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## Progress in Search for Genetic Trigger of Pancreatic Cancer

Researchers are reporting progress in the search for a gene mutation that triggers pancreatic cancer, the fifth leading cause of cancer death in the United States. Genetic studies of a family that has a long history of pancreatic cancer have led researchers to a region of chromosome 4 that is the likely location of a gene mutation that causes cancer in members of this family.

Pancreatic cancer is difficult to detect, spreads quickly, and kills almost all affected patients within six months of diagnosis. Of an estimated 29,200 cases of pancreatic cancer diagnosed each year in the United States, 28,900 patients succumb to the disease, usually within four to six months of diagnosis.

Identification of the genomic region, or locus, on chromosome 4 that contains the gene will be published in the April 2002 issue of the *American Journal of Human Genetics*. The research team included Teresa A. Brentnall of the University of Washington Medical Center, Howard Hughes Medical Institute investigator Leonid Kruglyak and Michael Eberle of the Fred Hutchinson Cancer Research Center, David C. Whitcomb and Roland Pfützner of the University of Pittsburgh and the VA Pittsburgh Health Care System.

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One of the keys to finding the gene locus was Family X, whose members have inherited a gene mutation that predisposes them to pancreatic cancer. Brentnall and her colleagues have studied Family X for more than seven

years, observing that the pancreatic cancer usually occurs in members of this family by age 43.

“There have certainly been cases of family clustering of pancreatic cancer,” said Kruglyak. “But this is the largest family yet found where pancreatic cancer segregates in a clearly Mendelian fashion in an autosomal-dominant pattern.” Autosomal dominance occurs when one of the two copies of a gene has a variation that is sufficient for expression of a specific trait.

Pancreatic cancer has also been associated with hereditary predisposition to other cancers -- including some colon and breast cancers and melanomas -- as well as inflammatory pancreatitis. But approximately ten percent of cases of pancreatic cancer are inherited in an autosomal dominant fashion in families like Family X that don't have another disease.

As promising as the study of Family X appeared to be, Kruglyak said that tracking members of the far-flung family, collecting blood samples for analysis and monitoring the family for precancerous signs using endoscopic techniques proved highly challenging. “It has taken a lot of very hard work by Teri Brentnall and her colleagues to trace the complex branches of this family and obtain material for study,” he said.

Kruglyak, who made the decision to study pancreatic cancer after his cousin died of the disease, set out to pinpoint the location of the mutated gene carried by members of Family X. By doing detailed analysis of genomic landmarks, called “microsatellite markers,” that span the entire genomes of family members, Kruglyak and his colleagues identified landmarks that were consistently passed down through the generations along with the gene mutation that conferred a predisposition to pancreatic cancer.

The scientists first analyzed a subset of the family to detect regions of the genome that were consistently inherited together with the disease. That initial study revealed that a region of chromosome 4 showed the best evidence of such “segregation.” The researchers next added more family members and additional markers in the target region, obtaining a highly significant association of inheritance of the chromosome 4 region with the disease.

“We typed all of the available family members for the initial and new markers just in that area, and we got a clear statistical signal, way above chance, that this region cleanly segregated with the disease,” said Kruglyak.

“From these data, it became clear that four generations ago one man with this inherited locus passed the gene it contained on to five of his six sons, all of whom died of pancreatic cancer,” said Kruglyak. “But not before they passed it on to future generations. And critically important, none of the unaffected individuals in the family inherited this locus.”

The discovery of the pancreatic cancer susceptibility locus on chromosome 4 has led to an intense effort to identify the specific gene mutation that causes the disease, said Kruglyak. Identification of the gene should be of immediate benefit to members of Family X because it will enable earlier identification of family members who will develop cancer later in life.

“So far, that’s the only direct impact,” he said. “But we hope that once we pinpoint the gene, its identity will suggest many more research avenues.” For example, he said, spontaneous mutations in the susceptibility gene itself might play a role in triggering sporadic, or non-inherited, pancreatic cancer. Also, identification of the gene might reveal a pathway in which other malfunctions may also cause the sporadic form of the disease. While the existence of such a pancreatic cancer pathway is still speculative, said Kruglyak, the genes involved in such a pathway might be targets for drugs that could prevent pancreatic cancer.