

PEARL



The Pancreas Education and Research Letter

Genetic Links to Chronic Pancreatitis

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Discovery of the hereditary pancreatitis gene by Dr. Whitcomb's group in 1996 highlighted the significance of genetic mutations in the cause of all types of acute and chronic pancreatitis. Over the past few years, a number of new genetic mutations have been identified by research teams from around the world. Some of these genetic mutations may be of general importance because the findings have been confirmed by other scientists evaluating patients in other countries. Genes with mutations that clearly increase the risk for acute and chronic pancreatitis are listed in **Table 1**. It is likely that the list will continue to grow as teams of physicians and scientists work together to find answers to what causes pancreatitis.

What have we learned from these studies?

The first thing we learned is that acute and chronic pancreatitis are linked. In fact, all of the genes that cause chronic pancreatitis seem to do so by first causing *acute* pancreatitis. Acute pancreatitis is inflammation caused by a pancreatic injury. Genetic studies suggest the digestive enzyme *trypsin* is the culprit in causing pancreatic injury. Unlike things that can injure organs and tissue directly (like the sun causing skin injury or aspirin tablets injuring the lining of the stomach), the pancreas is injured by a molecule it makes in an inactive form, which is *trypsinogen*. Inactive trypsinogen is safe, but under extreme circumstances it can change into the active enzyme trypsin. This change happens in less extreme conditions in people who are prone to developing recurrent acute and chronic pancreatitis.

What does trypsin do?

Trypsinogen is the inactive form of trypsin. Trypsin represents one of the most important molecules made by the pancreas for the digestion of food, especially meat. Normally, the pancreas squirts trypsinogen from the pancreas into the intestine to mix with food where trypsinogen is activated into trypsin. Digestion occurs when the powerful enzyme trypsin cuts dietary proteins into the small fragments that eventually become amino acids. The amino acids are absorbed from the intestine into blood circulation, travel to muscles and other tissues, and are then reassembled into new proteins. Digestion is why

people who eat meat do not have pieces of hamburger floating around in their blood after a meal – just amino acids. The process is like breaking down an old building into bricks, transporting the bricks to a new location, and building a new and better building. Trypsin plays another valuable role as the master switch that turns on almost all of the other digestive enzymes, in order for other nutrients in a meal to be digested.

How is the pancreas protected from trypsin?

While in the pancreas, trypsinogen is prevented from becoming active. If it does become active as trypsin, then trypsin digests the pancreas itself, causing injury and inflammation. All the genes listed in Table 1 work to prevent trypsinogen from becoming active, or to quickly inactivate trypsin before it causes too much pancreatic damage. Mutations in the trypsinogen gene

Symbol	Common name	Effect Size
PRSS1	Cationic Trypsinogen	Very, very strong
CFTR	Cystic Fibrosis gene	Very strong
SPINK1	Pancreatic secretory trypsin inhibitor	Very strong
CTRC	Chymotrypsin C	Strong
CASR	Calcium Sensing Receptor	Weak

Table 1. Genes that are linked to chronic pancreatitis.

On the Internet:
www.pancreas.org

Toll-Free Phone:
1-888-PITT-DNA
(1-888-748-8362)

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Healthy Eating

One important part of staying healthy is eating well. While ice cream cones, potato chips, and candy may taste good, they are not the healthiest for your body!

Here is a recipe you can try with your parents from Dr. Julia Greer in her recent cookbook.



Cocoa Crunch Berry Parfait

This is one of my very favorite desserts. It is light and healthy, with the sweet and crunchy flavor combination of berries and wheat germ. Strawberries or blackberries can be substituted for the raspberries for variation.

Ingredients:

- 2 cups fresh raspberries, plus 12 fresh raspberries*
- 2 tablespoons sugar, divided
- 2 cups (16 ounces) plain low-fat yogurt
- 2 tablespoons unprocessed cocoa powder
- 1-1/2 tablespoons wheat germ*

*This recipe's ellagic acid (raspberries) and vitamin E (wheat germ) may help prevent pancreas and colon cancers.

Preparation: In a medium bowl, place 2 cups raspberries and sprinkle with 1 tablespoon sugar; stir until sugar is evenly distributed. In a separate medium bowl, whisk together yogurt, cocoa powder and remaining tablespoon of sugar until creamy. In four 8-ounce parfait glasses, spoon alternating layers of yogurt, raspberries and wheat germ, until 3 layers are formed, ending with yogurt. Top each parfait with 3 fresh raspberries. Makes 4 parfaits.

Nutritional information per parfait:

Calories: 131.7
 Fat: 2.5 g
 Saturated fat: 1.5 g
 Carbohydrate: 19.4 g
 Total sugars: 15.8 g
 Protein: 7.9 g
 Sodium: 86 mg
 Cholesterol: 7.4 mg



"The Anti-Cancer Cookbook: How to Cut Your Risk with the Most Powerful, Cancer-Fighting Foods" by Dr. Julia Greer is available from Sunrise River Press.

PAGER Study: Thanks for your Help!

Thank you to everyone who has participated in our Pancreatic Adenocarcinoma Gene-Environment Risk (PAGER) study. We encourage you to complete and return your questionnaire if you have not already done so. If you have misplaced your questionnaire, please call our toll-free phone number **1-888-PITT-DNA** for a new copy. We appreciate your participation in this important research.

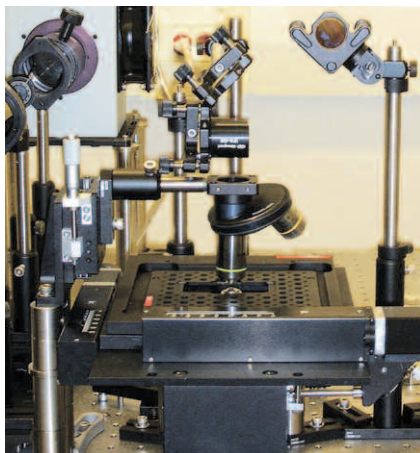
We continue to enroll individuals in our PAGER study. We are currently seeking individuals to participate in a study of familial pancreatic cancer who either:

- Have had at least two relatives diagnosed with pancreatic cancer or
- Have themselves been diagnosed with pancreatic cancer and have had at least one relative who has been diagnosed with pancreatic cancer.
- Participation includes completing a questionnaire and providing a blood sample. Right now, we are seeking individuals who are able to visit one of our Pittsburgh locations for a blood draw (UPMC Presbyterian, UPMC Shadyside, or UPMC Hillman Cancer Center). If you are interested in participating, please call our toll-free phone number **1-888-PITT-DNA**. Other sites are planned in the future.

If you wish to be a partner of the PAGER study through financial gifts of any amount, checks may be payable to the University of Pittsburgh GI Division (School of Medicine) and sent to 3708 Fifth Avenue, Pittsburgh, PA 15213. Gifts may also be made by credit card by calling (412) 623-4700. Please mention that you would like your gift to support the University of Pittsburgh GI Division (School of Medicine). 100% of your donation will go directly to pancreatic cancer research. Your support is greatly appreciated by all of us who are dedicated to the prevention and cure of pancreatic cancer. ○

Using New Techniques to Study Pancreatic Cancer

Dr. Yang Liu and Dr. Randall Brand are working to develop a less invasive screening test for pancreatic cancer. Research is underway at the University of Pittsburgh where Drs. Brand and Liu are developing novel biophotonic devices (light-based technologies) to analyze single cells and detect structural changes 20 to 50 times smaller than what can be detected by a state-of-the-art microscope. Drs. Liu and Brand have had some promising results in predicting the presence of pancreatic cancer through assessing cells from an easily accessible organ – the duodenum (upper small intestine). Though the research is in an early stage, the hope is that it will lead to developing a minimally invasive tool for the early detection and screening of pancreatic cancer.



Dr. Liu's specialized microscope and camera.

How are samples collected and analyzed?

An endoscope is used to visualize the walls of the esophagus, stomach, and small intestine during an

endoscopy. Using a brush, the physician can collect cells from the wall of the small intestine near the opening of the pancreatic duct. After placing cells onto slides for viewing, Dr. Liu analyzes these cells using a novel optical microscope called a Partial-Wave Spectroscopic (PWS) microscope. A lamp shines white light onto the cells and the light that is scattered from a single cell will be collected and analyzed by the spectrometer, coupled with a highly sensitive camera. These scattering patterns exhibit distinct characteristic features in duodenal cells from patients with pancreatic cancer as compared to patients without cancer (control subjects). Under a conventional microscope, cells from both groups (patients with pancreatic cancer, and controls) would look normal, even to an experienced cytologist.

The work described above is being performed as part of a collaborative effort with Dr. Vadim Backman at Northwestern University. ○

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(*PRSS1*) cause trypsinogen to switch to trypsin too easily, or else they prevent trypsin from being inactivated.

Scientists have learned that **calcium** levels are very important in changing trypsinogen to trypsin, and preventing trypsin from becoming inactive. Mutations in the Calcium Sensing Receptor (*CASR* gene) disrupt the ability of the pancreatic cell to keep calcium at safe levels, and increase the risk of attacks of pancreatitis. The *CTRC* gene makes a protein that inactivates



trypsin. Mutations in this gene can result in damage to the pancreas by active trypsin when the mechanism that deactivates trypsin fails. The *SPINK1* gene makes a very powerful trypsin inhibitor, but *SPINK1* is not made unless there is active inflammation. Mutations in the *SPINK1* gene prevent the pancreas from protecting itself from future episodes of trypsin activation, causing recurrent acute pancreatitis. Finally, mutations in the *CFTR* gene, which also cause cystic fibrosis, slow the movement of trypsinogen out of the pancreas. If the transport of trypsinogen is

delayed, there is an increased risk of conversion to trypsin, triggering attacks of acute pancreatitis.

Conclusions

The work on pancreatitis and pancreatic cancer genetics has led to major breakthroughs in understanding the causes of pancreatic diseases. These data are being used to design new approaches to prevent pancreatic disease, and to limit the severe effects in people who are already experiencing problems. The years and years of hard work of many researchers are finally paying off! ○

Ask Dr. Whitcomb

We keep hearing about genes that are linked to pancreatic cancer. But how many genes exist and what do they mean?



Answer: There are two very different types of genetic mutations that physicians and scientists talk about. The first is called a "germline" (egg or sperm cell) mutation. Every cell in the body contains the germline mutation, because it is part of the DNA code found in each cell. Genetic counselors focus on germline mutations when discussing familial risk, because they are passed from generation to generation.

The second type of gene mutation is called a "somatic" (non-germline) mutation. These mutations are acquired throughout your life, and occur when DNA in a single cell is damaged by a toxin, x-ray, or other

environmental factor. Normally, your body functions to repair these mutations, but when the genes controlling repair and growth are damaged, cells can build up more and more mutations, advancing towards cancer.

A team of scientists recently analyzed somatic mutations in 24 pancreatic cancers. They found that a typical pancreatic cancer has over 63 somatic genetic abnormalities, damaging 12 major processes that regulate normal cells. These changes do not occur all at once, but accumulate over time (50-60 years) until a cell becomes cancerous (reported in the journal *Science* in September 2008).

The bottom line is that germline mutations increase inherited risk; but environmental factors create additional risk by causing new DNA damage that eventually leads to cancer. Understanding the interplay of genes and environmental factors at a deeper level will help us provide targeted therapy and prevention tools for people at risk of pancreatic cancer. ○

Follow-up Questionnaires

Subjects who enrolled in the North American Pancreatitis Study with recurrent acute pancreatitis, chronic pancreatitis and controls will be contacted either by mail, or by the site from which they were referred in the next few months. Please fill out this questionnaire and return it in the stamped and addressed envelope provided. If you have questions, please call 1-888-PITT-DNA. ○

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