OMICS Group Conferences
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International Conference on
Functional and Comparative Genomics & Pharmacogenomics

November 12-14, 2013 DoubleTree by Hilton Hotel Chicago-North Shore, IL, USA

Pancreatic cancer genetics: Fine-mapping and functional characterization of the chr5p15.33/ CLPTM1L/TERT risk locus

Laufey Amundadottir
National Cancer Institute, USA

Pancreatic cancer is the fourth leading cause of cancer deaths in the US. Through genome wide association studies (GWAS), we have identified multiple loci that significantly associate with risk of pancreatic cancer in individuals of European ancestry. One of these lies in a region on chromosome 5p15.33 that harbors the *TERT* and *CLPTM1L* genes, the former encoding the catalytic subunit of telomerase reverse transcriptase and the latter, which may play a role in apoptosis. This region has been identified in GWAS of at least nine cancers. To investigate the complex genetic architecture of this region, we have performed imputation and an agnostic subset based meta-analysis across 11 GWAS scans including 6 distinct cancers in over 60,000 subjects. We identified six independent risk loci in this region, five in the *TERT* gene and one in the neighboring *CLPTM1L* gene. Between 3-5 cancers mapped to each of the loci, with effects in both directions. Furthermore, we have investigated the *CLPTM1L* gene and its encoded protein and revealed a positive effect on growth *in vitro* and *in vivo* indicating a possible role in carcinogenesis. This effect was abrogated by deletion mutants of predicted functional domains of the protein. Through a proteomics screen we have identified protein partners for *CLPTM1L* and shown that it may play a role in cytokinesis. Our results provide strong support for extensive pleiotropy across this region of 5p15.33, at a level not previously observed in other cancer susceptibility loci and indicate that *CLPTM1L* may play a role in cancer.

Biography

Laufey Amundadottir completed her Ph.D. from Georgetown University and postdoctoral studies from Harvard Medical School. She was the head of the Division of Cancer Genetics at deCODE genetics in Iceland before joining the NCI where she is an investigator in the Laboratory of Translational Genomics. Her work focuses on genome wide association studies in pancreatic and prostate cancer, fine-mapping and functional characterization of plausible causal variants in order to understand how common sequence variation plays a role in the development of cancer. She has published more than 40 papers in reputed journals and is a leading member of the Pancreatic Cancer Cohort Consortium, PanScan.

amundadottirl@mail.nih.gov