A Large-scale SNP Evaluation Reveals an Association of a TSC2 SNP with Sporadic Neuroendocrine Tumor Risk

Monica Ter-Minassian, Zhaoxi Wang, Kofi Asomaning, Michael Wu, Chen-Yu Liu, Jessica Paulus, Geoffrey Liu, Penny Bradbury, Li Su, Christine Frauenhoffer, Susanne M. Hooshmand, Jamie Silver, Immaculata De Vivo, Xihong Lin, David C. Christiani, Matthew H. Kulke

Environmental and Occupational Medicine and Epidemiology (EOME) Program, Department of Environmental Health, Department of Biostatistics, Harvard School of Public Health; Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA

Background: Neuroendocrine tumors (NET) are rare hormone-secreting cancers arising primarily in the gastrointestinal and respiratory tracts. We performed a case-control analysis with a large scale assessment of common single nucleotide polymorphisms (SNPs) in known cancer genes to evaluate their potential association with neuroendocrine tumor risk.

Methods: We evaluated 261 neuroendocrine tumor cases and 319 controls (N= 580, Caucasian), all obtained from Dana-Farber/Harvard Cancer Center Institutions. 1334 tagging and functional SNPs in 354 known cancer genes were evaluated after genotyping with the Illumina BeadArray platform. The associations were evaluated using multiple logistic regression, after adjusting for age, gender, and smoking status, with the dominant model and test for trend and the Benjamini-Hochberg false discovery rate (FDR) multiple testing correction.

Results: The neuroendocrine tumor cases comprised 55 patients with pancreatic neuroendocrine tumor and 207 patients with carcinoid tumors, of whom 91 had primary small bowel carcinoid. Thirty-seven SNPs in 19 genes were associated (after covariate adjustment) with overall NET risk at p<0.01, under either model. The top 3 genes were TSC2, IL1RN and CYP1B1. After multiple testing adjustment, only the TSC2 synonymous SNP rs13337626, Phe860Phe, remained significant for all cases at PFDR-dominant =0.0005 and PFDR-trend=0.004. The TSC2 association was significant in the subgroup of small bowel carcinoids, where the PFDR-dominant =0.001 and PFDR-trend=0.01, but not in the subgroup of pancreatic neuroendocrine tumor.

Conclusion: Genetic variation in TSC2, and potentially in other genes, may be associated with neuroendocrine tumor risk.