ACTIVITY 1: CLASSIFYING CANCER GENES

OVERVIEW

Refer to the "Overview of Cancer Discovery Activities" for Key Concepts and Learning Objectives, Curriculum Connections, and Prior Knowledge, as well as background information, references, and additional related resources.

MATERIALS

- *Cancer as a Genetic Disease* video clip (http://www.hhmi.org/biointeractive/cancer-genetic-disease-video-highlights)
- *Activity 1: Classifying Cancer Genes* student document, which includes the *Video Worksheet* (one per student)
- Set of 139 *Cancer Gene Cards*. Cut out the cards before class. You may wish to laminate the cards for future use.
- *Human Chromosomes* sheets or poster. Print 24 sheets, each with a different chromosome, or a poster with all the chromosomes on it.
- Classification of Cancer Genes poster
- Functions of Cancer Genes poster
- Colored stickers, colored pencils or pens, bingo markers, or beads in five colors (red, green, purple, blue, and yellow)

PROCEDURE

This activity consists of the following:

- A before-class assignment in which students watch a video clip (8:30 minutes) and complete the *Video Worksheet* (included in the *Activity 1: Classifying Cancer Genes* student document) to learn about the genetic basis of cancer
- An in-class activity using the *Cancer Gene Cards*
- A 3-2-1 analysis assignment, which can be done in class or as homework
- An optional research project and presentation (in the *Overview of Cancer Discovery Activities* document)

Before Class

Distribute the *Activity 1: Classifying Cancer Genes* student document to students. Ask them to watch the *Cancer as a Genetic Disease* video clip and complete the *Video Worksheet* before class.

- Note: Some students find the gas pedal and brake analogy confusing (around 2:30 in the film). A mutated oncogene is like putting the foot on the gas pedal, and a mutated tumor suppressor gene is like taking the foot off the brake. Tumor suppressor genes normally act as brakes in the cell cycle.

ANSWERS TO VIDEO WORKSHEET

1. *What was the main purpose of the large-scale cancer study that Dr. Sawyers describes in the video?* ***The study's aim was to identify the genetic causes of cancer.***
2. *As of spring 2013, about _____ genes associated with cancer had been identified. What is the approximate breakdown of oncogenes versus tumor suppressor genes?* ***140 cancer genes; 60 oncogenes and 80 tumor suppressor genes***
3. *Using Dr. Sawyers' analogy (the gas pedal and brake), a mutated oncogene is like _____ and a mutated tumor suppressor gene is like _____. What does this mean in terms of how the cell grows and divides?* **A mutated oncogene is like putting the foot on the gas pedal, and a mutated tumor suppressor gene is like taking the foot off the brake**.
4. *Distinguish between a proto-oncogene and an oncogene.* **Proto-oncogenes normally stimulate cell growth and division in a carefully controlled way; oncogenes are mutated genes whose protein products cause cells to divide faster.**
5. *The mutated allele (oncogene) is dominant/recessive compared to the normal, non-mutated allele (proto-oncogene) on the other chromosome. (Circle a choice.)* **The mutated allele is dominant**.
6. *The mutated allele of a tumor suppressor gene is dominant/recessive compared to the normal, non-mutated allele on the other chromosome. (Circle a choice.)* **The mutated allele of a tumor suppressor gene is recessive.**
7. *Does Dr. Sawyers think many more cancer genes will be identified? Will the number grow exponentially?* **More will be identified, but not exponentially more.**
8. *List the three "buckets" in which scientists categorize cancer genes. Approximately how many genes are in each bucket?* **The three buckets are cell growth and survival (~70 genes), cell fate (~60 genes), and gene maintenance (~10 genes).**
9. *p53 is a tumor suppressor gene/oncogene. Cyclin D1 is a tumor suppressor gene/oncogene? (Circle a choice.)* **p53 is a tumor suppressor gene and cyclin D1 is an oncogene. Students may point out that cyclin D1 is actually a proto-oncogene and the mutated form of the gene is an oncogene.**
10. *How do p53 and cyclin D1 differ in how they affect the cell cycle?* **p53 limits cell growth and division (brakes), and cyclin D1 stimulates the cell cycle, causing cells to divide.**
11. *Consider genome maintenance genes:*
    a. *Does DNA polymerase make mistakes during DNA replication?* **Yes**
    b. *How often?* **DNA polymerase makes a mistake about once every billion bases.**
    c. *Explain the proofreading system.* **Enzymes in the cell correct errors in DNA sequence made during DNA replication.**
    d. *Explain what happens if a mutation occurs in the genes that encode proofreading enzymes.* **Without proofreading enzymes, errors would not be corrected and there would be many more mutations in the DNA of cells.**
12. *Why is it that the longer we live, the more likely we are to develop cancer?* **Over time, more errors and mutations occur.**

In Class: Discussion and Cancer Gene Cards

Video Discussion

As a class, discuss the video clip and address students' questions or points of confusion. Suggested discussion questions include the following:

- What does Dr. Sawyers mean when he says that cancer is a genetic disease?
- What is the difference between oncogenes and tumor suppressor genes?
- How do mutations in genes involved in cell growth and survival, cell fate (differentiation), and genome maintenance (or the repair of mistakes in DNA replication) cause cancer?

Cancer Gene Cards Activity

1. Hang the *Human Chromosomes* sheets or poster, the *Classification of Cancer Genes* poster, and the *Functions of Cancer Genes* poster in prominent places in the classroom.

2. Distribute the colored stickers and all 139 *Cancer Genes Cards* to students. Each student should have multiple gene cards. Note that in the video Dr. Sawyers says there are about 140 cancer genes. The 139 genes used in this activity were obtained from a 2013 *Science* paper by Vogelstein et al. (see the references in the overview document); a few additional genes may have been identified since then.

> Note: With only one class or very small classes, working through all 139 cards will take students some time. Consider selecting only a subset of the cards for a smaller class.

3. With their cards in hand (**Figure 1**), have students visit the HUGO Gene Nomenclature Committee's online repository of gene nomenclature to search for the gene abbreviations on their cards and discover the full name of each gene.

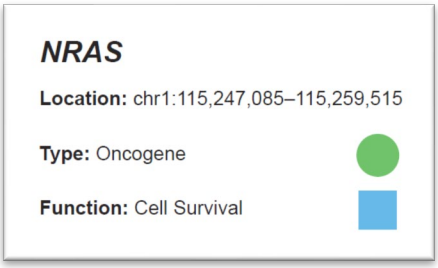

Figure 1. Example of a cancer gene card.

4. Using the information on their cards, students look for the locations of their genes on the *Human Chromosomes* sheets.

5. Once they locate a gene on the correct chromosome, they will place either a green or a red dot in the first blank circle to the right of the location to indicate whether the gene is an oncogene (green) or a tumor suppressor gene (red). The information is found on the card next to "Type." (See **Figure 2**.)

6. In the second circle to the right of the location, they will place a sticker to indicate the function affected by a mutation in that gene. The information can be found on the card next to "Function" and is either labeled "Cell Survival" (blue), "Cell Fate" (purple), and/or "Genome Maintenance" (yellow). Some genes will have more than one function. (See **Figure 2**.)

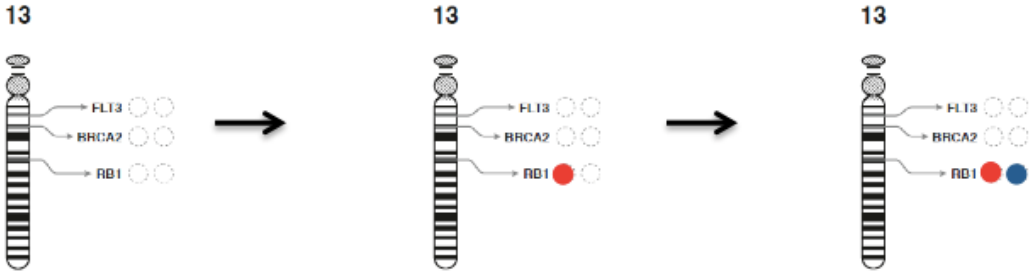

Figure 2. Adding colored dots to the chromosomes. Locate your gene on the appropriate chromosome. Place a green or red dot in the circle next to the gene name. (In this example a red dot shows that RB1 is a tumor suppressor gene.) Then place a blue, purple, or yellow dot in the circle next to the first one. (In this example, a blue dot shows that RB1 functions in cell survival.)

7. Next, students move to the *Classification of Cancer Genes* poster and place a red or green dot in the appropriate column representing the classification indicated on their cards. Instruct students to fill in each row of blank circles from the bottom to the top with their dots, as if building a bar graph, first completing one row and then the other.

8. Students then move to the *Functions of Cancer Genes* poster and place a blue, purple, or yellow dot in the appropriate column representing the cellular function indicated on the cards, again filling each row from
bottom to top.

Whole Class Discussion

After completing the human chromosomes map and two posters, ask students to make observations and identify patterns in the data. This analysis can be done as a whole class or in small groups. This is mostly an opportunity for students to ask questions about specific observations; there are no right or wrong answers. (You may refer to the sample completed human chromosomes map and completed posters at the end of this document as a reference.)

Students may make the following observations:

- The mutated genes involved in cancer are located on many different chromosomes.
- There are fewer genes associated with genome maintenance than with the other two cellular processes.
- There are similar numbers of tumor suppressor genes and oncogenes (although slightly more tumor suppressor genes).

Discuss the function of an oncogene and ask students to think about the types of mutations oncogenes may have. Note that the 10 amplified genes (genes labeled "amp") on the human chromosomes are all oncogenes. Why is that? Discuss the function of tumor suppressor genes and think about what kinds of

mutations tumor suppressor genes may have. Note that the three deleted genes (genes labeled "del") on the human chromosomes are all tumor suppressor genes. Why is that?

Ask students to describe the processes of "cell survival," "cell fate," and "genome maintenance." Why would genes involved in genome maintenance lead to cancer? How about genes involved in cell survival and cell fate?

- In a healthy tissue or organism, cell division and cell death balance each other. Mutations in genes that regulate these processes upset this balance and can lead to unregulated cell growth and cancer.
- Many cancer genes regulate cell fate, or differentiation. Differentiated cells often stop dividing and eventually die. Mutations in genes that regulate differentiation may cause cells to not differentiate or dedifferentiate, which in turn leads to excess cell division and cancer.
- Genome maintenance genes code for proteins that correct errors in DNA replication and spontaneous mutations. When these genes are mutated, the proteins don't work, errors are not corrected, and more mutations are introduced in the genome with every cell division. This means that more genes, including the subset of genes that can cause cancer, will have mutations.

After completing the *Classification of Cancer Genes* and *Functions of Cancer Genes* posters, ask students to analyze the results. This analysis can be done as a whole class or in small groups. Pose the following questions to students:

- How many are oncogenes or tumor suppressor genes? Oncogene/green = 65; tumor suppressor gene/red = 74
- How many genes are in each of the three different functional categories? Cell survival/blue = 73; cell fate/purple = 60; genome maintenance/yellow = 8

Note that these numbers are not exactly the numbers that Dr. Sawyers mentions in the video clip. He says that there are about 60 oncogenes and 80 tumor suppressor genes. The exact numbers are not that important. The main point is that there are a similar number of oncogenes and tumor suppressor genes.

Assign a 3-2-1 Analysis

Assign the students to do a 3-2-1 analysis as follow-up homework after the activity either individually or in small groups. The analysis should include three things the student learned from the activity, two things that surprised or particularly interested them, and one question they still have. If students are assigned to do the analysis individually, they can complete it either in class or as homework. A grading rubric for this analysis can be found in the "Overview of Cancer Discovery Activities" document.

TEACHING TIPS

- Rotate among the students as they are adding dots to the various posters and sheets and ask them to consider the following questions: Are there more oncogenes or more tumor suppressor genes?

Do you see any obvious clusters of genes on the human chromosome map? Do you see any patterns here?

- If students want more details about tumor suppressor genes and oncogenes, point them to "The Eukaryotic Cell Cycle and Cancer" Click and Learn and the article "The Evolution of Cancer" on the BioInteractive website.
- Instead of using stickers, you can lay the posters on a large, flat surface and use five colors of bingo markers, beads, or other small objects. You could also laminate the posters and ask students to color the circles using erasable markers.
- If you cannot print the posters, you can draw the graph axes and titles on a standard poster board or whiteboard and ask the students to fill them in in a similar manner.

SOCIAL MEDIA SUGGESTIONS

- The two posters could be assembled using a pre-prepared Google Docs spreadsheet. Students add their data to the spreadsheet, and the whole class can see it build collectively. If the tally column is built as a formula, it will grow as the students enter their data. You could draw an analogy between the collaborative, online building of a data set accomplished by the students and the genome analysis done by the researchers (on a larger scale).
- Students could post their 3-2-1 analyses as blog posts (on a class blog or individual student blogs). Once posted, the comments feature could be used to facilitate peer review. With the suggested rubric, students could be assigned to review their own blog post plus those of two other students.
- As an alternative optional extension project, students could create a "genetics of cancer" infographic, intended for patient education at an oncologist's office. Free, online infographic creation tools (Easel.ly or Piktochart) make this sort of brochure or handout easy to create.

AUTHORS

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EXAMPLE OF COMPLETED CLASSIFICATION OF CANCER GENES POSTER

Classification of Cancer Genes

Cancer genes fall broadly in two classes: oncogenes and tumor suppressor genes.

Oncogenes are genes that, when mutated, are over active or overexpressed, pushing cells to grow and multiply uncontrollably.

Tumor suppressor genes normally regulate the cell cycle and limit growth and division, or promote programmed cell death. When both copies are deleted or disrupted by mutation, the cell may grow and multiply uncontrollably.

EXAMPLE OF COMPLETED CLASSIFICATION OF CANCER GENES POSTER

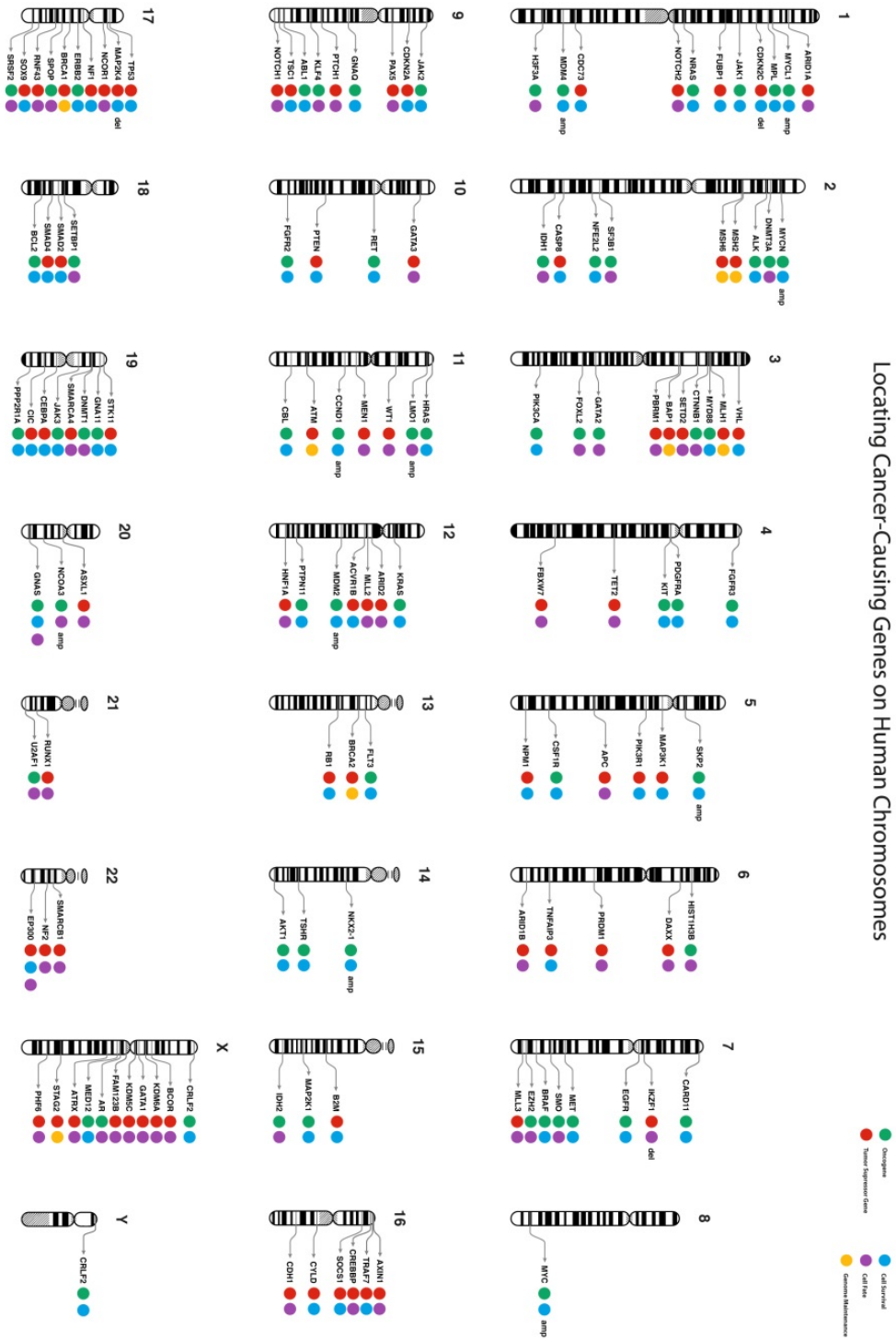
Functions of Cancer Genes

The normal versions of genes that, when mutated, cause cancer can be assigned to three functional categories: cell growth and survival, cell fate, and genome maintenance.

Cell Growth and Survival
Cell division and cell death balance each other. Mutations in genes that regulate these processes offset the balance and results in excessive cell division.

Cell Fate
Many cancer genes regulate differentiation. Differentiated cells often stop dividing. Failure to differentiate can produce excessive cell division and lead to cancer.

Genome Maintenance
These genes correct errors in DNA replication and spontaneous mutations. When genome maintenance genes are mutated, more errors are introduced into the genome with every cell division, vastly increasing the chances of mutating other cancer genes.


Locating Cancer-Causing Genes on Human Chromosomes
Oncogene
Tumor Suppressor Gene
Cell Survival
Cell Fate
Genome Maintenance
1
ARID1A
MYCL1
MPL
CDKN2C
JAK1
FUBP1
NRAS
NOTCH2
CDC73
MDM4
HSF1A
amp
del
2
MYCN
ALK
DNMT3A
MSH2
MSH6
IDH1
CASP8
NFE2L2
SF3B1
3
VHL
MLH1
MYD88
CTNNB1
SETD2
BAP1
PBRM1
PIK3CA
FOXL2
GATA3
4
FGFR3
PDGFRA
KIT
TET2
FBXW7
5
SKP2
MAP3K1
PIK3R1
APC
CSF1R
NPM1
6
HIST1H3B
DAXX
PREM1
TNFAIP3
ARID1B
7
CARD11
IKZF1
EGFR
MET
SMO
BRAF
EZH2
MLL3
8
MYC
9
JAK2
CDKN2A
PAX5
GNAQ
PTCH1
KLF4
ABL1
TSC1
NOTCH1
10
GATA3
RET
PTEN
FGFR2
11
HRAS
LMO1
VFT1
MEN1
CCND1
ATM
CBL
12
KRAS
ARID2
MLL2
ACVR1B
MDM2
PTPN11
HNF1A
13
FLT3
BRCA2
RB1
14
NKX2-1
TSHR
AKT1
15
B2M
MAP2K1
IDH2
16
AXIN1
TRAF7
CREBBP
SOCS1
CYLD
CDH1
17
TP53
MAP2K4
NCOR1
ERBB2
BRCA1
NF1
SPOP
RNF43
SOX9
SRSF2
del
18
SETBP1
SMAD2
SMAD4
BCL2
19
STK11
GNA11
DNMT1
SMARCA4
JAK3
CEBPA
CIC
PPP2R1A
20
ASXL1
NCOA3
GNAS
amp
21
RUNX1
U2AF1
22
SMARCB1
NF2
EP300
X
CRLF2
BCOR
KDM6A
GATA1
KDM5C
FAM123B
AR
MED12
ATRX
STAG2
PHF6
Y
CRLF2