Five novel genetic changes linked to pancreatic cancer risk

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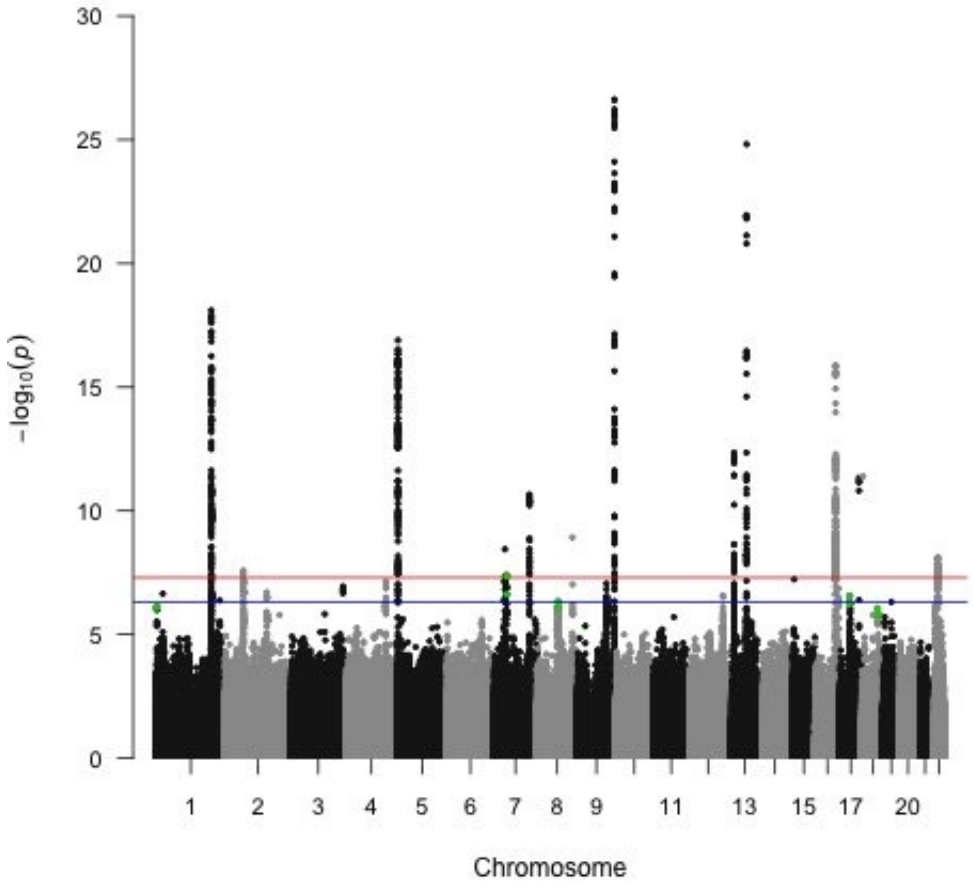

A Manhattan plot of the study results show taller peaks that denote genetic loci most significantly associated with pancreatic cancer risk. Green dots show the location of the new loci reported in this paper. Credit: Alison Klein, Ph.D., M.H.S.

In what is believed to be the largest pancreatic cancer genome-wide association study to date, researchers at the Johns Hopkins Kimmel Cancer Center and the National Cancer Institute, and collaborators from over 80 other institutions worldwide discovered changes to five new regions in the human genome that may increase the risk of pancreatic cancer.

The new findings represent one more step toward fully capturing all of the genetic changes that lead to pancreatic cancer risk. This is important because a better understanding of how pancreatic cancer develops could lead to more targeted treatments and methods of early detection screening, the researchers say. Pancreatic cancer is among the leading causes of cancer death in the U.S. and Europe and is expected to result in nearly 150,000 annual deaths by 2020.

The newly identified genetic variants—located on human chromosomes 1 (position 1p36.33), 7 (position 7p12), 8 (position 8q21.11), 17 (position 17q12) and 18 (position 18q21.32)—may increase the risk of pancreatic cancer by 15 to 25 percent for each copy present in the genome, says Alison Klein, Ph.D., M.H.S., the study leader and a member of the Sol Goldman Pancreatic Cancer Research Center at Johns Hopkins. The group previously reported 17 variants in 13 genetic regions.

The findings, published online Feb. 8 in *Nature Communications*, included genetic information from 9,040 pancreatic cancer patients and 12,946 healthy individuals of European ancestry from the Pancreatic Cancer Cohort Consortium (PanScan) and the Pancreatic Cancer Case-Control Consortium (PanC4). The scientists analyzed more than 11.3 million variants in 21,536 people.

"On an individual level, having one of these variants isn't very predictive of cancer, in that they're only associated with a modest change in risk,

but when taken together, they help to create the fuller picture of how pancreatic cancer develops," says Klein, professor of oncology, pathology and epidemiology.

One of the new variants was found in NOC2L, a protein that binds directly to the tumor protein p53, a major driver gene in pancreatic cancer, Klein says. It also binds with another tumor suppressor gene called p63, and in previous work Klein and colleagues identified that variants in p63 gene are associated with increased pancreatic cancer risk. Variants in the HNF4G and HNF1B genes—called hepatocyte growth factors that are involved in the regulation of cell growth—have been shown to play a role in regulation of the pancreas and in the development of cancer. Variation in HNF1B has also been linked to maturity onset diabetes of the young, a familial form of diabetes that develops in people age 25 or younger, Klein says.

The additional variants were found near the GRP gene, which is involved in the release of gastrointestinal hormones, and on TNS3, a gene involved with the regulation of cell adhesion and migration and possibly metastasis.

Pancreatic cancer is the third leading cause of cancer-related deaths in the United States and the fifth leading cause in Europe. Though deadly, incidence of the cancer is relatively rare, with about 55,000 new diagnoses each year in the U.S., so large-scale research collaborations such as this study are needed to generate sufficient data for study, Klein says.

Continuing studies will delve deeper into the genetics of pancreatic cancer, Klein says: "There is still a lot more that we don't know about hereditary factors in pancreatic cancer risk."

More information: Alison P. Klein et al. Genome-wide meta-analysis

identifies five new susceptibility loci for pancreatic cancer, *Nature Communications* (2018). DOI: 10.1038/s41467-018-02942-5