Gene Linked to Pancreatic Cancer

By Mike Fillon

A new study found that the ataxia telangiectasia mutated (ATM) gene—a gene linked with breast cancer and suspected in many others—may increase the hereditary risk for pancreatic cancer. According to the study, published in the January 2012 Cancer Discovery, knowledge of the presence of the ATM gene could lead to better screening for pancreatic cancer, the fourth-most-common cause of cancer-related death.

Pancreatic cancer is one of the most lethal cancers, with less than 5% of those diagnosed with the disease surviving 5 years. Lead author Alison Klein, Ph.D., associate professor of oncology at the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins in Baltimore, said that approximately 10% of these cases occur in families with multiple cases of pancreatic cancer. Although the hereditary basis for predisposition in almost all affected families is unknown, she said, substantial reason existed to believe that genetics was responsible for this clustering. “However, until now, researchers had not been able to find the causative genes that explained the cluster of pancreatic cancer” for most of these families, she said. Klein added that the research team identified ATM as a predisposition gene for pancreatic ductal adenocarcinoma.

In the study, genomic DNA from familial pancreatic cancer cases was extracted from peripheral blood lymphocytes or Epstein–Barr virus–transformed peripheral blood lymphocytes. The researchers used next-generation sequencing, including whole-genome and whole-exome analyses, and identified heterozygous, constitutional ATM gene mutations in two relatives with familial pancreatic cancer. Mutations segregated with disease in both kindreds, and tumor analysis demonstrated loss of heterozygosity of the wild-type allele.

Klein said that by using sequence analysis of an additional 166 familial pancreatic cancer probands, she and the other researchers identified four additional patients with deleterious mutations in the ATM gene, whereas they did not identify deleterious mutations in 190 spouse control patients. When they considered

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only the mostly severely affected families with three or more pancreatic cancer cases, the researchers found four deleterious mutations in 87 families. “Our results indicate that inherited ATM mutations play an important role in familial pancreatic cancer predisposition,” said Klein, a genetic epidemiologist with a focus on cancer research. “Our results have important implications for the management of patients in affected families and illustrate the power of genome-wide sequencing to identify the basis of familial cancer syndromes.” Klein is also the director of the National Familial Pancreas Tumor Registry (http://www.nfptr.org), the world’s largest pancreatic cancer family registry.

Because of its central role in cell division and DNA repair, the ATM protein is of interest in cancer research. According to the U.S. National Library of Medicine, the ATM protein assists cells in recognizing damaged or broken DNA strands. Breaks in DNA strands also occur naturally when chromosomes exchange genetic material during cell division and can be damaged by agents such as toxic chemicals or radiation. The ATM protein coordinates DNA repair by activating enzymes that fix the broken strands. Efficient repair of damaged DNA strands helps maintain the stability of the cell’s genetic information.

Cells missing one copy of the ATM gene produce half the normal amount of ATM protein, preventing efficient repair of DNA damage and leading to the accumulation of mutations in other genes. This buildup of mutations is likely to allow cancerous tumors to develop. About 1% of the U.S. population carries one mutated copy of the ATM gene in each cell.

In addition to breast and pancreatic cancer, research suggests that people who carry one mutated copy of the ATM gene in each cell may have an increased risk of developing several other types of cancer. In particular, some studies have shown that cancers of the stomach, bladder, lung, and ovaries occur more often in ATM mutation carriers. To date, study results have been inconclusive.

“I think this study is important, since it connects another breast cancer susceptibility gene to pancreatic cancer,” said Johan de Winter, Ph.D., associate professor in the oncogenetics section of the department of clinical genetics at VU University Medical Center in Amsterdam. “It seems that the pathogenesis of breast and pancreas cancer is similar, maybe because both tissues are composed of ducts from which a tumor can arise, but this is pure speculation.”

De Winter said the studies indicate that double-strand break repair, probably through homologous recombination, is important to prevent genetic changes that contribute to pancreas and breast cancer. However, the rather high carrier frequency for ATM mutations in the general population suggests that other modifier genes also determine the risk for pancreatic cancer in ATM mutation carriers, so it is definitely more than ATM that determines whether a tumor develops. “These tumors that have a defect in ATM or homologous recombination may be treated with specific inhibitors of pathways that are essential for these tumors, and so it is important to know that part of the inherited pancreatic cancers have a defect in ATM.”

Klein said finding ATM’s role—or any other gene’s—for that matter—and a link to pancreatic cancer has been especially challenging. She said researchers usually find high-risk genes by looking at the blood or DNA samples of many affected family members, which is challenging for pancreatic cancer. “Since pancreatic cancer is so rapidly fatal, with most patients dying only months after diagnosis, even if you have families with three or four or even more pancreatic cancer cases, you often can’t get DNA on multiple family members.”

Klein says that no recommended screening tests yet exist for familial pancreatic cancer. “Many doctors use endoscopy as a screening tool for pancreatic cancer, but researchers are still evaluating this technique in clinical trials.”