The Genetics of Cancer

Bi 10
October 25, 2013

Adapted from a case study by Janet De Souza-Hart

Agenda

• Administrative Stuff and Reminders
• Concept Review
• Case Study: Cancer Genetics, Inheritance, and Gene Expression
  • Pedigree Analysis
• Wrap-up

Test and Due Date Reminders

Lab Practical: Wednesday, Oct 30 and Friday, Nov. 1.
Lecture Exam: Friday, Nov. 1
Study Guides: Friday, Nov. 1
Reading Quiz (Ch 10 + 11): Friday, Nov. 1
Flash Cards Extra Credit: Friday, Nov. 1
Essay: Wednesday, Nov. 6
Extra Credit Study Guides: Friday, Nov. 8
**DNA: The ‘Recipe’ of Life**

DNA carries instructions for how and where to make RNA. RNA carries instructions to make proteins. **Gene** = piece of DNA that codes for mRNA.

Almost every cell in your body has the same DNA! But different parts of the DNA are “turned on” in different cells.

Every cell in your body contains **3 meters** of DNA! How is this possible if your cells are so small?

(Figure source: http://katlegophd.com/wp-content/uploads/2011/01/central-dogma.jpg)

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**An analogy...**

Your **genome** is like a bookshelf full of books!

By this analogy, what do the books represent?

How many books are in the genome for most people?

What are the sentences in the books?

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**Do All of Your Cells Undergo Mitosis?**

Almost all of the cells in your body **came from** mitosis. (Exception: Eggs, sperm)

However, **most of the cells in your body have stopped dividing**!

This is a good thing! When cells that are not supposed to divide do so, the result is cancer.

(Figure 8.29 in text)
Using Pedigrees to Trace Genetic Diseases

A pedigree is a chart that shows which members of an extended family have shown a trait (phenotype).

Males are represented by squares, and females by circles. The shapes representing individuals with the disease are shaded in.

Not All Mutations Are Inherited!

If a change in DNA (mutation) happens in one of your skin cells before you have children, will you pass it on to them? This is a **somatic mutation**.

What if the mutation happens in the cells that make your sperm or eggs? This is a **germ-line mutation**.

Somatic and germ-line mutations can both cause cancer. Agents that cause mutations are called **mutagens**. Agents that increase cancer risk are called **carcinogens**.
A Family in Need
(Adapted from a Case Study by J. De Souza-Hart)

Lee, a 17-year-old boy, has a tumor-like growth in one of his adrenal glands (glands near the kidney). The oncologist does a biopsy and takes a careful family history from his parents.

Is this cancer based on an inherited mutation? If so, what kind of inheritance is involved – dominant or recessive? Is it sex-linked?

Make a Pedigree
Lee has a healthy brother, Luke, and a healthy sister, Leah.
Grace, Lee’s mother, developed bilateral breast cancer.

Grace is the youngest of four children. Her eldest brother, Greg, and sister, Greta, never had any signs of cancer. Her brother Geoff, the third child of the four, died of leukemia in childhood.

Greg’s two daughters are healthy.
Grace’s father, Roger, died of cancer at age 35. Grace’s mother is healthy.
Roger’s mother died of a brain tumor at age 30; Roger’s father was healthy.
There is no history of cancer on the father’s side of the family – neither Lee’s father nor his paternal grandparents had cancer.

Is this Hereditary Cancer?
How Is It Inherited?
Doing Some Detective Work

Useful References:


Online Mendelian Inheritance in Man:

Using the Scientific Method

Observations:

Question:

Hypothesis:

Experiment:

There are several types of genetic testing available for cancer-causing mutations.

To test for an inherited mutation, would we test DNA from healthy cells from Lee, or cells in the biopsy? What if we wanted to test for a somatic mutation?

To sequence the DNA, we need to make lots of copies of it. The technique for doing that is called PCR – the polymerase chain reaction.
**PCR**

Used to copy DNA

Steps:
- Separate the strands.
- Copy each strand.
- Repeat.

Can make LOTS of DNA from a tiny sample!

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**Results**

Lee has a heritable mutation in the TP53 gene. This dominant allele causes Li-Fraumeni syndrome.

However... when you sequence his TP53 gene... you see no difference in the codons that code for amino acids? What’s going on?

To understand, we will need to consider *gene expression*, and the nature of proto-oncogenes and tumor suppressors.

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**Proto-Oncogenes and Tumor Suppressors**

Proto-oncogenes normally make the cell cycle faster. When they are mutated to become (overactive / inactive), the risk of cancer increases. (choose one)

Tumor suppressor genes normally make the cell cycle slower. When they are mutated to become (overactive / inactive), the risk of cancer increases. (choose one)
Measuring Gene Expression

<table>
<thead>
<tr>
<th>Table 3: Different Genes Implicated in ACC</th>
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<tr>
<td>Patient 1</td>
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* gene symbols are consistent with HUGNC & OMIM
  R=red (high expression in disease compared with normal cells)
  G=green (low expression in disease compared with normal cells)
  Y=yellow (same expression in both cell types)

Which of these might be proto-oncogenes? Which might be tumor suppressors?

mRNA Splicing

Conclusions

Could Lee possibly be cured via gene therapy? Why or why not? Could we somehow put a working TP53 gene into his cells?