamental to an exploration of the molecular genetics of human disease – in fact, this course may be one of the most challenging courses you have taken with respect to developing expertise and familiarity with a wide range of materials, techniques, publications, etc. All students are expected to do all of the required readings and to follow up with additional readings if something is not understood. Additional readings are listed in the textbook and can be found in the references in the journal articles (a glossary of basic terms is also provided in

the textbook). Furthermore, students should become familiar with searching PubMed for supplementary, follow-up, or original readings. Finally, there are suggested textbooks to provide additional and supplementary material. Although basic molecular biological concepts will be reviewed, some knowledge of Mendelian genetics and molecular biology (such as Intro Bio, BCS 2011), and a willingness to immerse yourself in the data, is expected.

Reading materials: There are two required reading sources, a textbook and journal articles available on the e-Learning course website. The main textbook for the course is Human Molecular Genetics, 3rd edition by Peter & Ian Sudbery. The third edition was released in 2010 so make sure you buy the correct edition since there are significant changes between the 2nd and 3rd editions. Related journal articles and news-and-views articles will also be discussed and are available on the e-Learning site. Supplemental texts (for additional background on molecular genetics and more information on genetic diseases, specifically cancer) include How the Human Genome Works by Edwin H. McConkey, Medical Genetics by Lynn Jorde et al. and Medical Genetics at a Glance (very brief and short-hand-written) by Pritchard and Korf. All textbooks are available at campus bookstores and through online sources such as amazon.com and half.com. In general, at least one journal article will be discussed for each disease that we discuss in detail. If students know of additional articles or diseases that they would like to discuss, please contact me.

Course format: The course meets once a week for three hours and the course format is lecture plus discussion with substantial class participation. Evaluation of student performance is based on class participation, two types of written assignments, and an exam.

Grading: Final grades will be determined by the following five categories: participation (100 pts), weekly journal article commentary/questions (10 pts each for 100 pts total), ~4 quizzes (total of 100 pts), ~4 homework exercises (100 pts total), 1 exam (100 pts).

- **Participation** is required of all students and will be based on each student's contribution of original comments, questions, etc. to the class. Simply showing up for class does not constitute participation. Remaining silent in class means that the highest grade a student can receive is a B. Punctuality is important and participation points will not be awarded to students who are late to class.
- At the beginning of each class, students will hand in at least **three original commentary/question statements** based on the reading material. The commentary/questions should be fairly detailed and developed, i.e. "What does 'epigenetics' mean?" will earn no points because you should look up the meaning of the 'epigenetics' as part of reading to understanding the course material. Students should incorporate material from other sources and research questions or ideas that occur while reading the article in each commentary/question. Each commentary/question should be ~1 paragraph. The commentary/questions should cover all assigned peer-reviewed journal articles and textbook reading for the week (it's not necessary to cover the news-and-views type articles) and are intended to ensure that each student is prepared to actively participate in class discussions. Please indicate which journal article or textbook chapter relates to each commentary/question. The lowest grade will be dropped. Missed commentary/questions cannot be made up.
- There will be approximately 4 **quizzes** taken in class during the semester. The quizzes consist of several short answer questions and are intended to ensure that you are doing the readings every week and to help prepare you for the exam.
- There will be approximately 2-4 homework **exercises** involving the analysis of hypothetical or real molecular data. The exercises are intended to give students an opportunity to perform analyses similar to those conducted in the discussion papers and will be graded on effort and accuracy. Exercises must be turned in two weeks after they are assigned. Students who miss a class in which an exercise is assigned are expected to make up any missed material and to turn in exercises on time, i.e. two weeks after the missed class.
- There will be 1 **exam** that will consist of essay and short answer questions and exercises (similar to the homework exercises). Questions must be answered during the exam period without reference to books or notes of any kind. Calculators may be used, but no personal communication devices will be allowed.

Make-up exams will be scheduled only in extenuating circumstances and will require a doctor's note, police report, or similar supporting documentation.

Letter grades will be assigned based on the total percent of points according to the following scale:

A	=	90 or above
A-	=	87-89
B+	=	84-86
B	=	80-83
B-	=	77-79
C+	=	74-76
C	=	70-73
C-	=	67-69
D+	=	64-66
D	=	60-63
D-	=	57-59
E	=	56 or below

The University implemented minus grades beginning in Summer 2009 and, under the new system, a grade of C- will not qualify for major, minor, Gen Ed, Gordon Rule, or College Basic Distribution credit. Please see the following for more information:

Grades and Grading

<https://catalog.ufl.edu/ugrad/current/regulations/info/grades.aspx>

FAQs about Minus Grades

<http://www.isis.ufl.edu/minusgrades.html>

Strategies for success:

- "Learning is not a spectator sport. Fundamentally, the responsibility to learn is yours and yours alone. For learning to happen in any course, you must take an active role in the process. For our class, you are expected to come to class 'prepared' and 'ready to learn', which requires you to read and to study the assigned reading before you come to class." Excerpted from Romack 2010, Enhancing Students' Readiness to Learn, Faculty Focus Special Report: 11 Strategies for Getting Students to Read What's Assigned.
- Furthermore, to get the most out of class, you must arrive on time (5 minutes late is not on time) and you must not use computers for non-class-related activities or use cell phones during class. While you may think that you can multi-task and follow the lecture while playing on your phone, you will definitely learn less than if you give class your undivided attention. Finally, punctuality is a show of respect for your instructor and classmates and is important not just in class but in your job and eventual career.
- It is important to complete all the readings on time and it is best to read the readings throughout the week. In this way, you have time to think about and process the information during the week and in between different readings. Ideally, you would read some every night of the week. The amount of reading material is very modest, particularly for an anthropology course. This is because it is expected that you will re-read (gasp!) anything you do not understand the first time. I often re-read journal articles and find myself discovering things that I completely missed on the first read. Or new items will come to light after having read a different, but related article. This is the intent of the readings – that they relate to each other and increase your knowledge and expertise in an exponential way. During your reading, you should take copious notes and these notes will form the basis of the commentary/questions you will turn in.

- You have two weeks to work on the exercises. The intent is that you will use the first week to start on the exercise and come to class the next week (i.e. the week before the exercise is due) with any questions you have about the exercise. Do not wait until the second week to start the exercise. Also, I am always available by email to ask questions about the exercises.
- Finally, you should review material throughout the course rather than trying to cram everything in the night before the exam. Ask for help in taking notes, comprehending the material, or preparing any of the written or oral assignments – I am available during office hours, you can schedule an appointment outside of office hours, and I am always available by email.

Useful websites:

Additional information is provided by several websites:

e-Learning course website – course website

<http://www.pearsoned.co.uk/highereducation/booksby/sudbery/> - website companion to the textbook

<http://uh7qf6fd4h.search.serialssolutions.com/> - UF database of available electronic journals (may only be available from a campus computer)

<http://www.ncbi.nlm.nih.gov/sites/entrez> - National Library of Medicine database of over 11 million journal articles dating back to the 1960s

<http://www.genome.gov/glossary.cfm> – NIH-maintained glossary of genetic terms

<http://www.genome.gov/gwastudies> - status of genome wide association studies

<http://www.genomesonline.org/> - status of genome sequencing projects

<http://www.genomesize.com/statistics.php?stats=amphibs> – Animal genome size database

<http://geneticassociationdb.nih.gov> - NIH database of gene, variants, etc involved in diseases

www.hgmd.org – Human Gene Mutation Database, database of genetic variants that cause disease, maintained by Cardiff University, UK

www.pitt.edu/~super1 – more than 2600 free lectures on public health and disease

<http://cgap.nci.nih.gov/Chromosomes/Mitelman> - Database of chromosome aberrations in cancer

<http://www.proteinatlas.org/> - Database that shows expression and localization of proteins in human cells

<http://www.genome.gov/LegislativeDatabase> - Database of federal and state laws focused on genetic issues, such as genetic testing and counseling, insurance and employee discrimination, etc.

Class attendance policy: Because the class meets only one time per week and because the class format is mainly discussion, it is very difficult to make up missed classes by borrowing notes, etc. Therefore, students are strongly encouraged to attend all classes. Computers should be used sparingly in class. In a seminar format, it is more important to participate in class discussions than record everything on your computer. Plus it can be very off-putting for me or a guest lecturer to lecture to a sea of laptop backs. Class discussions/lectures cannot be recorded in any manner without special permission.

Copyright information: Lectures may not be tape-recorded without the prior express written permission of Dr. Connie Mulligan. The contents of the syllabus, lectures, lecture outlines, and handouts for this course are copyrighted and intended for the private use of students registered in ANG 6532/ANT 4531. These materials, therefore, cannot legally be reproduced, in part or in whole, by any commercial enterprise or for any commercial purposes.

Accommodations for students with disabilities: If you require accommodation due to a disability, please make an appointment or visit during my office hours so that we may discuss your needs. Students requesting classroom accommodation must first register with the Dean of Students Office. The Dean of Students Office will provide documentation to the student who must then provide this documentation to the Instructor when requesting accommodation.

Academic honesty: As a result of completing the registration form at the University of Florida, every student has signed the following statement: “I understand that the University of Florida expects its students to be honest

in all their academic work. I agree to adhere to this commitment to academic honesty and understand that my failure to comply with this commitment may result in disciplinary action up to and including expulsion from the University.” An excellent website that explains plagiarism (provides a definition and many useful examples) is <http://www.csubak.edu/ssric/Modules/Other/plagiarism.htm>. All students should read this material at least once.

UF Counseling Services: On-campus services are available for students having personal problems or lacking clear career and academic goals. They include:

1. University Counseling Center, 301 Peabody Hall, 392-1575, personal and career counseling
2. Student Mental Health, Student Health Care Center, 392-1171, personal counseling
3. Sexual Assault Recovery Services (SARS), Student Health Care Center, 392-1161, sexual assault counseling
4. Career Resource Center, Reitz Union, 392-1601, career development assistance and counseling
5. Additionally, student web-based resources on sexual harassment are available at <http://www.ufsa.ufl.edu/students/sh/sexualharassment.shtml>

Course schedule:

August 27 – First day of classes

Introduction

Video – Cracking your Genetic Code, NOVA PBS - <http://video.pbs.org/video/2215641935/>

Reading assignment

- The Myth of the Single Genome -

http://www.biotechniques.com/news/biotechniquesNews/biotechniques-347272.html?utm_source=BioTechniques+Newsletters+%26+e-Alerts&utm_campaign=b9fb8b22a1-sequencing&utm_medium=email&utm_term=0_5f518744d7-b9fb8b22a1-87593510#.Ulg_vH9cmkA

- Improving genome understanding, George Church asks why so few people are opting to inspect their genome, http://www.nature.com/news/improving-genome-understanding-1.13907?WT.ec_id=NATURE-20131010

September 3 – The structure of the human genome

Reading assignment

- *Human Molecular Genetics* (HMG), Chpt 2
- e-Learning:
 - Challenges in human genetic diversity: Demographic history and adaptation, Balaesque et al., Hum Mol Genet, 2007, 16:R134-R139
 - Evolution and public health, Omenn, 2010, PNAS, 107:1702-1709
 - Chromosomal distribution of disease genes in the human genome, Cooper et al., 2010, Genetic Testing and Molecular Biomarkers, 14:441-446
 - Our fallen genomes, Macosko & McCarroll, Science, 2013, 342:564-565
 - “Medical genomics: Gather and use genetic data in health care”, Nature, April 24, 2014
 - “The continuing evolution of genes”, NYT, April 28, 2014
 - “Senator’s thesis turns out to be remix of others’ work, uncited”, NYT, July 23, 2014
 - Optional - The case for junk DNA, Palazzo & Gregory, 2014, PLoS Genetics, 10(5):e1004351

Lecture

- Background material
- How to read a scientific article

- PubMed search
- Plagiarism

September 10 - Mapping the human genome /The sequence of the human genome

Reading assignment

- *Human Molecular Genetics* (HMG), Chpt 3
- e-Learning:
 - “Population geneticists move beyond the single gene”, Science, June 22, 2007
 - “Science after the sequence”, Nature, 2010, 465:1000-1001
 - “A patchwork mind: How your parents’ genes shape your brain”, Scientific American, 2009, <http://www.scientificamerican.com/article.cfm?id=a-patchwork-mind>
 - “Why can some kids handle pressure while others fall apart?” Bronson & Merryman, NYT, Feb 6, 2013
 - Genomics meets proteomics: identifying the culprits in disease, Stunnenberg & Hubner, 2014, Hum Genet, 133:689-700.
 - Optional – Prader-Willi syndrome and Angelman syndrome, Buiting, 2010, Am J Med Gen, 154C:365–376
- Quiz 1
- Exercise 1 assigned – due in 2 weeks – skip ahead to Chpt 4 for info relevant to the exercise

Guest speaker – Dr. James Resnick, Associate professor, Dept of Molecular Genetics and Microbiology – imprinting, genetics of Prader-Willi and Angelman syndromes – Confirmed

September 17 – The sequence of the human genome & Heritability

Reading assignment

- *Human Molecular Genetics* (HMG), Chpt 4 (Lot of methods - CAN SKIM SECTIONS!!!)
- e-Learning:
 - “Human genetics: Genomes on prescription”, Nature, 2011, 478:22-24
 - Parental mosaicism is underrecognized and influences recurrence risk of genomic disorders, Campbell et al, 2014, Am J Hum Genet, 95(2):173-182
 - A genomic storm in critically injured humans, Xiao et al. 2011, J Experimental Medicine, 10.1084/jem.20111354

Guest speaker – Dr. Henry Baker, Professor and Chair, Dept of Molecular Genetics and Microbiology – Use of microarray data to diagnose brain tumors

September 24 - Human genetic disease/alpha 1-antitrypsin deficiency AND Epigenetics

Reading assignment

- *Human Molecular Genetics* (HMG), Chpt 1
- e-Learning:
 - Hunting human disease genes: Lessons from the past, challenges for the future, Brunham & Hayden, 2013, Hum Genet, 132:603-617
 - “Up and down in Down’s syndrome”, Pope & Gilbert, 2014, Nature, 508:323-324
 - “Epigenetics at the epicenter of modern medicine, Feinberg, JAMA, 2008, 299:1345-1350.

- Alpha one antitrypsin deficiency: From gene to treatment, Wood and Stockley, Respiration, 2007, 74:481-492
- Optional – Mitochondrial DNA copy number in peripheral blood cells declines with age and is associated with general health among the elderly, Mengel-From et al, 2014, Hum Genet, 133(9):1149-1159
- Optional - A systematic characterization of genes underlying both complex and Mendelian diseases, Jin et al, 2012, Hum Mol Genet, 21(7):`611-1624

○ Exercise 1 due

Guest lecturer - Dr. Mark Brantly, Professor, Dept of Medicine and Molecular Genetics and Microbiology – alpha 1-antitrypsin deficiency –

October 1 - Single gene disorders/cystic fibrosis and myotonic dystrophy

Reading assignment

- *Human Molecular Genetics* (HMG), Chpt 5.1-5.5 (pp 152-178)
- e-Learning:
 - “Human Genetics: One gene, twenty years”, Nature, 2009, 460:165-169
 - Correcting the cystic fibrosis disease mutant A455E CFTR, Cebotaru et al, 2014, PLOS ONE, 9(1):e85183
 - RNA-mediated neurodegeneration in repeat expansion disorders, Todd and Paulson, 2010, Ann Neurol, 67:291–300

- Quiz 2 (covers Sept 24 and Oct 1)
- Exercise 2 assigned – due in 2 weeks

Guest speaker (2:30-3:30) – Dr. Laura Ranum, Director, Center for Neurogenetics, Professor, Dept of Genetics and Microbiology – Confirmed

October 8 – Single gene disorders/Inherited cancers and thalassemias

Reading assignment

- *Human Molecular Genetics* (HMG), Chpt 5.6-5.8 (pp 178-201)
- e-Learning:
 - Realizing the promise of cancer predisposition genes, Rahman, 2014, Nature, 505:302-308
 - Pompe disease gene therapy, Byrne et al. 2011, Hum Mol Genet, 20:R61–R68, doi:10.1093/hmg/ddr174

Guest speaker – Dr. Thomas Conlon, Assistant Professor in Pediatrics, Director of Powell Gene Therapy Center Toxicology Center – Pompe disease (disease in movie ‘Extraordinary Measures’) -

October 15 – The genetic components of complex disease/Alzheimer’s disease

Reading assignment

- *Human Molecular Genetic* (HMG), Chpt 6.1-6.5 (pp 205-241)
- e-Learning:
 - Bioinformatics challenges in Genome-wide association studies (GWAS), De et al, 2014, Clinical Bioinformatics, Methods in Molecular Biology, 1168:63-81

- Current status on Alzheimer disease molecular genetics: From past, to present, to future, Bettens et al. 2010, Hum Mol Genet, 19:R4-R11.
- Alzheimer's disease: The forgetting gene - http://www.nature.com/news/alzheimer-s-disease-the-forgetting-gene-1.15342?WT.ec_id=NATURE-20140605

○ Exercise 2 due

Guest speaker – Dr. Jada Lewis, Associate Professor of Neuroscience, Center for Translational Research in Neurodegenerative Disease – Alzheimer's disease and frontotemporal dementia -

October 22 - The genetic components of complex disease/Diabetes

Reading assignment

- *Human Molecular Genetic* (HMG), Chpt 6.6-6.7 (pp 241-252)
- e-Learning:
 - “Deep genealogy and dilution of risk”, Roberts RG, 2013, PLoS Biology, 11(9): e1001660
 - In search of low-frequency and rare variants affecting complex traits, Panoutsopoulou et al., 2013, Hum Mol Genet, 22: R16-R21
 - The structure of common genetic variation in United States populations, Guthrey et al., Am J Hum Genet, 2007, 81:1221-1231
 - Comparative genetics: Synergizing human and NOD mouse studies for identifying genetic causation of Type 1 diabetes, Driver et al, 2013, Rev Diabetic Stud, 9(4): 139-157.

○ Quiz 3

○ Exercise 3 assigned – due in 2 weeks

Guest speaker – Dr. Clayton E. Mathews, Sebastian Family Professor for Diabetes Research, College of Medicine – genetics of diabetes - Confirmed

Oct 29 - Human population genetics and evolution

Reading assignment

- *Human Molecular Genetic* (HMG), Chpt 10
- e-Learning:
 - Genomics for the world, Bustamante et al, Nature, 2011, 475:163-165
 - Ancestry and disease in the age of genomic medicine, Rotimi and Jorde, 2010, N Engl J Med, 363:1551-1558
 - Genomics and drug response, Feero and Guttmacher, 2011, N Engl J Med, 364:1144-53.

Guest speaker - Dr. Larisa Cavallari, Associate Professor, Dept of Pharmaceutical Sciences and Director, UF Center for Pharmacogenomics – Pharmacogenomics – Confirmed

November 5 – Evolution of *Homo sapiens* – implications for disease

Reading assignment

- e-Learning:
 - “Jocks vs Geeks – the Downside of Genius”, 2014, PLOS Biology, 12(5):e1001872
 - “Parsing the genetics of behavior”, Science, Nov 7, 2008

- “Scientists trace memories of things that never happened”, NYT, July 25, 2013
- The genomic landscape of Neanderthal ancestry in present-day humans, Sankararaman et al, 2014, Nature, 507:354-357 (and look at the figures in the supplemental info)

Exercise 3 due

Video - NOVA Becoming Human (part 3 on Neanderthals)

November 12 - Genetic testing

Reading assignment

- *Human Molecular Genetic* (HMG), Chpt 8 AND Chpt 12, pgs 385-392
- e-Learning:
 - “A geneticist’s research turns personal”, NYT, June 2, 2012
 - “A spot of trouble”, Carmichael, Nature, 2011
 - Guidelines for investigating causality of sequence variants in human disease, MacArthur et al., Nature, 2014, 508: 469-476
 - Preimplantation genetic diagnosis: State of the ART 2011, Harper & SenGupta, 2012, Hum Genet, 131:175-186

- Exercise 4 assigned – due in 2 weeks

Guest speaker – Dr. Charles Williams, MD, Professor, Dept of Pediatrics - Genetic testing

November 19 – Gene therapy

Reading assignment

- *Human Molecular Genetic* (HMG), Chpt 9
- e-Learning:
 - p11 and gene therapy for severe psychiatric disorders: A practical goal? Chen et al, 2010, Sci Transl Med, 2(54):54ps51
 - Gene therapy for Leber congenital amaurosis caused by RPE65 mutations: Safety and efficacy in fifteen children and adults followed up to three years, Jacobson et al., Arch Ophthalmology, in press

Quiz 4

Guest speaker – Prof. William Hauswirth, Professor, Dept of Ophthalmology and Molecular Genetics – Gene therapy and eye disease - Confirmed

November 26 - Thanksgiving

December 3 - DNA profiling in forensic criminology AND Human genetics and society

Reading assignment

- *Human Molecular Genetic* (HMG), Chpts 11 AND 12
- e-Learning:
 - “Researchers to return blood samples to the Yamomamo”, Science, June 4, 2010
 - “Taking the least of you”, The New York Times, April, 2006
 - How race becomes biology, Gravlee, 2009, Am J Phys Anthropol, 139:47-57

- Ethical, legal, and social issues in pharmacogenomics, Allen, Pharmacogenomics: Applications to patient care, 2004, American College of Clinical Pharmacy, Kansas City Mo

- Exercise 4 due

Guest speaker – Bill Allen, Director, Program in Bioethics, Law and Medical Professionalism – Ethical, legal and social issues – Confirmed

Review for exam

December 10 - Exam