B9

Genetic Associations with Sporadic Neuroendocrine Tumor Risk

Monica Ter-Minassian[1,6], Zhaoxi Wang[1], Kofi Asomaning[1], Michael C. Wu[3], Chen-Yu Liu[1], Jessica K. Paulus[2], Geoffrey Liu[5], Penelope A. Bradbury[5], Rihong Zhai[1], Li Su[1], Christine S. Frauenhoffer[6], Susanne M. Hooshmand[6], Immaculata DeVivo[2], Xihong Lin[3], David C. Christiani[1,2,4], Matthew H. Kulke[6]

[1]Environmental and Occupational Medicine and Epidemiology Program, Department of Environmental Health, Harvard School of Public Health, Boston, MA 02115; [2]Department of Epidemiology, Harvard School of Public Health, Boston, MA 02115; [3]Department of Biostatistics, Harvard School of Public Health, Boston, MA 02115; [4]Massachusetts General Hospital, Harvard Medical School, Boston, MA 02115; [5]Princess Margaret Hospital, Ontario Cancer Institute, Toronto, ON M5G 2C1, Canada; [6]Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA 02115.

BACKGROUND: Genetic risk factors for sporadic neuroendocrine tumors (NET) remain poorly understood. To identify single nucleotide polymorphisms (SNPs) associated with NET risk, we performed a large-scale assessment of common SNPs in candidate genes in independent discovery and replication sets of incident and prevalent Caucasian NET cases and controls.

METHODS: We designed a custom array containing 1536 tagging and functional SNPs in 355 candidate genes implicated in established cancer pathways. We tested risk associations using multiple logistic regression, adjusting for age and gender and smoking, with dominant and additive models in a 261 NET case and 319 control discovery set. We then evaluated the top associated SNPs in a 235 case and 113 control replication set. We also evaluated associations in subgroups of small bowel carcinoid and pancreatic NET.

RESULTS: The discovery phase revealed that 18 SNPs were associated with NET risk at a p-value<0.01, meeting the criterion for replication. Two of these SNPs were also found to be significantly associated with NET risk in our independent replication set at a p-value <0.05. *IL12A* rs2243123 replicated with an adjusted odd ratio (95%CI) (aOR) = 1.47 (1.03, 2.11) p-trend=0.036. *DAD1* rs8005354 replicated at aOR= 1.43 (1.02, 2.02) p-trend= 0.04. In a combined analysis of 181 small bowel

cases or 99 pancreatic NET vs. 432 controls, *IL12A* rs2243123 was associated with both small bowel and pancreatic NET, and *DAD1* rs8005354 only with small bowel NET.

CONCLUSIONS: Our findings suggest that variation in *IL12A* and *DAD1*, genes involved in inflammation and apoptosis respectively, is associated with NET risk.