Why do Some People Inherit a Predisposition to Cancer? A small group activity on cancer genetics

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Abstract

Before undergraduate students take a genetics course they generally know cancer has a genetic basis and involves the proliferation of cells; however, many are uncertain about why only a subset of people have a predisposition to cancer and how that predisposition is inherited from one generation to the next. To help students learn about these concepts, we designed a teaching unit that centers on a small-group, in-class activity. During this activity students learn how to:

1. determine inheritance patterns for different types of cancer,
2. explain why a person with or without cancer can pass on a genetic predisposition to cancer, and
3. distinguish between proto-oncogenes and tumor suppressor genes.

In addition to participating in the small-group activity, students watch short video clips from a documentary about breast cancer, answer clicker questions, and engage in a whole-class discussion. A combination of pre/posttest results, clicker question answers, and performance on subsequent exam questions suggests that this unit helps students learn about the hereditary basis of cancer.

Learning Goal(s)

Students will understand how a genetic predisposition to cancer can be inherited. Specifically, they will be able to describe how a person who inherits one nonfunctional copy of a tumor suppressor gene can develop cancer in a somatic cell.

Learning Objective(s)

At the end of this activity, we expect students will be able to:

- Use family pedigrees and additional genetic information to determine inheritance patterns for hereditary forms of cancer
- Explain why a person with or without cancer can pass on a mutant allele to the next generation and how that impacts probability calculations
- Distinguish between proto-oncogenes and tumor suppressor genes

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Materials and Supplemental Materials: Table 1. Predisposition to Cancer-Teaching Timeline, Figure 1. Predisposition to Cancer-Figure describing the impact of proto-oncogenes at the cellular level, Figure 2. Predisposition to Cancer-Figure describing the impact of tumor suppressor genes at the cellular level, Table 2. Predisposition to Cancer-Student performance on pretest, posttest and exam questions, Supplemental File S1. Predisposition to Cancer-Questions on the pre-posttest on type of cancer that affects females, Supplemental File S2. Predisposition to Cancer-Questions on the pre-posttest on type of cancer that affects males, Supplemental File S3. Predisposition to Cancer-Questions about proto-oncogenes and tumor suppressor genes, Supplemental File S4. Predisposition to Cancer-Small group activity question about a family affected by breast cancer, Supplemental File S5. Predisposition to Cancer-Description of how individual can have a cell with no functional BRCA1 alleles, Supplemental File S6. Predisposition to Cancer-Student performance on clicker question asked at the end of the small-group activity, Supplemental File S7. Predisposition to Cancer-Student performance on exam questions related to the cancer activity, Supplemental File S8. Predisposition to Cancer-Student performance on a final exam question about cancer, Supplemental File S9. Predisposition to Cancer-Student small-group activity handout without answers and Supplemental File S10. Predisposition to Cancer-Student small-group activity handout WITH answers.

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INTRODUCTION
Cancer is an important topic to teach in undergraduate genetics courses because it affects many people and is the topic of ongoing medical research. Furthermore, the genetics of cancer is listed as one of the key elements suggested for a 21st century genetics course (1). However, despite the importance of this disease, a recent survey of undergraduate students indicates that they feel they know little about it (2).

The in-class small-group activity described here helps instructors integrate a cancer unit into their genetics courses and addresses student conceptual difficulties regarding cancer inheritance. The intended audience is undergraduate students in either a majors or non-majors genetics class. The learning time includes: 10 minute pretest, short video clip, 30-40 minute small-group activity, 10 minute wrap-up with clicker questions from the activity, another short video clip, 10 minute posttest, and 10 minute discussion of the posttest questions (Table 1).

Student pre-requisite knowledge for this activity includes the ability to:
1. interpret information from a pedigree,
2. distinguish between different inheritance patterns (autosomal dominant, autosomal recessive, X-linked dominant, X-linked recessive, and Y-linked) and use that information to calculate the probability a person will have a specific phenotype,
3. distinguish between somatic and germline cells,
4. describe the sequence of events involving DNA in mitosis and meiosis, and
5. discuss how nondisjunction can have an impact on chromosome number.

Students also need to be comfortable using shorthand ways to represent wild-type and mutant versions of genes. Throughout this activity a “+” stands for the wild-type copy of the gene and a “-” stands for the mutant copy of the gene. For example, the Breast Cancer 1 (BRCA1) gene has been implicated in breast and ovarian cancer. A person who is BRCA1+/BRCA1- has one wild-type allele and one mutant allele of this gene; in other words, this person is a heterozygote.

Brief Background on Genes Important for Cell Division and Cancer
Cancer can result from mutations in two types of genes: proto-oncogenes and tumor suppressor genes. Many of these genes are involved in cell division. Proto-oncogenes include positive regulator genes, typically ones that produce factors stimulating the cell cycle. Tumor suppressor genes include factors that inhibit behaviors leading to cancer, such as inhibiting cell division under normal conditions (3).

At the cellular level, mutations in proto-oncogenes are generally dominant-acting and mutations in tumor suppressor genes tend to be recessive-acting. Inherited mutations in tumor suppressor genes are a common cause of a genetic predisposition to cancer (4). Specifically, individuals inherit a germ-line mutation in a tumor suppressor gene but show no signs of the disease. At some point in their life they can acquire a deleterious somatic mutation in the same tumor suppressor gene and consequently have a cell with no functional copies of that tumor suppressor gene. At this point, cell division can go unchecked and cancer can develop. Because acquiring a somatic mutation during the course of a lifetime is common, cancer often appears to have a dominant-acting inheritance pattern in pedigrees that include individuals who are heterozygous for a tumor suppressor mutation (5,6).

The in-class small-group activity described here is designed to help undergraduate students explore the genetics of inherited forms of cancer. Pre/post formative assessment results show that students begin the cancer unit with several conceptual difficulties such as thinking that cancers that affect females are due to mutations in X chromosome genes and cancers that affect males are due to mutations in Y chromosome genes. However, after working through the group activity, students are able to address their misunderstandings, which positively impacts their performance on the posttest and on exam questions given later in the course.

SCIENTIFIC TEACHING THEMES
Inclusive teaching.
This in-class group activity acknowledges and leverages diversity in the classroom and beyond by:

• Providing an opportunity for students to work in groups. To help ensure students are participating and including others, the instructor and teaching assistants should walk around the classroom and ask questions to bring disengaged students into the group.
• Asking the most difficult questions on the activity worksheet as clicker questions at the end of class. Students who are confused about the worksheet questions and not getting the help they need from their peers are able to signal to the instructor that they do not understand by their votes on clicker questions. After the clicker responses come in, the instructor can gauge class understanding, and immediately begin to address any confusion by initiating a whole-class discussion.
• Focusing on types of cancer that are common in different racial/ethnic groups. In this unit, students answer questions about prostate cancer; African American men have the highest incidence rate for prostate cancer in the United States (information found at the National Cancer Institute website, http://www.seer.cancer.gov/)
• Students also answer questions about breast cancer; White women have the highest incidence rate but African American women are more likely to die from the disease (2).

Active Learning
Students actively engage in the concepts by:

• Watching two video clips from a PBS Power of Voice Documentary called In the Family (7). The first video clip, “Hanke Family Test Results,” is about a family receiving genetic testing results for breast cancer. The second video clip, “Gene Mutation Animation,” illustrates why people who inherit a mutant allele of a gene important for cancer are likely to develop the disease.
• Working in small groups to learn about the differences between proto-oncogenes and tumor suppressor genes, inheritance patterns of cancer that affects only one sex, and how mutations in tumor suppressor genes often appear recessive-acting at the cellular level and dominant-acting at
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the organismal level.

• Answering clicker questions at the end of the activity to help the instructor gauge how well students understand the concepts. Students also participate in instructor-facilitated whole-class discussions for each clicker question.

Assessment

Student learning is measured by:

• A pre/posttest given at the beginning and the end of the activity
• Formative clicker questions at the end of the activity
• Summative exam questions

LESSON PLAN

The timeline for the entire unit is shown in Table 1 (on page 4).

Pretest

Students begin the class period by answering a four-question written pretest (Supplemental Files S1 and S2). The assessment questions target conceptual difficulties that were revealed on short answer exam questions given in previous years. An initial version of the pre/posttest questions was sent to five geneticists who teach genetics courses at their respective institutions. The geneticists offered comments on the questions and we revised them accordingly. The pretest is given on paper on the first day of this unit. Students need 10 minutes to take the pretest and receive a few points of participation credit regardless of their answers. Students should also be told that pretest answers will be discussed at a later time.

Video

To motivate students for this activity, they watch a short video clip about a family with three sisters who are being tested for a mutation in the BRCA1 gene. The freely available video clip, entitled: “Hanke Family Test Results” is from a Power of Voice documentary (7). This video shows an emotional moment when two of the three sisters discover they have inherited a deleterious mutation and will likely need to have their breasts and ovaries removed. Although not included in this article, additional clicker questions could be added that directly reference this story. For example, students could be asked if the parents in this story have another child, what is the probability that he/she would have the mutation.

Small-group activity

After watching the video clip, the class should divide themselves up into groups of 4-6 students and start on the worksheet activity (the full activity without answer key Supplemental File S9 and with answer key Supplemental File S10 are in the Supporting Materials section). Each student is given his/her own worksheet. The instructor and teaching assistants should circulate around the classroom, answer questions, and encourage disengaged students to participate.

The activity starts by comparing proto-oncogenes and tumor suppressor genes. Proto-oncogene products can stimulate cell division under normal conditions. By looking at a figure that describes proto-oncogenes at the cellular level (Figure 1) and answer whether mutations in these genes are generally dominant- or recessive-acting.

Because a mutation in one copy of a proto-oncogene can lead to excessive cell proliferation, students are able to conclude that mutations in proto-oncogenes are generally dominant-acting at the cellular level.

Students then learn that tumor suppressor gene products can inhibit cell division under normal conditions. By looking at a figure that describes tumor suppressor genes at the cellular level (Figure 2) they should realize that excessive cell proliferation typically occurs when both copies of a tumor suppressor gene are mutant, indicating that mutations in tumor suppressor genes are generally recessive-acting at the cellular level.

Students are then asked to apply their knowledge to two new scenarios (Supplemental File S3). One scenario describes a mutation in a tumor-suppressor gene called gene P and the other describes a mutation in a proto-oncogene called gene M.

Next students are given information about the BRCA1 gene and a pedigree about a family that has mutations in this gene (Supplemental File S4). Information given to students includes that: the BRCA1 gene has been implicated in breast cancer, females who are BRCA1+/BRCA1- have a high chance of developing breast cancer, there are no BRCA1-/BRCA1- individuals in this family (which is always true because this genotype is embryonic lethal [8]), and two people who have children with members of this family are homozygous for the normal allele (BRCA1+/BRCA1+).

Students then determine the mode of inheritance for breast cancer. The only possible mode of inheritance based on the information given in the problem and the pedigree is autosomal dominant (Supplemental File S4 shows the genotype of each member of the family in red font, this information is not included on the student handout, see Supplemental Material). When students try to answer this question, they often discuss...
## Table 1: Predisposition to Cancer-Teaching Timeline

| Activity                              | 50-60 Minute Course | 75-90 Minute Course |
|---------------------------------------|---------------------|---------------------|
|                                       | Day 1               | Day 2               | Day 1               | Day 2               |
| Pretest                               | 10 min              |                     | 10 min              |                     |
| “Hanke Family Test Results” video     | <5 min              | <5 min              |                     |                     |
| In class activity                     | 30-40 min           | 30-40 min           |                     |                     |
| Clicker questions and whole class     |                     | 10 min              | 10 min              |                     |
| discussion                            |                     |                     |                     |                     |
| “Gene Mutation Animation” video       | <5 min              | <5 min              |                     |                     |
| Posttest                              | 15-30 min           |                     | 15-30 min           |                     |
| Discussion of posttest questions      | 15-30 min           |                     | 15-30 min           |                     |

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how the mode of inheritance could be X-linked dominant because several females are affected. To help students with this misunderstanding, the instructor and teaching assistants can ask guiding questions to reveal why the inheritance pattern is not X-linked dominant. For example, students could be asked to look for clues written in the problem such as genotype of male II-5 is BRCA1+/BRCA1+. Students could be asked to write the genotypes of person II-1 and II-2 and see if an X-linked dominant inheritance pattern fits the information in the pedigree. If the pattern were X-linked dominant, female II-1 would have to be XBRCA1+/XRBCA1+ because of information given in the problem; thus, male II-2 would have to be XBRCA1-/Y. However, if male II-2 is XBRCA1-/Y, all four of his daughters would likely have breast cancer. Since in generation III, one of the daughters is unaffected, the inheritance pattern is not likely to be X-linked dominant.

After students determine that the inheritance pattern is autosomal dominant, they then answer the question:

“If a man has a BRCA1 mutation (remember, there are no BRCA1+/BRCA1- individuals in this family), what is the chance he will pass the mutation on to his daughter? What about his son?”

In both cases the answer is 50%. This question is designed to reinforce the conclusion that the inheritance pattern is autosomal dominant and help students realize that even if a man is unaffected, he can pass the mutation onto his children.

Next students read about how women who are BRCA1+/BRCA1- can develop breast cancer (Supplemental File S5). They learn that even when a woman inherits one normal allele of the BRCA1 gene, subsequent somatic changes such as a mutation or mitotic nondisjunction can leave an individual without a functional BRCA1- allele in a given cell. A cell without any normal BRCA1 alleles can begin to divide uncontrollably, leading to cancer.

To help students apply this information, they are asked the following questions:

“A woman is BRCA1+/BRCA1-. If you could analyze 10 of her non-cancerous somatic cells, how many wild-type and how many mutant copies of BRCA1 would you expect to find in each cell?” Because this question is asking about non-cancerous somatic cells, the cell will reflect the genotype of the individual. Each cell will have one wild-type BRCA1 copy and one mutant BRCA1 copy.

“If you analyzed 10 of her tumor cells, how many wild-type copies of BRCA1 would you expect to find in each cell?” Each cell will have zero wild-type copies, because there are no functional BRCA1 alleles in tumor cells.

“A man is BRCA1+/BRCA1- but does not have breast cancer. If you could analyze 10 of his sperm cells, how many wild-type and how many mutant copies of BRCA1 would you expect to find in each cell?” Because sperm are haploid you would find either a mutant copy or a wild-type copy of BRCA1. This question is designed to reinforce an earlier classroom unit on meiosis.

Finally, students are told that the BRCA1 gene is a tumor suppressor gene and are asked to reflect on an earlier question in the activity:

“At the cellular level, are mutations in tumor suppressor genes dominant-acting or recessive-acting?”

Based on the information in Figure 2, students would likely conclude that tumor suppressor genes are recessive-acting. Then students are asked to look at the family pedigree (Supplemental File S4) and are asked: At the organisinal level, does the BRCA1- allele behave as a dominant or recessive allele? Here students would say dominant because BRCA1+/BRCA1- females are likely to get breast cancer. Students are then asked to explain the paradox between the mutation appearing to be recessive-acting at the cellular level and dominant-acting at the organisinal level.

Clicker questions

Because it can be difficult for an instructor to reach every student group in a large lecture class, clicker questions that are based on questions in the activity can be asked at the end of the class period to structure whole class discussions and to help the instructor verify that the majority of the class understands the concepts in the activity. Supplemental File S6 shows possible clicker questions to ask.

Discussion

Because students often struggle with the paradox between tumor suppressor mutations appearing to be recessive-acting at the cellular level and dominant-acting at the organisinal level, this concept is important for the instructor to reinforce through class-wide discussion. This discussion could include the following information on how individuals can inherit a predisposition to cancer: one mutation in BRCA1 is inherited and consequently BRCA1+/BRCA1- women require additional mutations to convert a normal somatic cell into a cell that is dividing uncontrollably. Because it is so likely that those additional mutations will occur during a person’s lifetime, the trait appears to be dominant at the organisinal level. Most women who are BRCA1+/BRCA1- will get an additional mutation in one somatic cell and will likely get cancer.

To explain this concept from another prospective, students watch a short video clip entitled “Gene Mutation Animation”, part of the In the Family video (7), which explains the concept of carrying one mutant allele and acquiring another one in a single cell leading to the development of cancer. This video can be played in class and included on a course website so students can review the information.

One question students often ask is: why are individuals with BRCA1 mutations more likely to get breast/ovarian cancer and not all types of cancer? In adults, BRCA1 is expressed in a variety of tissues including ovary, breast, fallopian tube, testis, pancreas, prostate, thymus, and spleen and mutations in BRCA1 can be associated with cancer in all of these organs (9-14). The reason why individuals with BRCA1 mutations are more likely to have tumors in their breasts and ovaries rather than these other tissues is an area of active research. One leading hypothesis is that the control of BRCA1 gene expression and different mRNA splice variants may contribute to the varying levels of cancer risk in different organs (11,15).

Posttest and Discussion

To help the instructor monitor student learning, at the next class session, students take a posttest that has identical questions as the pretest. The posttest is also administered on paper and students may be given a few points of participation
credit regardless of their answers.

After students turn in the posttest, all four assessment questions should be discussed in class. To facilitate this discussion, a slide showing each question can be projected and students can be asked to volunteer the choice they made and the reasoning behind that choice. For each question, once the class discussion is complete, the instructor should state the correct answer choice and the reasoning behind each answer (9). The posttest discussion also provides an opportunity for the instructor to talk about cancer health disparities in different ethnic groups, including information on prostate and breast cancer (2). This discussion can include information about how a lack of health care coverage and low socioeconomic status contributes to these disparities.

**Summative assessment**

To determine longer-term impact of this activity on student learning, questions on cancer genetics can be included on subsequent exams. Example questions are shown in Supplemental Files S7 and S8.

**TEACHING DISCUSSION**

The activity described above was taught by author MS in an undergraduate genetics course that included both majors and non-majors (56% of the students were Biology/Botany/Zoology majors; the other students were primarily Animal Science students who take classes typically focused on animal care): 98% of the students were juniors/seniors.

**In-class clicker question results**

The clicker question results from the end of the activity indicate that students were generally able to learn about cancer genetics by talking with their peers (Supplemental File S6). Because a subset of the students still struggled to answer these questions correctly, it was important to lead a whole-class discussion where students explained their answers and the course instructor stated the correct answer with a corresponding explanation (16).

**Pre/posttest and exam results**

The students showed steady improvement from pretest to posttest to exam questions (Table 2).

| Question Subject and Learning Objective (LO) | Pretest/Posttest | Exam/Final |
|---------------------------------------------|-----------------|------------|
|                                             | Question # | Pretest % Correct | Posttest % Correct | Question # | % Correct |
| Female Inheritance Pattern LO1              | 1           | 49            | 76            | Final Exam 1 | 90         |
| Female Probability LO2                      | 2           | 81            | 81            | N/A         | N/A        |
| Male Inheritance Pattern LO1                | 3           | 30            | 62            | Exam 1      | 87         |
| Male Probability LO2                        | 4           | 21            | 41            | Exam 3      | 68         |

The pre/posttest and exam questions primarily focused on LO1 and 2. At the beginning of the activity the majority of the students could not correctly determine the inheritance patterns when given a pedigree and other information about families that were impacted by cancer (LO1; Table 2, Supplemental File S1 Pre/posttest Question 1, and Supplemental File S2 Pre/posttest Question 3), but on the exams greater than 85% of the students could answer these types of questions correctly (Table 2, Supplemental File S7 Exam Question 1, Supplemental File S8 Final Exam Question 1).

At the time of the pretest, students also struggled to answer one of the probability questions about an unaffected female in a family where several members have a male-specific cancer (LO3, Table 2 and Supplemental File S2 pre/posttest question 4). Many students did not understand that even though the woman in question is unaffected, she still has a 50% chance of being a carrier of the mutant allele. By the time of the exam, 68% of the students answered a similar probability question correctly (Table 2 and Supplemental File S7 Question 3). Although the scores improved, future versions of this unit will place more emphasis on helping students learn how to solve this type of problem. For example, similar probability problems could be added to the in-class activity and homework assignments.

Although not explicitly addressed on the pre/posttest, LO3 was assessed on an exam (Supplemental File S7 Exam Question 4). Students scored 87% correct on this question indicating their ability to distinguish between scenarios that describe proto-oncogenes and tumor suppressor genes.

**Student impact**

Student reactions to the lesson were positive, with several students coming up after class to talk about personal experiences they have had with cancer and genetic testing. In addition, a few months after this lesson was taught, news broke that the actress and director Angelina Jolie carries a BRCA1 mutation and had a double mastectomy (17). Over the summer break, several students sent emails to the course instructor detailing how they were able to apply their genetics knowledge to a popular press story. Future iterations of this activity can also include having students read this Op-Ed story in the New York Times.
IRB Statement
Approval to publish student pre/posttest, clicker, and exam data was granted by the Institutional Review Board at the University of Maine (exempt status, protocol no. 2012-12-14).

SUPPLEMENTAL MATERIALS
- Table 1. Predisposition to Cancer-Teaching Timeline
- Figure 1. Predisposition to Cancer-Figure describing the impact of proto-oncogenes at the cellular level
- Figure 2. Predisposition to Cancer-Figure describing the impact of tumor suppressor genes at the cellular level
- Table 2. Predisposition to Cancer-Student performance on pretest, posttest and exam questions
- Supplemental File S1. Predisposition to Cancer-Questions on the pre-posttest on type of cancer that affects females
- Supplemental File S2. Predisposition to Cancer-Questions on the pre-posttest on type of cancer that affects males
- Supplemental File S3. Predisposition to Cancer-Questions about proto-oncogenes and tumor suppressor genes
- Supplemental File S4. Predisposition to Cancer-Small group activity question about a family affected by breast cancer
- Supplemental File S5. Predisposition to Cancer-Description of how individual can have a cell with no functional BRCA1 alleles
- Supplemental File S6. Predisposition to Cancer-Student performance on clicker question asked at the end of the small-group activity
- Supplemental File S7. Predisposition to Cancer-Student performance on exam questions related to the cancer activity
- Supplemental File S8. Predisposition to Cancer-Student performance on a final exam question about cancer
- Supplemental File S9. Predisposition to Cancer-Small group activity handout without answers
- Supplemental File S10. Predisposition to Cancer-Small group activity handout WITH answers

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