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Genetics Education

Innovations in Teaching and Learning Genetics

Edited by Patricia J. Pukkila

PubMed, *The New York Times* and *The Chicago Tribune* as Tools for Teaching Genetics

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ABSTRACT

An elementary course in human heredity for students not planning to major in the sciences can be based on current scientific literature and on the popular media. Examinations are constructed from questions on recent abstracts obtained from PubMed. The course is designed to promote writing skills in the sciences, and students write two papers in the course of a quarter. In the first paper, students trace the primary source of media reports on genetics and attempt to evaluate the reporter's translation. In a second paper, students write popular articles on the basis of current primary sources.

Teaching science to liberal arts students: There is widespread agreement that all undergraduate students should have some familiarity with science. However, it is not always clear what the science requirement is intended to accomplish. It is a common experience that irrelevant information is not retained long so the goal of such courses can hardly be the accumulation of factual material. Since genetics is a logical discipline, some insight into the way geneticists look at problems and at the phenomenon of life itself may be the goal. In addition, genetics differs from most sciences in its immediate applicability to human life and decisions. Young adults, about to establish their own families, are particularly involved in decisions based on genetics. They are much involved with the question of when life begins, they are involved with the question of the risk of nondisjunction, and some of them will be involved with the desire for a compatible donor for stem cells. Very few of the questions these young adults have will be completely answered by the scientific facts but all of the answers will be based on their attitude to the facts and, as importantly, on what are perceived to be the facts. A course in genetics might then have as its goal educating students to obtain, evaluate, and explain the available information. Modern-day students appear to use one major source for their information and that is the internet. Magazines, newspapers, television, and radio may be used but any instructor can testify to the widespread use of the internet. Arguing with this trend is not worthwhile. What is needed is to put it to use.

I assume that we are in some agreement about the major concepts we would like students to understand about genetics. My personal hope is that students will have some intuitive understanding of meiosis as the physical basis of genetics. The details of what we would like to get across differ with each instructor. What I wish to describe is a methodology that can work with almost any variation of topics in (human) genetics. The course I describe is not designed for students majoring in biology or chemistry, although the method is adaptable to such courses. All undergraduates at The University of Chicago are required to register for at least four quarters of natural science. Many choose to register for two quarters of physical sciences and two quarters of biological sciences. Students planning to major in the biological or chemical sciences will usually take a professionally oriented series of courses. Students who do not intend to specialize in science register for a general sequence. When the new requirements were adopted, the first quarter of Biological Science was designed as a course in first principles taken by all students. Students read, discussed, and wrote papers on the basis of general

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interest books such as *The Beak of the Finch* by Jonathan Weiner and *One Renegade Cell* by Robert Weinberg (replaced after a few years by *Genome* by Matt Ridley). With time, the common first quarter has been replaced by one of six courses, with an emphasis on Cell and Molecular Biology, Genomics, Pharmacology, Infectious Disease, Organisms and Ecosystems, and Quantitative Biology, respectively. This is followed by a second quarter of more idiosyncratic content, determined in large part by the interest of the instructors. Our college requires that *bona fide* faculty (as opposed to teaching assistants) teach undergraduate courses. Given the demands on faculty time at a research university, the problems of staffing are solved in part by encouraging faculty, including our full-time clinical faculty, to teach basic biological principles via courses based on their own research specialties. The Human Heredity course I describe here is one of the second-quarter courses. As should be clear from the description above, there is little common background. Almost all students will have heard about DNA but almost none will have learned or remembered meiosis, even those who took good high school courses many years earlier. The Human Heredity course is based on an initial discussion of cells, chromosomes, cell division, and meiosis. Meiosis leads to the genetics of sex determination, which leads to X-linked traits, which leads to autosomal traits and to chromosomal aberrations. Quarters last a whirlwind 10 weeks, and the second half of the course concentrates on the structure of human DNA, the DNA code, mutation, including triplet-repeat diseases, and biochemical genetics with an emphasis on the genetic, biochemical, and psychological aspects of phenylketonuria as a paradigm for the personal problems posed by genetic disease. The outline of this year's course as handed out to students is included in the supplemental material (see http//www.genetics.org/supplemental/). The content of the course is orthodox and there are several excellent and up-to-date textbooks that cover the material.

Examinations based on current abstracts: Notwithstanding any reality about the half-life of information, some objective way needs to be used to judge whether students have understood what we are trying to teach. The standard method is to ask questions about the material. These may be straightforward questions or, particularly in genetics, they may be problems that require the application of understood principles. This is a time-honored and entirely appropriate method for professional students. I suggest that abstracts from current articles from the PubMed database provide a useful alternative. Consider the following abstract (chosen not so much for its intrinsic merit but because it happens to lend itself to a set of questions):

> Xu, L., K. Tsuji, H. Mostowski, M. Otsu, F. Candotti *et al.* 2004 A convenient method for positive selection of retroviral producing cells generating vectors devoid of selectable markers. J. Virol. Methods. **118**(1): 61–67.
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> Early retroviral vectors containing both a therapeutic gene and a dominant selectable marker gene offered some distinct advantages with respect to gene therapy, in that they simplified the generation, isolation, and titration of retroviral producer cell clones, as well as the evaluation and selection of successfully targeted cells. However, a number of problems were engendered by this strategy: the promoter driving the selectable marker gene could interfere with transcription of the therapeutic gene, and immune responses could be induced to cells expressing foreign proteins of selection marker origin. Simplified retroviral vectors, which lack a selection marker gene, were constructed to address these problems, but the inability to use a selection marker has made identification and cloning of virus producing transfected cells a heavy burden. To maintain the benefits of simplified retroviral vectors, while providing a facile means to select packaging cells transfected with retroviral DNA, we cloned the bacterial selection marker gene encoding neomycin phosphotransferase (neo) into the plasmid backbone of the vector, but outside of the provirus, resulting in efficient selection of transfected packaging cells and generation of packaged virus which lacks the neo gene. This novel approach generates greater numbers of high infectious titer producing clones, after selection in G418 media, than does a co-transfection approach, due to integration of higher construct copy numbers per cell. No transmission of the selection marker gene to target cells was observed following retroviral transduction. Thus, our strategy eliminates the adverse consequences of a selection-based method, while diminishing the burden of identification of packaging cells transfected with vectors devoid of selectable markers.

Here are the questions that I asked:

a. What is a retroviral vector?
b. What is a dominant selectable marker gene and why is it important for cloning?
c. Why is it often necessary to associate a therapeutic gene with such a marker gene?
d. What does the abstract suggest is the problem with this approach?
e. How did the investigators attempt to solve the problem?

The questions had been preceded by lectures on cloning and genetic engineering and the text had a chapter devoted to this and related subjects.

All the abstracts used for examinations (see Tables 1 and 2 for the articles from which the abstracts were taken) were selected to illustrate the content of the lectures, insofar as 8–10 questions can mirror the content of 10 weeks of lectures. However, understanding genetics is cumulative and a question on trisomy, for example, makes sense only if one understands normal segregation. Therefore, even 10 questions, if reasonably chosen, will require the understanding of a considerable body of knowledge. The abstracts selected illustrate what I thought was most significant in the lectures, and 2 weeks before each examination I did indicate to students the general topics I considered most important. One of the miracles of the electronic age is the ability to send an individual e-mail message to every registered

TABLE 1

First examination articles and questions

Simerly, C., C. Navara, S. H. Hyun, B. C. Lee, S. K. Kang *et al.*, 2004 Embryogenesis and blastocyst development after somatic cell nuclear transfer in nonhuman primates: overcoming defects caused by meiotic spindle extraction. Dev. Biol. **276**(2): 237–252.

a. What is the problem that the use of embryonic stem (ES) cells might solve? Why should ES cells be of particular use?
b. How (in outline) would one proceed to derive a blastocyst by somatic cell nuclear transfer? What is a blastocyst?
c. The abstract speaks of enucleation just prior to metaphase-II arrest. Explain what metaphase-II arrest is and where and when it happens.
d. What evidence does the abstract give related to the possibility of actually deriving cloned monkeys by somatic cell nuclear transfer?
e. What is an aneuploid preimplantation embryo and why might a centrosome deficiency result in the production of such embryos?
f. How might these results be used to argue that ES cell research is fundamentally different from attempts to clone primates? (Alternatively, or if the question offends you, argue that these results show that ES cell research is *not* fundamentally different from attempts to clone primates.)

Melo, K. F., B. B. Mendonca, A. E. Billerbeck, E. M. Costa M. Inacio *et al.*, 2003 Clinical, hormonal, behavioral, and genetic characteristics of androgen insensitivity syndrome in a Brazilian cohort: five novel mutations in the androgen receptor gene. J. Clin. Endocrinol. Metab. **88**(7): 3241–3250.

a. According to the abstract, is AIS an "all or none" condition or are there varying degrees of severity?
b. The abstract suggests that the family history was suggestive of X-linked inheritance. Draw the type of pedigree that might have been seen and that would suggest X-linked inheritance.
c. What does the abstract suggest is the cause of AIS and what evidence does it give to support this idea?
d. Although the abstract does not specify, what might be the reason for the distinction between CAIS and PAIS?
e. Comment on the following sentence in the abstract: "All subjects with PAIS maintained at postpubertal age the gender identity and social sex that was assigned to them in infancy, in contrast to other forms of pseudohermaphroditism."

Shaffer, L. G., C. K. Jackson-Cook, B. A. Stasiowski, J. E. Spence and J. A. Brown, 1992 Parental origin determination in thirty *de novo* Robertsonian translocations. Am. J. Med. Genet. **43**(6): 957–963.

(rob in a chromosome designation indicates a Robertsonian translocation)

a. What would you expect the phenotype of the balanced Robertsonian translocation individuals to be?
b. What chromosomes were involved in the translocations?
c. What would be the phenotype of all rob(14q21q) ascertained through unbalanced probands (20/20)?
d. What was unexpected about the origin and composition of these unbalanced probands?
e. Draw a diagram indicating the authors' explanation for the homozygosity of the chromosome 21 loci (considering only the maternal-derived loci).

Ottman, R., M. R. Winawer, S. Kalachikov, C. Barker-Cummings, T. C. Gilliam *et al.*, 2004 LGI1 mutations in autosomal dominant partial epilepsy with auditory features. Neurology **62**(7): 1120–1126.

a. Draw a pedigree of a family with a member showing ADPEAF. Make the pedigree extensive enough to eliminate alternative interpretations.
b. What is meant by penetrance?
c. How would low penetrance show up in the pedigree you have drawn?
d. Just from the abstract, and notwithstanding any conclusion the authors reach, what question(s) might one ask about the relation of the mutations in LGI1 and the epilepsy?

student providing such information. The abstracts to be used as the basis of the questions were posted on the internet (via the course "Chalk" site) several days before the examination, and we had sessions in which the teaching assistants (TAs) would answer any question that the students had about the abstracts. I tried to select abstracts that did not require reading the entire paper. I did not discuss the abstracts in the regular lecture sessions, mostly because they had not been selected in advance of the examination. However, I wanted to make sure the students were not held up by technical words and phrases and so tried to provide a venue in which they could ask questions to make things clear. It also seemed to me that providing the class with these abstracts during the period in which they would be studying for an examination would promote discussion in the different study groups and act as an additional learning device. Providing the abstracts early also helps alleviate the inevitable panic on seeing an absolutely unfamiliar question.

In the particular case of this year's selections, I had spent several lectures discussing cloning and was anxious to make clear that there were technical difficulties in cloning primates, hence the selection of the first article (Table 1). I use the development of sex differences to illustrate the multiple steps between gene and phenotype with an emphasis on Androgen Insensitivity Syndrome, hence the selection of the second article. In the lectures we talked about chromosome nomenclature, translocations, and abnormalities in chromosome number and I looked for an abstract in which these

TABLE 2

Second examination articles and questions

Consugar, M. B., S. A. Anderson, S. Rossetti, V. S. Pankratz, C. J. Ward *et al.*, 2005 Haplotype analysis improves molecular diagnostics of autosomal recessive polycystic kidney disease. Am. J. Kidney Dis. **45**(1): 77–87.
a. What is an exon?
b. How is the ARPD gene different from almost any gene in bacteria?
c. What is the meaning of:
1. Allelic heterogeneity
2. Missense mutation
3. Polymorphism
d. Give an example of a simple sequence repeat marker:
e. How would screening for a larger DNA deletion help detect unknown consanguinity?
f. How would recombination lead to divergence from an ancestral genotype (draw a diagram as an example)?

Kirman, C. R., L. M. Sweeney, M. J. Teta, R. L. Sielken, C. Valdez-Flores *et al.*, 2004 Addressing nonlinearity in the exposure-response relationship for a genotoxic carcinogen: cancer potency estimates for ethylene oxide. Risk Anal. **24**(5): 1165–1183.
a. Draw a dose response curve where risk is proportional to the square of the dose.
b. Why might it be necessary to extrapolate to low dose?
c. Draw curves showing risk linearly proportional to dose (1) and with no risk at low dose (2).
d. What is the dose at which an effect is first seen called?
e. What might be the practical implications for the manufacturers and/or users of ethylene oxide of the different hypotheses?

Xu, L., K. Tsuji, H. Mostowski, M. Otsu, F. Candotti *et al.*, 2004 A convenient method for positive selection of retroviral producing cells generating vectors devoid of selectable markers. J. Virol. Methods **118**(1): 61–67.
a. What is a retroviral vector?
b. What is a dominant selectable marker gene and why is it important for cloning?
c. Why is it often necessary to associate a therapeutic gene with such a marker gene?
d. What does the abstract suggest is the problem with this approach?
e. How did the investigators attempt to solve the problem?

Eisensmith, R. C., D. R. Martinez, A. I. Kuzmin, A. A. Goltsov, A. Brown *et al.*, 1996 Molecular basis of phenylketonuria and a correlation between genotype and phenotype in a heterogeneous southeastern US population. Pediatrics **97**(4): 512–516.
a. Explain briefly how the direct sequence analysis was done (*i.e.*, indicate briefly the theoretical basis of the method).
b. What might be the basis of different serum phenylalanine levels or phenylalanine tolerance in the different patients?
c. Why might the different mutations lead to somewhat different clinical outcomes?
d. Why was it necessary to use non-related patients in the study?

el-Hazmi, M. A., A. S. Warsy, A. R. al-Swailem, A. M. al-Swailem and H. M. Bahakim, 1996 Sickle cell gene in the population of Saudi Arabia. Hemoglobin **20**(3): 187–198.
a. What would the electrophoretic patterns look like in the heterozygous and homozygous states (draw a diagram on the back of this page)?
b. What was the overall population in Hardy-Weinberg equilibrium? How do you (and the authors) know?
c. Given the gene frequency stated, what would be the expected frequency of sickle-cell anemia?
d. Why might one expect a close connection between HbS gene frequency and malaria?

topics were discussed (the third article). A course in human genetics inevitably includes pedigrees and a discussion of dominance. I wanted an abstract that permitted me to ask questions about these topics and, in addition, permitted a question on penetrance, hence, the fourth article. This was actually the hardest to select with the possible exception of an abstract dealing with Hardy-Weinberg equilibrium (Table 2, the fifth article). The second examination (Table 2) covered molecular genetics, and I picked the first abstract of the second examination to permit questions about DNA structure and the structure of genes. There is so much written in the popular press about the carcinogenic or mutagenic effects of this or that environmental agent that I try to give this group of future worried parents some idea of dose-effect relationships, which accounts for the second article of the second set. There were several lectures dealing with genetic engineering and its applications, and I wanted an abstract that required some idea of what vectors are and how selection works. I had spent almost 2 hours trying to establish the basis for an understanding of metabolic disease and, in addition, there had been news reports of a wider applicability of the testing of newborns for metabolic disease and I selected the abstract of the fourth article of this second set to illustrate some of these points. As stated above, finding a recent and understandable abstract illustrating Hardy-Weinberg equilibrium was more difficult (for me) but an article in the *New York Times* about the problem of inbreeding in Saudi populations led to the abstract I used. What is striking about this procedure is that given the ability to search for key words simultaneously, it is

possible to identify several recent abstracts on the topics I talk about and then to select those abstracts that are accessible to a class of nonprofessionals.

The class was composed mostly of students who were planning to be economists, political scientists, lawyers, and possibly poets and they did pretty well with these questions. The average (and median) grade on the examinations was in the high 70s. Providing the abstracts ahead of time concentrates the student's attention. More importantly, the use of an abstract of a recent article indicates that the information is of immediate relevance (to somebody) and, even more important, that these nonprofessional students are able to understand a good deal about the subject matter of the paper. I first started using abstracts several years ago in an advanced undergraduate course along with standard problems. I found the abstracts particularly valuable in dealing with cytogenetics since a major hurdle to understanding seemed (to me) to be an understanding of the descriptive terminology. The availability of the internet has made it possible to post lectures and illustrations. I also started to post past examinations extending over the past 5 years. In my case I found that these examinations tended toward a sameness and a predictable character, possibly because of a personal aversion to short, machine-gradable questions. This sameness led to gratifyingly high grades among the students. I am all in favor of examinations with a high average grade. The morale of a class seems better to me when there is a decent median score. However, I wanted to avoid attaining that score via an absolutely predictable set of questions, and I started to look at abstracts as a source of new questions. It is also likely that the emphasis in this course on students writing abstracts of their work (see below) brought this device to my attention once again. At any rate, searching for appropriate abstracts is much more interesting than trying to find new ways to phrase "What is the difference between mitosis and meiosis?" I believe that use of these abstracts reinforces the thought that genetics is a continuing endeavor whose state is reflected in the current literature.

Evaluating and writing papers on genetics for a general audience: The second feature of our course builds on this principle. The College of the University of Chicago sponsors a program whose goal is to encourage writing in science courses and this program subsidizes extra TAs whose job includes helping students with their writing (and reading their papers!). The success of the course I describe depends in large part on the skill and enthusiasm of these instructors. Our students are asked to write two five-page papers during the quarter. Sixty percent of their grade is based on this written work (see the course outline at http://www.genetics.org/supplemental/). Students write a preliminary abstract, which I read and return with my comments well before the due date. I have been surprised over the 3 years in which papers have been an integral part of the course about the lack of understanding of what an abstract is. Many students do not understand that an abstract represents a summary of a completed paper—rather they submit a statement about what they plan to do. I either return the abstract or give it a low grade, which is revised when the completed paper (and revised abstract) is submitted. The final paper is then graded, in part, on how well a student has responded to the critical comments. To maintain some uniformity, the TAs are given a set of criteria to guide their grading and these criteria are shared with the students (Table 3).

TABLE 3

Criteria for grading second papers

Item	Points
On time	5
Primary source identified properly	5
Response to comments on abstract	20
Technical summary	
Accurate statement	15
Understandability by laymen	15
Nontechnical material	
Thoughtful/handwaving	15
Writing style	
Grammatical constructions	10
General interest/style	15
Total	100

For their first paper, students are asked to find a newspaper or magazine article (in practice it is often from some source on the internet although I have compiled a list of recent news articles that is available on the Chalk site) discussing some subject relevant to the material of the course (see the course outline at http://www.genetics.org/supplemental/). They are asked to identify the primary source of the factual material (or at least one of the primary sources) and to compare what the authors of the primary source say about their material with what the news article says. An even better paper (I tell them) is a report on two news sources reporting on the same primary source. Understanding what a primary source is and identifying it properly is a major problem, although almost all sources can be readily traced via PubMed. The second paper is based on the request that students find some primary source that they can understand (with the help of the TAs) and write a news article about it. Although the TAs grade the papers, any student can rewrite a paper, taking into account the criticisms of the TA, or write a rebuttal letter. I read and re-grade the rewritten paper. This winter I had about 15 resubmissions out of a class of 80. As in any required course, the response of students is mixed but they tend to be serious about their papers. I asked the class for permission to include their papers when I first thought about preparing this article and almost immediately received about 10 positive responses (with electronic copies of the papers). A sample, self-selected by students who responded to my request by granting permission,

TABLE 4

Student evaluations of examinations

	Examinations				Registration	
Year	Clarity	Length	Coverage	Response (no.)	No.	%
2005	3.9 ± 1.1	4.3 ± 0.85	4.0 ± 0.99	65	86	79
2004	4.0 ± 0.9	4.1 ± 0.93	4.1 ± 0.88	49	63	78
2003	3.7 ± 1.1	3.9 ± 1.0	3.9 ± 0.92	43	47	91

The numbers register agreement with a question, with a value of 5 indicating strong agreement. The exact wording of the questions was: clarity, exams were clear and in appropriate format; length, exams were an appropriate length; coverage, exams tested material covered by the course (lectures and outside readings). The registration no. gives the number of students registered for the course, and the response no. gives the number responding to the overall questionnaire. %, the percentage of registered students responding.

has been posted as supplemental material (see http://www.genetics.org/supplemental/). In general students are interested in the same things that concern the general public. There are the papers about stem cells and cloning but there are others about the genetics of homosexuality and about depression.

Evaluation of the course: How has the course been received by students and is there any evidence that it has achieved its primary purpose of helping this group of liberal arts students to obtain and evaluate information about genetics? The college utilizes teaching questionnaires to try to answer such questions and these are usually distributed at the time of the final examination. The questionnaires are in two parts, one covering the course and the other the instructor. Ratings are on a scale of 1–5 with 5 (strongly agree) being the highest. In addition, there is space for individual comments that are returned to the instructor. Our undergraduates are very generous, and the average course rating (including both elective and required courses) is 4.0. The overall rating of the Human Heredity course this year was 3.4 ± 1.2, and the overall rating of the instructor was 4.1 ± 0.89 (compared to all faculty of 4.2) (Table 4). The qualitative remarks indicate a split into students who think the course (and instructor) is great and those who do not understand why the university allows me to give it! The 2004–2005 year is the first in which abstracts were exclusively used for the examinations, and the data show no significant difference from the responses of the previous 2 years. Most students agreed that the examinations (*i.e.*, the abstracts) fairly covered the material in the lectures and reading. The qualitative comments and comments made to me personally convey mixed responses. Some of the written comments in this year's evaluations particularly praised the use of abstracts. On the other hand, one of my very assiduous students told me that she just did not like the abstracts as a basis for examinations because she did not know what to study. This is both an understandable comment and one that suggests to me that the format may be achieving its purpose. This very bright student came to Chicago from a small high school and was clearly trained to master very defined sets of information. If properly designed, the questions on the abstracts should require some general understanding of the subject as a whole, and even the fact that random abstracts will be selected indicates a requirement for general understanding. That does make it difficult to define just which bits of information to study but does reward students who can develop a general concept of the subject. I am happy to report that this student did very well in the course.

Students also vote with their feet and the enrollment in this course in Human Heredity has increased markedly over the past 3 years (Table 4). This increase started at the time written papers were introduced as a major factor in the grading (see course outline in supplemental material at http://www.genetics.org/supplemental/) but there is no decisive evidence that the emphasis on writing was a key factor in the increased enrollment, although I suppose it to be a major factor.

One very important fact is that even after many years I find the course fun to teach. *The New York Times* and the *Chicago Tribune* have been tremendously cooperative and it is fun to start lectures with some clipping from the mornings newspaper—as often as not from the financial section! These stories will be relevant to some portion of the course, although not necessarily the topic of the day's lecture. My purpose is to demonstrate that there is real-life interest in the topics we discuss. I also want to indicate that topics for the required written assignments are readily found. If the news parallels the development of the course it should be possible to use the news stories as leads to appropriate abstracts (as suggested by a reader of this manuscript) further integrating the examinations and lecture material. Perhaps my most important hope for this general education requirement is that a group of future lawyers, economists, and voters may have some idea as to how to obtain accurate information about genetics and how that information originated.

Communicating editor: P. J. Pukkila