

# Colon Cancer: A Case of Genetic Bad Luck?

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## Part I— Just Bad Luck?

*Brrrring! Brrrring!* Jane checked the caller ID on her phone. “Sam! Great!” she thought. It was always nice to get a call from her older brother. But a little twinge of worry tugged at her. It was just a couple of weeks ago that he had mentioned making an appointment with his doctor about some abdominal pain he had been having.

“Hi Sam! It’s great to hear from you,” Jane answered.

“Hi Jane. Well I appreciate that you still pick up, anyway. You know I call just to give you a hard time about something, little sis.”

“Very funny. So, how are you planning to pick on me today?”

“Honestly, I wish this call was for fun,” Sam said. “But it’s only serious stuff this time. Remember I said that I had made an appointment with my doctor? Well, the news isn’t good. My doctor says I have colon cancer.”

“Oh, no, Sam! I remember when Dad died from colon cancer when we were kids.” The words tumbled out all in a rush. Jane felt a lump gathering in her throat.

“Hold on,” Sam said. “This isn’t an early death sentence yet. The doctor says that although they found lots of tumors in my colon, it’s still at an early stage, so treatment is possible. Drastic, though. My doctor is suggesting that the best thing to do is to surgically remove my colon altogether. And Sis, the doctor said that since both Dad and I have the same type of cancer, it would be a good idea for you to have your colon checked, too.”

After the phone conversation with her brother, Jane was worried there could be more than just “bad luck” running in her family’s medical history. Their father’s too-early death from colon cancer was still a painful memory. She knew that her grandfather on her father’s side had died of some type of cancer even before she was born, although that was so long ago the family didn’t talk about it much. Had her grandfather died of colon cancer too, Jane wondered. Would it be her turn next? And what was the risk to her young twins, Mark and Caroline?

### Questions

1. Draw this family’s pedigree, focusing on the family relationships and shading the individuals affected with cancer.
2. Do you think Jane has good reason to be worried? Why or why not?

## Part II—A Visit to the Doctor

“Good afternoon, Jane,” Dr. Peters said as she entered the examination room. “I understand that you’re here to talk about some concerns related to cancer in your family.”

Jane explained the history of cancer in her family, including her father’s early death from colon cancer and her brother’s recent diagnosis of the same disease, ending with the recommendation from her brother’s doctor to have her own colon checked.

“What does that mean, to have my colon ‘checked?’” As she asked the question, Jane was already feeling a little uncomfortable about it.

“I know that the idea of having a procedure done to look at your colon is a little off-putting,” Dr. Peters began, “but it really can be one of the most important tests if your family has a history of colon cancer.” She continued to explain: “The procedure that allows the interior of the colon to be examined is called a colonoscopy. The purpose of such a screening is to look for sites of increased cell growth in the colon, called polyps or adenomas. These adenomas are small benign tumors that form in the intestinal lining. People who inherit a predisposition to colon cancer are at higher risk to form these adenomas, and at an early age. Although the adenomas are benign, the cells within them are one step closer to becoming malignant. So, colonoscopy screenings don’t prevent cancer, but they do allow sites of altered cell growth to be detected, so that treatment can begin as soon as they appear. By detecting these adenomas early and removing them before they become malignant, we can prevent colon cancer.

“So regular colonoscopy screenings, beginning at an early age, are highly recommended for people with a familial predisposition to colon cancer,” Dr. Peters continued. “And even if a person doesn’t have a family history of colon cancer, it’s still recommended to have a colonoscopy screening once a year beginning at age 50.”

“I understand now why it would be important to have my colon checked,” Jane said, “but is there some way I can find out for sure whether I have inherited a predisposition to colon cancer?”

“I was just getting to that topic,” Dr. Peters replied. “In some cases, genetic testing can reveal whether you are predisposed to colon cancer. Normally those kinds of genetic tests are done first on family members who are affected. Since your brother lives nearby, I’d suggest you talk with him about making an appointment together with a genetic counselor for more information about testing.”

### Questions

1. What does it mean if a tumor is classified as “benign”? What does it mean if a tumor is “malignant”?
2. Why is it easier to treat a benign tumor than a malignant tumor?
3. What does it mean to be predisposed to getting cancer?
4. If someone is predisposed to getting cancer, does that mean that he or she will definitely get cancer someday?

## Part III—Genetic Testing

“Hello Sam and Jane, I’m Diane Meeker, and I’ll be your genetic counselor. I understand that you’re both here to talk about possibly having genetic testing to see whether you inherited a predisposition to colon cancer.”

“Yes,” Jane replied, “I’m concerned because our dad died of colon cancer when we were kids, and now Sam has it too—and he’s only 30!”

“Why don’t we start there, then, and review your family history. First, do you know of any other family members that have been diagnosed with cancer?” Ms. Meeker asked.

“Well, besides Sam and our dad, I know that our grandpa on our father’s side also had cancer,” Jane replied. “But he died long before either of us was born and I don’t know what kind of cancer it was. No one else in our family has had cancer that I know of.”

“Based on what you’ve told me about the medical history of your family, I’ve created a pedigree to diagram your family relationships and which individuals have cancer. The extremely early development of colon cancer in both you, Sam, and your father, and the fact that a direct relative of your father died early from some type of cancer suggests that familial adenomatous polyposis (FAP) may be the cause of hereditary colon cancer in your family,” Ms. Meeker said.

“But what exactly is it that is being inherited in our family that causes us to develop colon cancer? It’s something about our DNA, right?” Jane asked.

“You’re right,” Ms. Meeker replied, “it does have to do with your DNA. The DNA in your cells contains genes, which are the instructions for making proteins. Proteins in the cell control how that cell grows and develops and divides. A mutation in the DNA sequence of a gene can alter the protein made from that gene, so that the protein no longer functions properly. So, some mutations can cause a change in protein function that allows a cell to grow out of control and become cancerous.”

“So maybe there’s a mutation in my DNA,” Sam replied. “But if you do a genetic test, how do you know what to look for in my DNA? Don’t humans have lots of DNA? What exactly would you be testing?”

“Finding an inherited mutation in a person’s DNA does sound like looking for a needle in a haystack, doesn’t it?” Ms. Meeker replied. “But we do have some clues to suggest where we can look. For example, from other families with FAP, we already know that this syndrome can be caused by an inherited mutation in the *adenomatous polyposis coli (APC)* gene.”

“I see,” Sam replied. “So you won’t be looking at all of my DNA. You only need to look at that one gene and see if it has a mutation, right?”

“You’ve got it,” Ms. Meeker said. “So, by taking some of your blood, isolating your DNA, and then sequencing your *APC* gene, we can compare your sequence to the known normal *APC* sequence and look for differences.”

“That sounds so simple. So then if you find a mutation in my *APC* gene, you could look to see whether or not my sister inherited that mutation too, right?” Sam said.

“Yes, because you have been diagnosed with colon cancer, we’ll start by looking for a mutation in your DNA first, Sam,” Ms. Meeker confirmed. “And I wish it was as clear-cut as it sounds, but actually I have to caution you both about this genetic test. The process of searching for mutations can be time-consuming and expensive, because often each FAP family carries a mutation at a unique site in the *APC* gene—and the *APC* gene is large! In fact, the gene is so large that we don’t actually sequence the DNA for the gene. Instead, we sequence the mRNA, which is the part of the gene that your body uses to make the *APC* protein. The mRNA is smaller because it cuts out some parts of the sequence of the gene, called introns. Here, let me show you in a drawing,” Ms. Meeker continued as she began to pull out a piece of paper.



In order to sequence the mRNA of a gene, scientists first make a DNA copy of the mRNA. This DNA copy is called a cDNA, and it is more stable and easier to work with than the original mRNA. The cDNA is then sequenced. Let’s compare Sam’s *APC* cDNA sequence with the known normal *APC* cDNA sequence. To do this, first go to the main NCBI home page (<http://www.ncbi.nlm.nih.gov>) and follow the instructions below.

- In the dark blue bar across the top, choose the link to “BLAST.”
- On the BLAST page, under the “Basic BLAST” category, click the link to “nucleotide blast.”
- On the next page, in the “Enter Query Sequence” section, click the box next to the option “Blast 2 sequences.”
- Find the normal sequence of *APC* cDNA on the NCBI website. Open a new browser window and go to the NCBI home page (<http://www.ncbi.nlm.nih.gov/>). In the top light blue bar, change the “All Databases” search to a search for “Nucleotide.” Then in the search box, enter M74088 (which is the accession number for *APC*) and click “go.” On the search results page, click on the blue link to M74088. You will need to scroll down the page to find the normal *APC* sequence. Copy and paste this sequence into the top box on the BLAST page (the Query sequence box).
- Ask your instructor where to find Sam’s sequence. Copy and paste Sam’s *APC* cDNA sequence in the bottom box on the BLAST page (the Subject sequence box).
- Click the “BLAST” button at the bottom of the page.
- On the BLAST results page, you can scroll down to see the alignment of normal *APC* (the Query sequence) with Sam’s *APC* (the Subject sequence). Note though that this format makes it difficult to see mismatches between these two sequences.
- To change the results format to one that makes it easier to look for mismatches, scroll back to the top of the BLAST results page, and click the blue “Formatting Options” link.
- In the “Alignment View” box, change the view from “Pairwise” to “Pairwise with dots for identities.” Then click the “Reformat” button in the upper right corner. On the re-formatted results page, each base of Sam’s *APC* (the Subject sequence) that matches normal *APC* (the Query sequence) is shown as a dot.

## Questions

1. What did you find when you compared Sam's *APC* sequence to the known normal *APC* sequence in the national database? Look carefully, and scroll all the way down through the comparison! *Check your answer with your instructor before moving on.*
2. What are three possible consequences of the mutation you found in Sam's *APC* sequence?

Now let's translate both the normal *APC* sequence and Sam's *APC* sequence into a protein in order to compare them. To do this, go again to the NCBI home page at <http://www.ncbi.nlm.nih.gov>.

- Choose the "Tools" link on the left side of the page (you may need to scroll down to find it).
- On the "Tools" page, scroll down until you find the link to "ORF finder."
- Copy and paste the normal *APC* sequence into the box and then click the "ORF find" button.
- You will see six colored bars at the top of the page. Each bar represents a possible protein translation of the entered sequence. You see six different bars because there are six different possible open reading frames for the sequence (three possible frames starting from each end). The ORF finder program colors in blue any codons between a start codon and a stop codon. You will see one reading frame that is nearly completely blue; this is the normal reading frame. This is the reading frame that you should compare with Sam's. Keep this browser window open while you do the next step.
- Open an *additional* browser window, go to the ORF Finder program, copy and paste Sam's *APC* sequence into the box and click the "ORF find" button.
- Looking at both browser windows, compare the translation of the normal *APC* sequence with Sam's *APC* sequence.

3. What do you notice when you compare Sam's *APC* protein translation to the normal *APC* protein?
4. Of the three possible consequences you listed in your answer to Question 2 above, which one is the consequence of the mutation in Sam's *APC* gene?
5. In a small number of patients whose families appear to have all the classical characteristics of FAP, a mutation cannot be found in the *APC* cDNA. What are two possible reasons for why mutations may not be found in some patients whose families appear to have FAP?

## Part IV—The APC Protein

“Sam, I’m really worried about seeing my test results today,” Jane said as they headed in for another visit with their genetic counselor. “After Ms. Meeker explained your results to us, I’ve been dreading hearing whether or not I have the mutation too.”

Sam nodded, saying, “I can understand how you feel. I’m glad I can be here at the appointment to support you. Whatever happens, you know your family is here for you.”

Ms. Meeker arrived in the waiting room. “Jane and Sam, I’m glad you’re here. Please come in and let’s talk,” she said, leading them into her office. “I’m sorry Jane, but your genetic testing results show that you inherited the same mutation in the *APC* gene that Sam has. As we discussed earlier, familial adenomatous polyposis, or *FAP*, is caused by a mutation in the *APC* gene. You inherited one normal copy and one mutant copy of the *APC* gene, and because of that, you are one step closer to cancer than a person who inherited two good copies of the gene. If the remaining good copy of the *APC* gene in your cells is damaged, this will lead to the development of colon cancer.”

Sam wrapped Jane in a bear hug. “I don’t know what to think,” Jane replied. “I guess I’m feeling numb. What is it about this *APC* protein that connects it to cancer? And what am I supposed to do next?”

“If you like, we can talk more about what *APC* does, and why this protein is important for control of cell growth,” Ms. Meeker offered. “And, I’d like to talk with you sometime soon about what we would recommend you should do next for your health management.”

“Why don’t we start with some more information about the *APC* protein,” Ms. Meeker continued. “*APC* interacts with and binds to other proteins in the cell. The *APC* protein is large, and we know that there are sub-regions within this protein. Each sub-region is specialized for binding to some other different protein. When *APC* binds to other proteins, it influences the function of these other proteins. I have two figures to show you that I think will help make this clearer. Let me walk you through them,” she said as she handed Jane and Sam a printout of two figures.

The two figures that Ms. Meeker presented to Jane and Sam are shown below. Figure 1 is a description of the *APC* protein domains, including which regions of *APC* are known to bind to other proteins. Figure 2 is a diagram showing one of *APC*’s cellular functions. Examine these figures and then use the information you learn from them to answer the questions that follow.

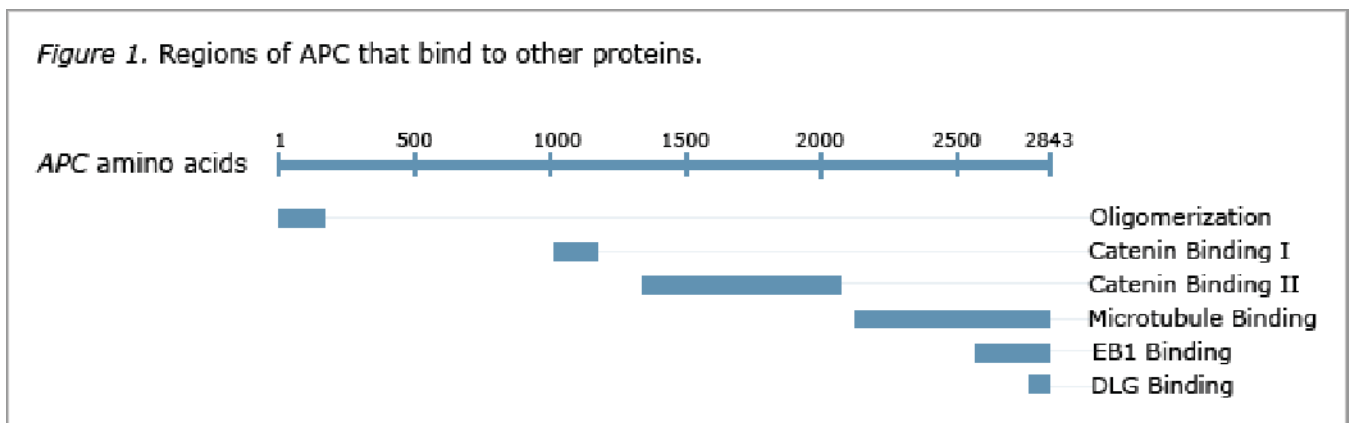
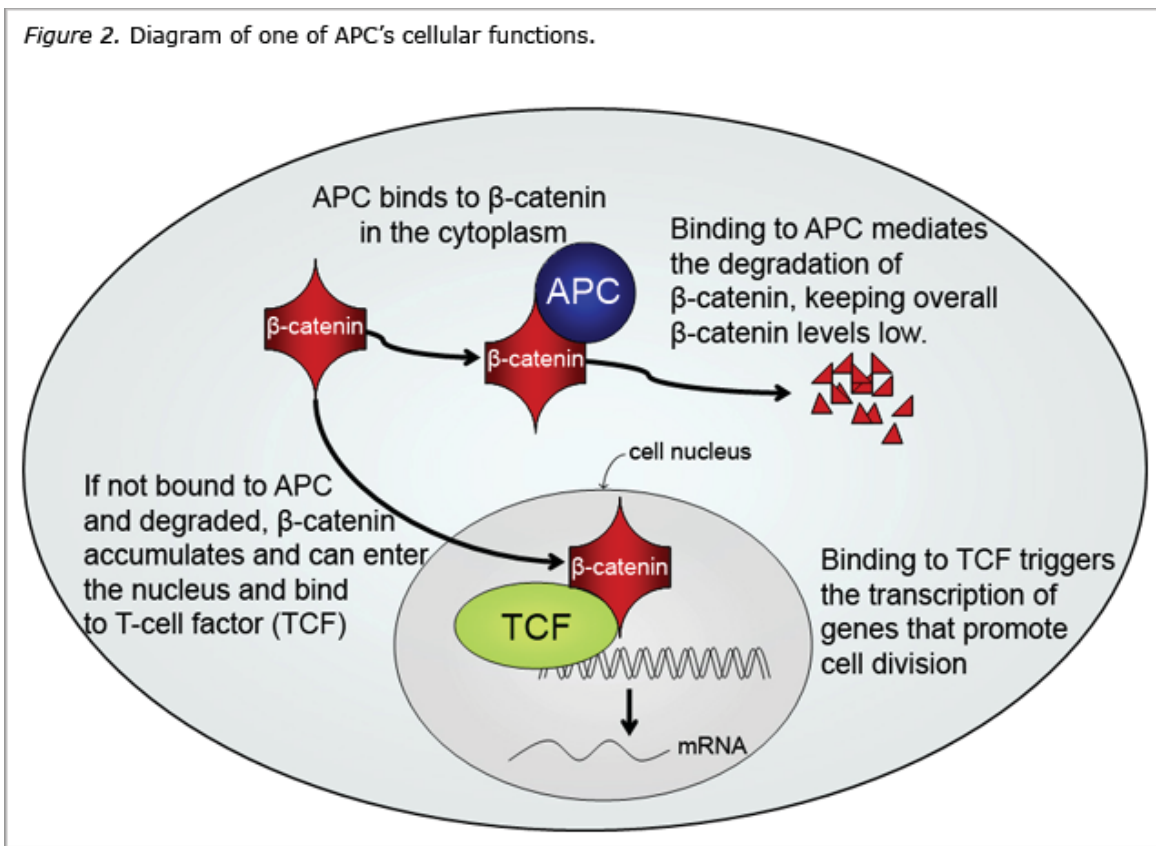


Figure 2. Diagram of one of APC's cellular functions.



### Questions

1. Would you expect Jane and Sam's *APC* mutation to increase or decrease the ability of the *APC* protein to bind to  $\beta$ -catenin?
2. If the remaining normal *APC* gene is damaged in one of Jane's cells, how would this affect  $\beta$ -catenin in that cell? How could this change affect the growth of that cell?
3. What are three categories of genes that when mutated can lead to tumor formation? Describe the characteristics of each category.
4. In which of these three categories would you classify *APC*? How would you classify  $\beta$ -catenin?
5. Based on what you learned in this case study, what do you think Ms. Meeker would recommend that Jane do to manage her condition?

Credits: Figure 1 is based on a figure in Kinzler and Vogelstein, *Cell* 87:159–170 (1996). Figure 2 is by the author of this case study, Anne M. Casper.

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