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Rare germline variants in MEN1, TSC1, ATM, and MSH2 are associated with higher risk of pancreatic neuroendocrine tumors

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BACKGROUND

Pancreatic neuroendocrine tumors (pNETs) comprise ~2% of all pancreatic malignancies, with pancreatic ductal adenocarcinoma (PDAC) being the most common type. The etiology of pNET is poorly understood, including an incomplete understanding of the heritable genetic factors. We investigated whether genes associated with PDAC susceptibility also predispose to pNET. We further verified associations for genes implicated in pNET development from smaller studies by performing the largest study to date on pNETs.

METHODS

We used a case-control design involving 842 pathologically confirmed incident pNET cases from the Mayo Clinic Biospecimen Resource for Pancreas Research and 52,760 control patients without pancreas cancer from the Mayo Clinic Biobank. Whole-exome sequencing was performed using germline DNA obtained from the participants. We evaluated eleven candidate genes known to be associated with *PDAC (APC, ATM, BRCA1, BRCA2, CDKN2A, MLH1, MSH2, MSH6, PALB2, PMS2, STK11, TP53)* and another six genes implicated in pNET (*MEN1, MEN2/RET, NF1, TSC1, TSC2, VHL*). We classified rare variants (minor allele frequency < 0.001) in these genes as pathogenic or likely pathogenic (P/LP) based on the American College of Medical Genetics and Genomics and the Association for Molecular Pathology consensus guidelines. Unconditional logistic regression was used to calculate odds ratios (ORs) and 95% confidence intervals (CIs), adjusting for age, sex, and the top two principal components of genetic ancestry. We computed two-tailed p-values using gene-burden test with SKAT-O, adjusting for multiple comparisons.

RESULTS

Germline P/LP variant carrier frequency was higher in the pNET cases (10%) than in the control patients (3%). We found a higher risk of pNET in patients who carry a P/LP variant in *MEN1* (OR = 56.7, 95% CI: 34.0-94.6, p = 5.0 x 10-38), *TSC2* (OR = 62.9, 95% CI: 12.7-312.0, p = 3.6 x 10-5), *ATM* (OR = 2.6, 95% CI: 1.7-4.0, p = 0.0001), or *MSH2* (OR = 9.0, 95% CI: 2.7-30.2, p = 0.002). No other significant association was observed.

CONCLUSIONS

Our results show that germline P/LP variants in *MEN1, TSC2, ATM*, and MSH2 are associated with a higher risk of pNET. We did not find significant associations for *APC, BRCA1, BRCA2, CDKN2A, MLH1, MSH6, PALB2, PMS2, STK11, TP53, MEN2/RET, NF1, TSC1, or VHL*. These findings are important for genetic risk assessment, genetic counseling, early detection of pNET through screening in genetically defined high-risk patients and might inform therapy selection for certain patients. Genetic testing of all pNET patients would be necessary for familial risk assessment.

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