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

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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.