

**Biology 76/176: Advanced Genetics**

Fall 2017

Lecture: M, W, F 11:30 AM-12:35 PM; x-hour Tu 12:00-12:50

C. Robertson McClung  
323 Life Sciences Complex

Office Hours: Monday-Friday 2:00-4:00 PM  
or by appointment

**Course Content**

This course provides in-depth coverage of the analysis of gene inheritance and function. Biology 76 will build on material covered in Biology 13 and Biology 45, emphasizing the use of model organisms to obtain information relevant to important problems.

**Text**

There will be no text, but your text from earlier Genetics classes (e.g., Russell iGenetics 3e) might prove useful as a resource.

**Evaluation**

Your grade will be based on four written assignments—study guides based on the analysis of a paper from the primary literature. The first three will be worth 20% each and the final assignment will be worth 30%. In addition, 10% of your grade will be based on class participation. This includes attendance (to paraphrase Woody Allen, 80% of success is showing up) as well as your willingness and ability to contribute meaningfully to class discussion. Examples of this would include your providing a clear explanation of a figure from the assigned reading to the class or asking thought-provoking questions about the topics under consideration. The first three assignments that will be discussed in class will be due at **the beginning** of the class in which they are to be discussed. The method of submission is electronic—email me your file before class begins. The fourth assignment will be due at 1130 AM on Nov 22 (the last day of final exams). **Late assignments will be penalized 25%** of the earned grade per day or part thereof unless a prior arrangement is finalized **in writing**.

Please note that the Discussions will be held Wednesdays in the regular class time (11:30 AM-12:35 PM).

**Disability Notice**

Students with disabilities who may need disability-related academic adjustments and services for this course are encouraged to see me privately as early in the term as possible. Students requiring disability-related academic adjustments and services must consult the Student Accessibility Services office (205 Collis Student Center, 646-9900, [Student.Accessibility.Services@Dartmouth.edu](mailto:Student.Accessibility.Services@Dartmouth.edu)). Once SAS has authorized services, students must show the originally signed SAS Services and Consent Form and/or a letter on SAS

letterhead to their professor. As a first step, if students have questions about whether they qualify to receive academic adjustments and services, they should contact the SAS office. All inquiries and discussions will remain confidential.

### **Religious Holidays**

Some students may wish to take part in religious observances that occur during this academic term. If you have a religious observance that conflicts with your participation in this course, please meet with me as soon as possible to discuss appropriate accommodations.

### **The Honor Principle**

**Academic honesty is essential.** The following is quoted directly from the [Dartmouth College Student Handbook](#): "Fundamental to the principle of independent learning are the requirements of honesty and integrity in the performance of academic assignments, both in and out of the classroom. Dartmouth operates on the principle of academic honor, without proctoring of examinations. Any student who submits work which is not his or her own, or commits other acts of academic dishonesty, violates the purposes of the college and is subject to disciplinary actions, up to and including suspension or separation." The complete text of the [Academic Honor Principle](#) is in the [Student Handbook](#). Please read it carefully. Graduate students should consult the [Graduate Student Handbook](#), with particular emphasis on [The Honor Principle and Code of Conduct](#). Any violations of the Honor Principle within the context of Biology 76/176 will be referred to the Committee on Standards or to the Dean of Graduate Studies, respectively.

Awareness of the Academic Honor Principle is not intended to inhibit discussion of the class material among the students. Indeed, such discussion is worthwhile and constitutes a valuable component of the learning process and is encouraged on the first four study guide assignments. However, the study guides must be written independently. Two assignments by two individuals who had discussed the assignment almost certainly will reflect ideas developed by the two together, but each student must phrase their assignment in their own words and acknowledge the "helpful discussions" with their collaborators. Do not share computer files! To do so constitutes plagiarism. The **Fifth Assignment** is in open book format (all written resources are permitted) but is to be **done entirely on one's own (no collaboration)**.

**Schedule** (subject to change)

	<u>Topic</u>	<u>Reading</u>
1. Sep 11	Introduction/Genetics in the Genomics Age	(Mushegian and Koonin, 1996; Glass et al., 2006; Hutchison III et al., 2016)
<b>Section 1, Forward Genetics</b>		
2. Sep 13	Mutation Rates & Mutant Selections	(Haag-Liautard et al., 2007; Lang and Murray, 2008; Ossowski et al., 2010; Winston and Koshland, 2016)
3. Sep 15	Mutant Screens: Heterochrony in Worms	(Ambros and Horvitz, 1984)
4. Sep 18	Complementation, Suppression, Enhancement	(Ambros and Horvitz, 1987)
5. Sep 20	Study Guide Warm-up: The molecular discovery of microRNAs	(Lee et al., 1993; Reinhart et al., 2000)
6. Sep 22	Epistasis	(Ambros, 1989; Avery and Wasserman, 1992)
7. Sep 25	Sex determination in <i>Drosophila</i> I	(Keyes et al.; Penalva and Sánchez, 2003)
8. Sep 27	Study Guide 1 (20%)	(Ecsedi et al., 2015)
9. Sep 29	Sex determination in <i>Drosophila</i> II	(Erickson and Quintero, 2007)
10. Oct 2	Cystic Fibrosis	(Fanen et al., 2014; Cutting, 2015)
11. Oct 4	Genetic Modifiers in Cystic Fibrosis	(Kiesewetter et al., 1993; Drumm et al., 2005)
12. Oct 6	Anteroposterior polarity in <i>Drosophila</i> I	(Frohnhofer and Nüsslein-Vollhard, 1986; Nüsslein-Vollhard et al., 1987)
13. Oct 9	Anteroposterior polarity in <i>Drosophila</i> II	(Berleth et al., 1988; Driever and Nüsslein-Vollhard, 1988; Spirov et al., 2009)
14. Oct 11	RNAi in <i>C. elegans</i> and plants	(Fire et al., 1998; Hamilton and Baulcombe, 1999)
<b>Section 2, Reverse Genetics</b>		
15. Oct 13	Anteroposterior polarity in <i>C. elegans</i>	(Griffin et al., 2011)
16. Oct 16	Screens in human tissue culture	(Zhang et al., 2009; Partch et al., 2014)

17. Oct 18 Study Guide 2 (20%) (Luo and Sehgal, 2012)
18. Oct 20 Gene replacement in Yeast (Boeke et al., 1985; Winzeler, 1999; Giaever et al., 2002)
19. Oct 23 Transgenic Mice (knockouts/knockins) I (Mansour et al., 1988; Garcia-Cao et al., 2012)
20. Oct 25 Transgenic Mice (knockouts/knockins) II (Mansour et al., 1988; Garcia-Cao et al., 2012)
21. Oct 27 RNAi Screens in mice (Beronja et al., 2013)
22. Oct 30 CRISPR-mediated genome editing (Gilbert et al., 2013; Gilbert et al., 2014)
23. Nov 1 Chemical Genomics (Baragana, 2015)
- Section 3, Quantitative Genetics**
24. Nov 3 Quantitative Trait Loci (Barton and Keightley, 2012)
25. Nov 6 Genome-Wide Association Studies (Consortium, 2007; Atwell et al., 2010; Chao et al., 2012)
26. Nov 8 Study Guide 3 (20%) (Norris et al., 2017)
27. Nov 10 Complex Traits: a soybean example (Lu and Xiaohui Zhao, 2017)
28. Nov 13 Complex Traits: a circadian clock example (Xie et al., 2015)
29. Nov 22 Study Guide 4 (30%) TBA  
(no meeting, but assignment due by 1130 AM)

## Reading List

- Ambros, V.** (1989). A hierarchy of regulatory genes controls a larva-to-adult developmental switch in *C. elegans*. *Cell* **57**: 49-57.
- Ambros, V., and Horvitz, H.R.** (1984). Heterochronic mutants of the nematode *Caenorhabditis elegans*. *Science* **226**: 409-416.
- Ambros, V., and Horvitz, H.R.** (1987). The *lin-14* locus of *Caenorhabditis elegans* controls the time of expression of specific postembryonic developmental events. *American Zoologist* **1**: 398-414.
- Atwell, S., Huang, Y.S., Vilhjálmsson, B.J., Willems, G., Horton, M., Li, Y., Meng, D., Platt, A., Tarone, A.M., Hu, T.T., Jiang, R., Muliya, N.W., Zhang, X., Amer, M.A., Baxter, I., Brachi, B., Chory, J., Dean, C., Debieu, M., de Meaux, J., Ecker, J.R., Faure, N., Kniskern, J.M., Jones, J.D., Michael, T., Nemri, A., Roux, F., Salt, D.E., Tang, C., Todesco, M., Traw, M.B., Weigel, D., Marjoram, P., Borevitz, J.O., Bergelson, J., and Nordborg, M.** (2010). Genome-wide association study of 107 phenotypes in *Arabidopsis thaliana* inbred lines. *Nature* **465**: 627-631.
- Avery, L., and Wasserman, S.** (1992). Ordering gene function: the interpretation of epistasis in regulatory hierarchy. *Trends Genet.* **8**: 312-316.
- Baragana, B., et al.** (2015). A novel multiple-stage antimalarial agent that inhibits protein synthesis. *Nature* **522**: 315-320.
- Barton, N.H., and Keightley, P.D.** (2012). Understanding quantitative genetic variation. *Nature Rev. Genetics* **3**: 11-21.
- Berleth, T., Burri, M., Thoma, G., Bopp, D., Richstein, S., Frigerio, G., Noll, M., and Nüsslein-Volhard, C.** (1988). The role of localization of bicoid RNA in organizing the anterior pattern of the *Drosophila* embryo. *EMBO J.* **7**: 1749-1756.
- Beronja, S., Janki, P., Heller, E., Lien, W.-H., Keyes, B.E., Oshimori, N., and Fuchs, E.** (2013). RNAi screens in mice identify physiological regulators of oncogenic growth. *Nature* **501**.
- Boeke, J.D., Garfinkel, D.J., Styles, C.A., and Fink, G.R.** (1985). Ty elements transpose through an RNA intermediate. *Cell* **40**: 491-500.
- Chao, D.-Y., Silva, A., Baxter, I., Huang, Y.S., Nordborg, M., Danku, J., Lahner, B., Yakubova, E., and Salt, D.E.** (2012). Genome-wide association studies identify heavy metal ATPase3 as the primary determinant of natural variation in leaf cadmium in *Arabidopsis thaliana*. *PLoS Genet.* **8**: e1002923.
- Consortium, T.W.T.C.C.** (2007). Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. *Nature* **447**: 661-678.
- Cutting, G.R.** (2015). Cystic fibrosis genetics: from molecular understanding to clinical application. *Nature Rev. Genetics* **16**: 45-56.
- Driever, W., and Nüsslein-Volhard, C.** (1988). A gradient of *bicoid* protein in *Drosophila* embryos. *Cell* **54**: 83-93.
- Drumm, M.L., Konstan, M.W., Schluchter, M.D., Handler, A., Pace, R., Zou, F., Zariwala, M., Fargo, D., Xu, A., Darrah, R.J., Dorfman, R., Sandford, A.J., Corey, M., Zielenski, J., Durie, P., Goddard, K., Yankaskas, J.R., Wright, F.A., and Knowles, M.R.** (2005). Genetic modifiers of lung disease in cystic fibrosis. *New Engl. J. Med.* **353**: 1443-1453.

- Ecsedi, M., Rausch, M., and Großhans, H.** (2015). The *let-7* microRNA directs vulval development through a single target. *Dev. Cell* **32**: 335–344.
- Erickson, J.W., and Quintero, J.J.** (2007). Indirect effects of ploidy suggest X chromosome dose, not the X:A ratio, signals sex in *Drosophila*. *PLoS Biol.* **5**: e332.
- Fanen, P., Wohlhuter-Haddad, A., and Hinzpetera, A.** (2014). Genetics of cystic fibrosis: CFTR mutation classifications toward genotype-based CF therapies. *Intl. J. Biochem. Cell Biol.* **52**: 94-102.
- Fire, A., Xu, S.-Q., Montgomery, M.K., Kostas, S.A., Driver, S.E., and Mello, C.C.** (1998). Potent and specific genetic interference by double-stranded RNA in *Caenorhabditis elegans*. *Nature* **391**: 806-811.
- Frohnhofer, H.G., and Nüsslein-Vollhard, C.** (1986). Organization of the anterior pattern in the *Drosophila* embryo by the maternal gene *bicoid*. *Nature* **324**: 120-125.
- Garcia-Cao, I., Song, Min S., Hobbs, Robin M., Laurent, G., Giorgi, C., de Boer, Vincent C.J., Anastasiou, D., Ito, K., Sasaki, Atsuo T., Rameh, L., Carracedo, A., Vander Heiden, Matthew G., Cantley, Lewis C., Pinton, P., Haigis, Marcia C., and Pandolfi, Pier P.** (2012). Systemic Elevation of PTEN Induces a Tumor-Suppressive Metabolic State. *Cell* **149**: 49-62.
- Giaever, G., Chu, A.M., Ni, L., Connelly, C., Riles, L., Veronneau, S., Dow, S., Lucau-Danila, A., Anderson, K., Andre, B., Arkin, A.P., Astromoff, A., El Bakkoury, M., Bangham, R., Benito, R., Brachat, S., Campanaro, S., Curtiss, M., Davis, K., Deutschbauer, A., Entian, K.D., Flaherty, P., Foury, F., Garfinkel, D.J., Gerstein, M., Gotte, D., Guldener, U., Hegemann, J.H., Hempel, S., Herman, Z., Jaramillo, D.F., Kelly, D.E., Kelly, S.L., Kotter, P., LaBonte, D., Lamb, D.C., Lan, N., Liang, H., Liao, H., Liu, L., Luo, C.Y., Lussier, M., Mao, R., Menard, P., Ooi, S.L., Revuelta, J.L., Roberts, C.J., Rose, M., Ross-Macdonald, P., Scherens, B., Schimmack, G., Shafer, B., Shoemaker, D.D., Sookhai-Mahadeo, S., Storms, R.K., Strathern, J.N., Valle, G., Voet, M., Volckaert, G., Wang, C.Y., Ward, T.R., Wilhelmy, J., Winzeler, E.A., Yang, Y.H., Yen, G., Youngman, E., Yu, K.X., Bussey, H., Boeke, J.D., Snyder, M., Philippsen, P., Davis, R.W., and Johnston, M.** (2002). Functional profiling of the *Saccharomyces cerevisiae* genome. *Nature* **418**: 387-391.
- Gilbert, L.A., Larson, M.H., Morsut, L., Liu, Z., Brar, G.A., Torres, S.E., Stern-Ginossar, N., Brandman, O., Whitehead, E.H., Doudna, J.A., Lim, W.A., Weissman, J.S., and Qi, L.S.** (2013). CRISPR-mediated modular RNA-guided regulation of transcription in eukaryotes. *Cell* **154**: 442-451.
- Gilbert, Luke A., Horlbeck, Max A., Adamson, B., Villalta, Jacqueline E., Chen, Y., Whitehead, Evan H., Guimaraes, C., Panning, B., Ploegh, Hidde L., Bassik, Michael C., Qi, Lei S., Kampmann, M., and Weissman, Jonathan S.** (2014). Genome-scale CRISPR-mediated control of gene repression and activation. *Cell* **159**: 647-661.
- Glass, J.I., Assad-Garcia, N., Alperovich, N., Yooseph, S., Lewis, M.R., Maruf, M., Hutchison III, C.A., Smith, H.O., and Venter, J.C.** (2006). Essential genes of a minimal bacterium. *Proc. Natl. Acad. Sci. USA* **103**: 425-430.
- Griffin, Erik E., Odde, David J., and Seydoux, G.** (2011). Regulation of the MEX-5 gradient by a spatially segregated kinase/phosphatase cycle. *Cell* **146**: 955-968.
- Haag-Liautard, C., Dorris, M., Maside, X.M., Steven, Halligan, D.L., Charlesworth, B., and Keightley, P.D.** (2007). Direct estimation of per nucleotide and genomic deleterious mutation rates in *Drosophila*. *Nature* **445**: 82-85.

- Hamilton, A.J., and Baulcombe, D.C.** (1999). A species of small antisense RNA in posttranscriptional gene silencing in plants. *Science* **286**: 950-952.
- Hutchison III, C.A., Chuang, R.-Y., Noskov, V.N., Assad-Garcia, N., Deerinck, T.J., Ellisman, M.H., Gill, J., Kannan, K., Karas, B.J., Ma, L., Pelletier, J.F., Qi, Z.-Q., Richter, R.A., Strychalski, E.A., Sun, L., Suzuki, Y., Tsvetanova, B., Wise, K.S., Smith, H.O., Glass, J.I., Merryman, C., Gibson, D.G., and Venter, J.C.** (2016). Design and synthesis of a minimal bacterial genome. *Science* **351**: 1414.
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- Lang, G.I., and Murray, A.W.** (2008). Estimating the per-base-pair mutation rate in the yeast *Saccharomyces cerevisiae*. *Genetics* **178**: 67-82.
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- Lu, S., and Xiaohui Zhao, Y.H., Shulin Liu, Haiyang Nan, Xiaoming Li, Chao Fang, Dong Cao, Xinyi Shi, Lingping Kong, Tong Su, Fengge Zhang, Shichen Li, Zheng Wang, Xiaohui Yuan, Elroy R Cober, James L Weller, Baohui Liu, Xingliang Hou, Zhixi Tian & Fanjiang Kong.** (2017). Natural variation at the soybean *J* locus improves adaptation to the tropics and enhances yield. *Nat. Genet.* **49**: 773-779.
- Luo, W., and Sehgal, A.** (2012). Regulation of circadian behavioral output via a microRNA-JAK/STAT circuit. *Cell* **148**: 765-779.
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- Mushegian, A.R., and Koonin, E.V.** (1996). A minimal gene set for cellular life derived by comparison of complete bacterial genomes. *Proc. Natl. Acad. Sci. USA* **93**: 10268-10273.
- Norris, A.D., Gracida, X., and Calarco, J.A.** (2017). CRISPR-mediated genetic interaction profiling identifies RNA binding proteins controlling metazoan fitness. *eLIFE* **6**: e28129.
- Nusslein-Volhard, C., Frohnhof, H.G., and Lehmann, R.** (1987). Determination of anteroposterior polarity in *Drosophila*. *Science* **238**: 1675-1681.
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- Partch, C.L., Green, C.B., and Takahashi, J.S.** (2014). Molecular architecture of the mammalian circadian clock. *Trends Cell Biol.* **24**: 90-99.
- Penalva, L.O.F., and Sánchez, L.** (2003). RNA binding protein Sex-Lethal (Sxl) and control of *Drosophila* sex determination and dosage compensation. *Microbiol. Mol. Biol. Rev.* **67**: 343-359.

- Reinhart, B.J., Slack, F.J., Basson, M., Pasquinelli, A.E., Bettinger, A.E., Rougvie, A.E., Horvitz, H.R., and Ruvkun, G.** (2000). The 21-nucleotide *let-7* RNA regulates developmental timing in *Caenorhabditis elegans*. *Nature* **403**: 901-906.
- Spirov, A., Fahmy, K., Schneider, M., Frei, E., Noll, M., and Baumgartner, S.** (2009). Formation of the bicoid morphogen gradient: an mRNA gradient dictates the protein gradient. *Development* **136**: 605-614.
- Winston, F., and Koshland, D.** (2016). Back to the future: Mutant hunts are still the way to go. *Genetics* **203**: 1007-1010.
- Winzler, E.A.e.a.** (1999). Functional characterization of the *S. cerevisiae* genome by gene deletion and parallel analysis. *Science* **285**: 901-906.
- Xie, Q., Lou, P., Hermand, V., Aman, R., Park, H.J., Yun, D.-J., Kim, W.Y., Salmela, M.J., Ewers, B.E., Weinig, C., Khan, S.L., Schaible, D.L.P., and McClung, C.R.** (2015). Allelic polymorphism of *GIGANTEA* is responsible for naturally occurring variation in circadian period in *Brassica rapa*. *Proc. Natl. Acad. Sci. USA* **112**: 3829-3834.
- Zhang, E.E., Liu, A.C., Hirota, T., Miraglia, L.J., Welch, G., Pongsawakul, P.Y., Liu, X., Atwood, A., Huss III, J.W., Janes, J., Su, A.I., Hogenesch, J.B., and Kay, S.A.** (2009). A genome-wide RNAi screen for modifiers of the circadian clock in human cells. *Cell* **139**: 199-210