

APCI1307K: Introduction

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In 1997, a Johns Hopkins research team found an inherited genetic mutation called APC I1307K. This mutation is found primarily in people of Ashkenazi Jewish heritage (Jews of Eastern European or Russian ancestry). Researchers believe that 6% of the Ashkenazi Jewish population carries this gene mutation, which gives them a significantly increased risk of developing colorectal cancer.

Both the APC I1307K mutation and mutations that cause FAP occur in the same gene, the APC (adenomatous polyposis coli) gene. The APC I1307K mutation is different from other APC mutations because the mutation itself does not cause colorectal cancer. Instead, this particular mutation creates an unstable spot in the gene that makes the gene more susceptible to additional genetic changes that may, in turn, lead to colorectal cancer.

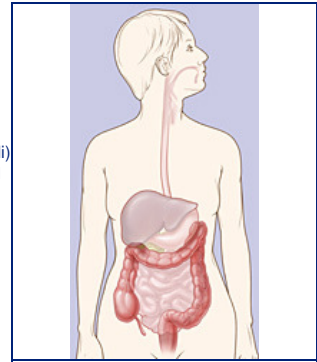


Figure 1. Location of the colon in the body.

What is APC I1307K?

Adenomatous polyposis coli is a tumor-suppressing gene that plays an important role in the carcinogenesis of colorectal cancer. If the APC gene is defective it fails to suppress colon cancer development. The mutation appears to make the gene unstable and prone to acquire mutations during normal cell division. The APC I1307K mutation is found in Ashkenazi Jews and has not been found in anyone who is not of Ashkenazi descent. This gene mutation causes a substantial increase in the risk of colorectal cancer (approximately 18–30% lifetime risk). Studies of APC I1307K are ongoing to better understand its role and implications.

Symptoms

Many patients with colorectal cancer experience no symptoms in the early stage of their disease. In fact, many people have no symptoms until the disease is quite advanced. Therefore, routine colorectal screening and an appreciation of risk factors are extremely important.

Since many of the symptoms of colorectal cancer are also symptoms of a variety of other colon diseases, it is important to see your physician so that the necessary tests can be run and a diagnosis made.

The following is a list of symptoms that may occur:

- Blood in the stool
- Diarrhea that is not the result of diet or illness
- A long period of constipation
- Crampy pain in the abdomen
- Change in bowel habits
- Persistent decrease in the size or caliber of stool
- Frequent feeling of distention in the abdomen or bowel region (gas pain, bloating, fullness, with or without cramping)
- Weight loss with no known reason
- Vomiting and continual lack of energy

In addition to polyps, abnormalities in other areas of the body may give early clues to the presence of FAP. These abnormalities may include bumps or lumps on the bones of the legs, arms, skull, and jaw; cysts of the skin; teeth that do not erupt when they should; and freckle-like spots on the inside lining of the eyes.

It should be emphasized that there is no safety in simply waiting for symptoms to develop. It is vital that parents and guardians make every effort to have examinations of their children starting at age 11 even if they do not have symptoms.

Resources

The American Cancer Society

The American Cancer Society
National Headquarters
1599 Clifton Road, N.E.
Atlanta, Georgia 30329
800-ACS-2345
<http://www.cancer.org/>

The ACS can offer assistance if cancer should occur. Check the telephone directory for your local chapter.

Hereditary Colorectal Cancer Registries

Registries may be contacted for the names of experts in the management of APC I1307K. Registries can also help to identify relatives at risk for the disorder. Further information concerning Hereditary Colorectal Cancer Registries may be obtained by clicking [here](#) or contacting:

Coordinator, Hereditary Colorectal Cancer Registry
The Johns Hopkins Hospital
550 North Broadway, Suite 108
Baltimore, MD 21250-2011
Phone: 1-888-77-COLON
Fax: 410-614-9544
E-mail: hcregistry@jhmi.edu

APCI1307K: Anatomy

The colon and rectum are part of the digestive tract. The digestive tract is a hollow tube that begins at the mouth and ends at the anus. It has several parts including the esophagus, stomach, small intestine, colon, and rectum (the colon and rectum make up the large intestine).

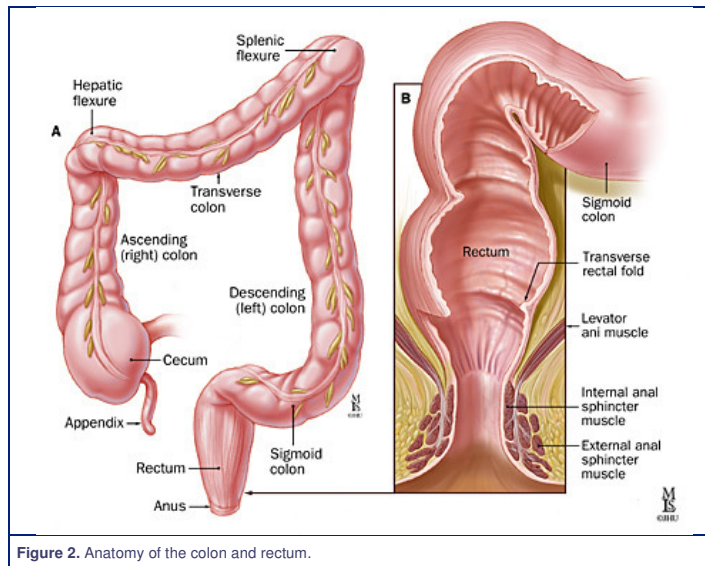


Figure 2. Anatomy of the colon and rectum.

The intestine is about 28 feet long. The last 5–6 feet of the intestine is called the colon or large intestine. This structure has six major divisions: cecum, ascending colon, transverse colon, descending colon, sigmoid colon, and rectum. The last 5 or 6 inches of the large intestine is the rectum.

The purpose of the digestive system is to remove nutrients (minerals, vitamins, carbohydrates, proteins, fats, and water) from the foods we eat and to store the waste. After food is digested, solid wastes move through the colon and rectum to the anus, where they are passed out of the body.

APCI1307K: Causes

Family History

The exact causes of colorectal cancer are not known. However, studies have shown that genetics, diet, and lifestyle can affect an individual's risk of developing colorectal cancer.

Family history is one of the most significant risk factors for colorectal cancer. People who have cancer, colorectal cancer, non-cancerous colon polyps, or inflammatory bowel disease are at increased risk of developing colorectal cancer. People who have previously been treated for colorectal cancer are at risk for recurrence. Women with uterine, ovarian, and breast cancer are also at increased risk.

Genetics

People with APC I1307K have a 50 percent chance of passing the condition to each of their children.

Why Is This Mutation Most Common in People of Ashkenazi Jewish Descent?

Recent scientific studies tell us that certain groups of people, including Ashkenazi Jews, have unique genetic mutations that increase their risk of certain cancers or diseases. In most cases, doctors who study genetics believe that the first time a gene change occurs in a group of people, it occurs by chance. When this group is small and separate from other groups, by geography or culture, for example, the gene change may become more frequent from one generation to the next. This is probably why the APC I1307K gene mutation is most commonly found in people of Ashkenazi Jewish descent.

How Is the APC I1307K Mutation Inherited?

People with the APC I1307K gene mutation have a 50% chance of passing the gene mutation to each of their children. Children who do not inherit the gene mutation cannot pass it to their own children.

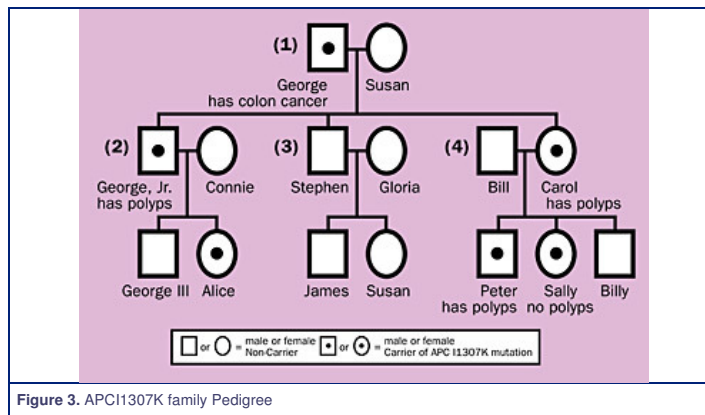


Figure 3. APCI1307K family Pedigree

(1) George has colon cancer and carries the APC I1307K gene mutation. His wife, Susan, does not have the gene mutation. They have three children, George, Jr., Stephen, and Carol. All were at 50% risk of inheriting the APC I1307K gene mutation from George. In fact, both George, Jr. and Carol do carry the mutation and both have developed polyps.

(2) George, Jr., and his wife, Connie, have two children. Both children had a 50% chance of inheriting the gene mutation. Their daughter, Alice, is affected.

(3) Stephen and his wife, Gloria, have two children. Because Stephen does not have the gene mutation, his children had no risk of inheriting the gene mutation from him.

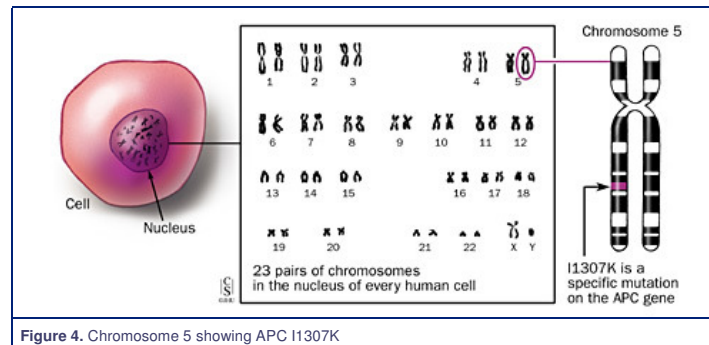
(4) Carol and Bill have three children. Each child had a 50% chance of inheriting the gene mutation from Susan. Peter and Sally carry the gene mutation, but neither one has yet developed polyps or colon cancer.

Children who do not inherit the gene mutation cannot pass it to their own children.

APC I1307K: Diagnosis

Genetic/DNA Testing

There is a gene test to look for this inherited gene mutation.



The test is performed on a small sample of blood. However, this gene test does not look for gene mutations that cause other forms of hereditary colorectal cancer.

Anyone who is thinking about having a gene test must receive genetic counseling. This is required because there are many issues to consider before testing. Genetic information can affect different people in many ways.

This gene test is performed at the Johns Hopkins University Pathology Molecular Diagnostics Laboratory in Baltimore, Maryland, and at a few other laboratories in the country. The cost of this gene test may vary. Genetic counseling may be required and would be an additional cost. Some insurance companies will pay for genetic counseling and testing, others will not. People who are thinking about having a gene test done should check with their insurance company before making a final decision.

A negative gene result can mean that there is a 99% chance that an individual does not carry the gene mutation. This person may still have a mutation in another gene that causes hereditary colorectal cancer. Other risk factors can be assessed during genetic counseling, where family history, lifestyle, and other issues may be discussed.

A positive gene result can mean that a person has an estimated 10–20% risk of developing colorectal cancer in his or her lifetime. The APC I1307K test results are 99% accurate. This is only a gene test; it does not detect the presence of cancer or polyps.

Who Should Consider Testing for the APC I1307K Mutation?

Any person of Ashkenazi heritage who has a personal or family history of colorectal cancer or colorectal polyps may wish to consider testing. A family history means having at least one close family member with colorectal cancer or polyps. Ashkenazi Jews without a family history of colorectal cancer may still wish to obtain genetic counseling to learn the value of gene testing in their own unique circumstances.

Genetic counseling is available, and recommended, for individuals who may have the APC I1307K mutation, and their family members. Genetic counselors will explain the inheritance pattern of APC I1307K, discuss which family members are at risk for developing the condition and provide necessary information regarding genetic testing. Counseling services are available through genetic and oncology departments in many hospitals. To make an appointment with a member of the Johns Hopkins professional medical team or to speak with someone at the Colorectal Cancer Risk Assessment Service, please call (410) 614-LIFE (5433). Also, it is recommended that APC I1307K families contact registries for access to resources and for help with identification of at-risk family members.

What Should You Do if You Receive a Positive Gene Test Result?

It is important to detect colon polyps or cancer early. Routine screening is the best way to do this. At this time, experts recommend the following:

Persons with a positive test result, who do not already have colon cancer or polyps, should have a routine colonoscopy every 2 years beginning at age 35 OR 5–10 years before the earliest age at which colon cancer or polyps occurred in the family, whichever is younger.

Patients with a personal history of colon cancer or polyps should have a routine colonoscopy every 2 years, or more often at the recommendation of their doctor.

Relatives of people testing positive for this gene mutation should consider counseling and testing as well.

Genetic Testing and Insurance

With any gene test there is a risk of insurance (life or health) or employment discrimination. At this time there are federal laws that offer protection against discrimination of people who have medical insurance through a group health plan. Some states have laws to protect people, but the laws on insurance and employment discrimination vary from state to state. The Americans with Disabilities Act may protect people with a positive gene test from discrimination in the workplace. These issues can be discussed with a genetic counselor.

Physical Examination

Doctors should keep a detailed history on each patient. This history should include the patient's personal and family medical history. The physician will perform a physical examination and may order laboratory tests. Diagnostic tests may also be performed.

Digital Rectal Examination

This is a painless examination of the rectal area. The physician inserts a gloved, lubricated finger into the rectum to gently feel for any abnormalities.

Fecal Occult Blood Test

This is a test for hidden (occult) blood in the stool. The patient is given three small cards and asked to provide samples from three consecutive bowel movements. A small amount of stool is placed on a special test strip on each card (figure 12). This stool may be tested in the doctor's office or sent to a laboratory to see if there is any occult blood in the specimen.

Endoscopic Diagnosis

Flexible Sigmoidoscopy

The flexible sigmoidoscopy is an examination of the rectum and the lower colon. It is done with a lighted, flexible, hollow tube, which is about the thickness of a finger.

The sigmoidoscope is inserted into the anus through the rectum and into the large intestine. Using the sigmoidoscope, the doctor can see whether polyps or cancer are present (Figure 16). At the time of sigmoidoscopy, a biopsy forceps may be inserted through a channel of the scope to remove a small sample of tissue for microscopic examination. Sometimes it is necessary for the doctor to introduce air into the sigmoid colon to improve visibility. Most patients feel a little cramping or discomfort when having a flexible sigmoidoscopy.

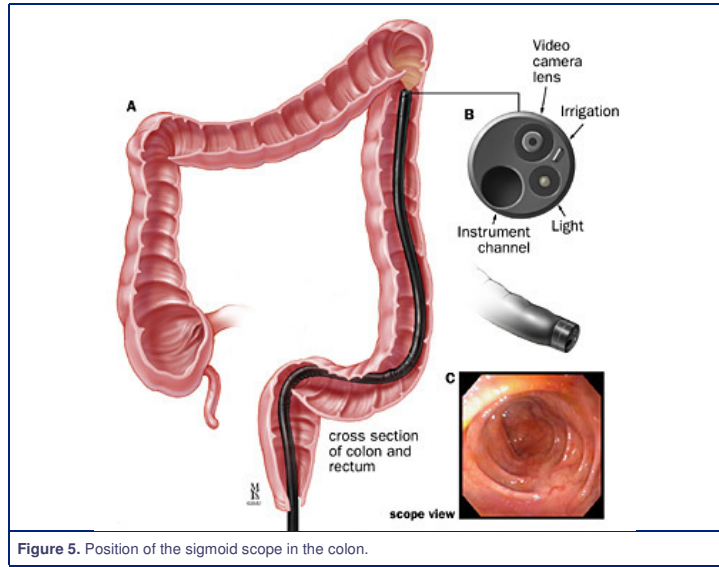


Figure 5. Position of the sigmoid scope in the colon.

Before having a sigmoidoscopy the colon must be clear of stool so that the doctor has good visibility. The patient must undergo a preparation that may include a liquid diet, enema and laxatives to clear stool for the colon. The technique for bowel preparation may differ by health facility.

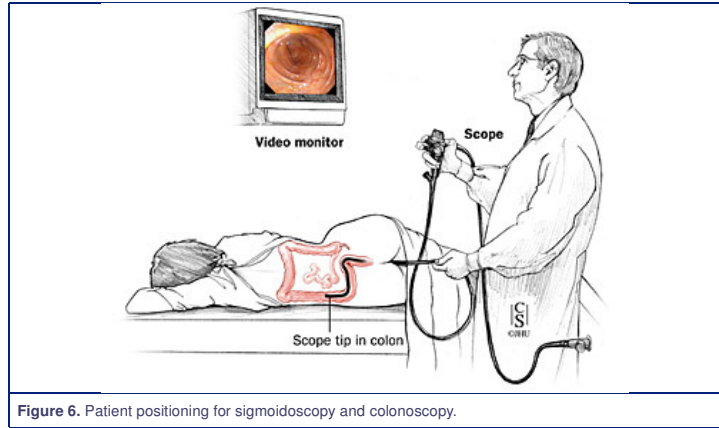


Figure 6. Patient positioning for sigmoidoscopy and colonoscopy.

Colonoscopy

Colonoscopy is the best way to detect polyps or cancer.

A colonoscopy is an examination of the rectum and the entire colon. It is performed with a lighted, flexible, hollow tube, which is slightly larger in diameter than an enema tube. Colonoscopy permits the doctor to see much farther into the bowel than sigmoidoscopy. The colonoscope allows the doctor to see whether polyps or cancer are present.

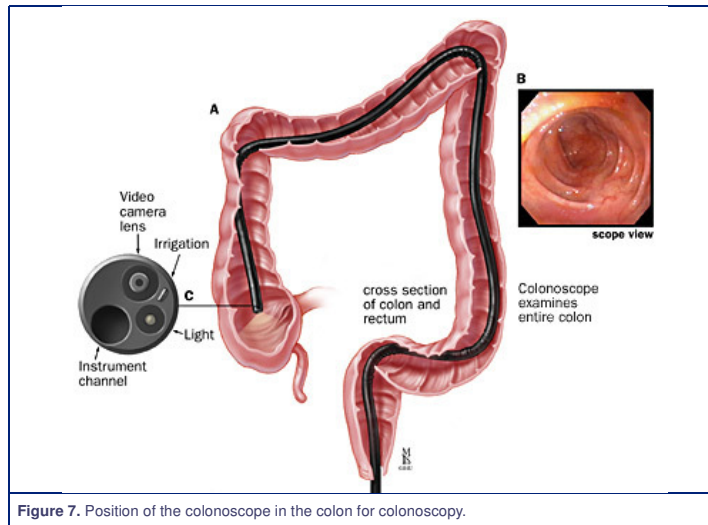


Figure 7. Position of the colonoscope in the colon for colonoscopy.

A biopsy forceps may be inserted through a channel in the colonoscope to remove a small sample of tissue for microscopic examination. Sometimes it is necessary for the doctor to introduce air into the colon to improve visibility. Before having a colonoscopy the colon must be clear of stool so that the doctor has good visibility. The patient must undergo a preparation that may include a liquid diet, enema, and laxatives to clear stool from the colon. The technique for bowel preparation may differ by health facility.

A sedative is given before a person undergoes colonoscopy. Many people sleep through the whole procedure and feel little or no discomfort. Occasionally, the insertion of air during the procedure may cause the same kind of discomfort as gas pain.

If a polyp is found, removal through the colonoscope may be sufficient, although surgery may be recommended for some patients.

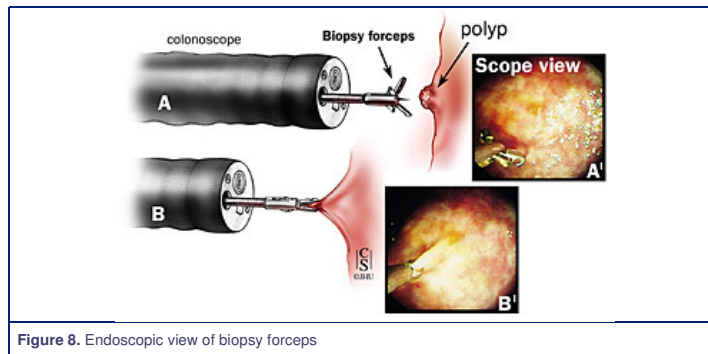


Figure 8. Endoscopic view of biopsy forceps

Barium Enema

A barium enema x-ray is a radiologic examination of the rectum and the entire colon. Prior to a barium x-ray, the patient may have to undergo a preparation that includes a liquid diet, enema or laxative to clear stool from the colon. This preparation may differ from exam to exam and from one doctor to another. Before having this exam, a barium preparation (a contrast material) is administered through a rectal tube. This contrast material outlines the colon. The test allows the colon to be visualized when the x-ray picture is taken. If polyps or cancer is present, it can usually be seen on the x-ray (Figure 9).

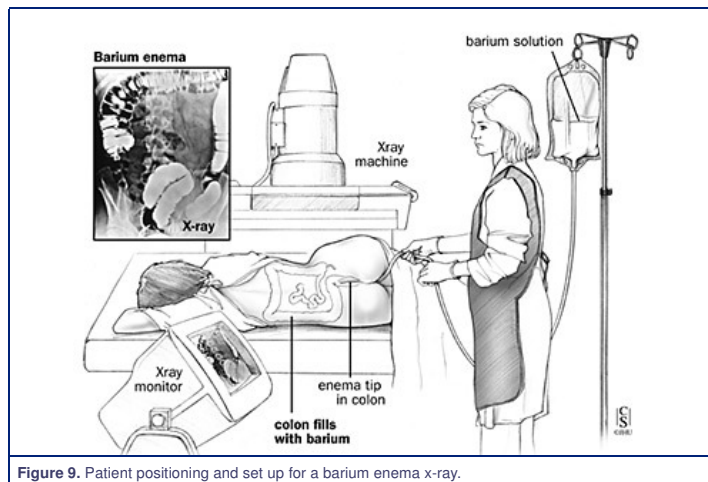


Figure 9. Patient positioning and set up for a barium enema x-ray.

The barium enema feels similar to an ordinary enema causing a feeling of fullness. This test should not be performed on pregnant women because of the risk of x-rays (radiation) to the fetus.

APCI1307K: Therapy

Overview

If cancer is found at examination, the doctor will recommend colorectal surgery. The amount of colon removed will depend upon the stage of the cancer as well as the age, overall health, and desires of the patient with respect to weighing potential changes in bowel function and risk of further cancer formation. Genetic and surgical counseling is encouraged.