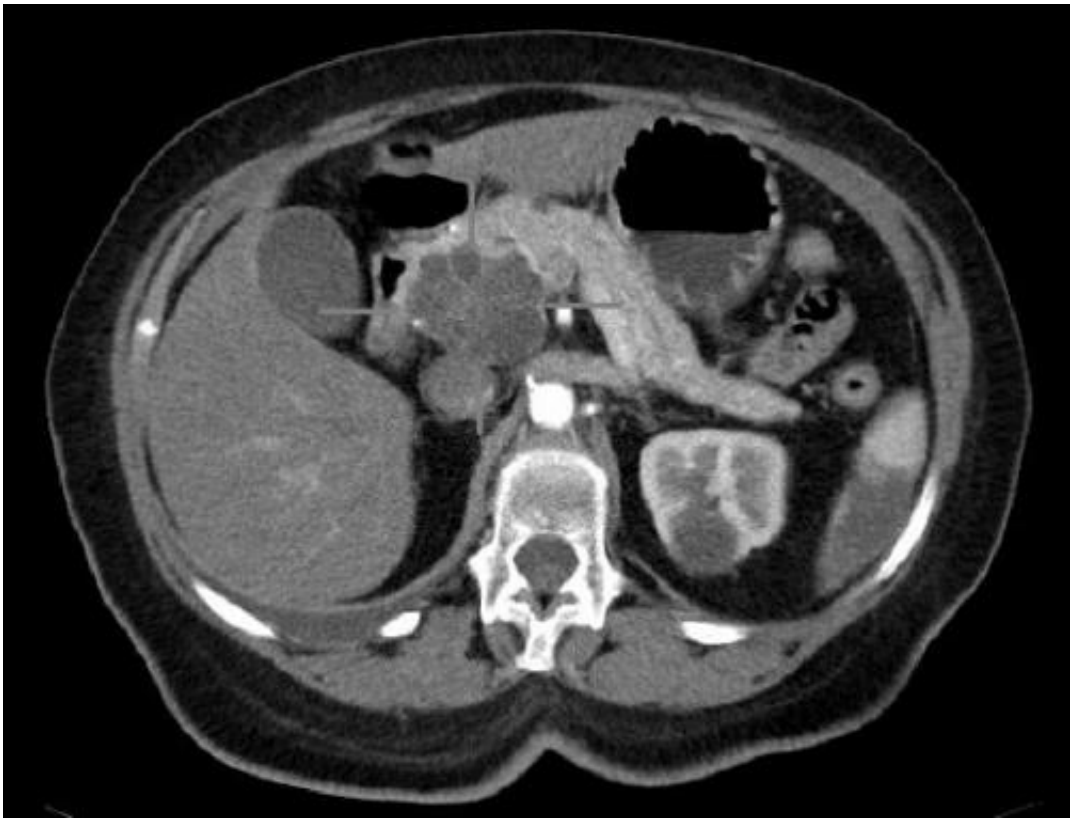
MedicalXpress

Study identifies multiple genetic changes linked to increased pancreatic cancer risk

June 23 2015



Axial CT image with i.v. contrast. Macrocystic adenocarcinoma of the pancreatic head. Credit: public domain

In a genome-wide association study believed to be the largest of its kind, Johns Hopkins researchers have uncovered four regions in the human genome where changes may increase the risk of pancreatic cancer.

The researchers say newly identified genetic variants are located at several positions on human chromosomes, including position 17q25.1, which may increase cancer risk by 38 percent for each copy that is present in the genome; position 7p13, which may increase the risk by 12 percent; and position 3q29, which may increase the risk by 16 percent. Position 2p13.3, another genetic region pinpointed in the study, was previously linked with pancreatic cancer risk in a study of Han Chinese people, and the current study provides more definitive evidence of different genetic changes in that region believed to increase pancreatic cancer risk by 14 percent.

"These variants are common in the population, and most individuals who have these variants will never develop pancreatic cancer in their lifetime," cautions Alison Klein, Ph.D., associate professor of oncology at the Johns Hopkins University School of Medicine. "However, identifying and understanding these changes can lead to a better understanding of why some people develop pancreatic cancer. If we combine this information with data on other pancreatic cancer risk factors, we may be able to identify and one day screen high-risk groups."

Further studies of the function of these genetic regions are already underway, Klein says, but several appear related to DNA repair, cell growth and tumor suppression.

Results of the genomic analysis, published online June 22 in *Nature Genetics* by Klein and her colleagues, included genetic information from 9,925 patients with pancreatic cancer and 11,569 healthy individuals. Some of the samples were newly genotyped, and others were analyzed in a so-called meta-analysis of already published data. The newly-genotyped blood samples were obtained from eight medical centers in North America, central Europe and Australia, and took four years to collect and analyze.

Klein, a member of the Johns Hopkins Kimmel Cancer Center and Sol Goldman Pancreatic Cancer Research Center, says the study also confirms the connection between pancreatic cancer risk and several genetic variants linked to other cancers. For instance, the scientists noted a connection between pancreatic cancer risk and variation in the TP63 gene, and other studies have suggested the TP63 variations also are related to lung and bladder cancers, among others.

"We knew there were more genetic variants to be found, and the large number of pancreatic cancers in the current analysis gave our study more power to find more novel genes," she says.

Pancreatic cancer is the fourth leading cause of cancer death in the United States, but it is not as commonly diagnosed as other cancers, such as breast or colorectal cancers. Patients with pancreatic cancer are also often diagnosed at late stages of the disease, making it tougher to identify genetic risk factors, says Klein.

Klein noted that for some of the new and previously reported variants identified by comparing the genomes of patients with pancreatic cancer and healthy people, scientists cannot say how or why they have an impact on pancreatic cancer. "Sometimes the variation doesn't have an effect on the gene it's in or near, but it could have a more distant target. We need further studies to learn how the increased risk arises."

Because smoking is a well-established risk factor for many cancers, the researchers also re-examined the changes in nine of the new and previously discovered genetic regions in smokers and nonsmokers. They found no evidence that smoking impacted the link between those particular variants and pancreatic cancer risk. She emphasized that this does not mean there is no increased risk among smokers, but that these changes are equally important in both smokers and non-smokers.

Klein and colleagues hope to increase the number of pancreatic cancer cases in future genome-wide association studies and include patients from other geographic regions, such as Asia. "While this study increases our understanding of the genetic basis of pancreatic cancer, we do know from our analysis that there are lots of other variants we need to find to fully understand it," says Klein.

The ultimate goal of these genetic studies, says Klein, is to pinpoint the causes of pancreatic cancer, helping scientists develop better treatment and early detection screening for the disease, which has only a 5 to 7 percent survival rate five years after diagnosis. Currently, these new variants are not included in any genetic screening of healthy individuals, but the aim, Klein says, is to identify high-risk populations.

"If we can identify high-risk populations, we can eventually get to the point where we can detect pancreatic cancer early, when the disease is most treatable, and save lives," Klein notes.

More information: Crystal structure of human stearoyl–coenzyme A desaturase in complex with substrate, *Nature Genetics*, DOI: 10.1038/nsmb.3049

Provided by Johns Hopkins University School of Medicine