

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

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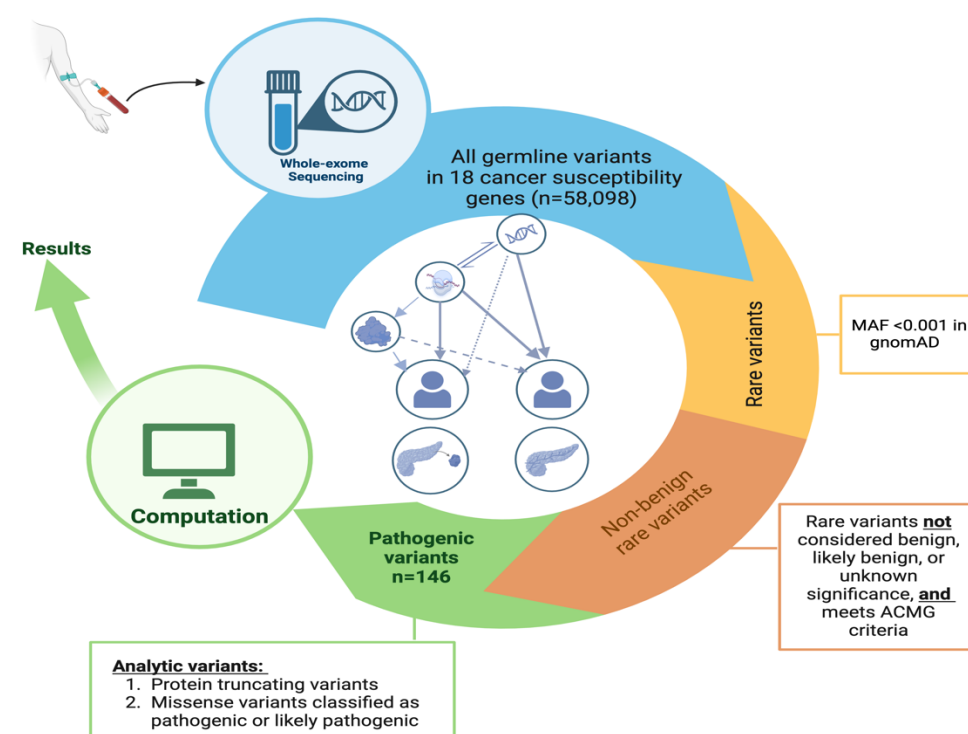
BACKGROUND & OBJECTIVES

- Pancreatic neuroendocrine tumors (pNETs) constitute ~2% of all pancreatic cancers and are the second most common type of pancreatic cancer.^{1,2}
- Unlike the more common pancreatic ductal adenocarcinoma (PDAC), constituting 90-95% of cases, genetic risk factors of pNET are poorly understood.^{2,3,4}
- To improve understanding of the genetic predisposition to pNET, we performed the largest case-control study to date to investigate whether:
 1. Rare pathogenic germline variants in PDAC susceptibility genes predispose to pNET.
 2. Genes implicated in pNET development from smaller studies are truly associated with pNET.

METHODS

- Design: A case-control study of 842 pathologically confirmed incident pNET cases and 52,760 controls without pancreatic cancer, recruited at the Mayo Clinic
- Whole-exome sequencing performed on germline DNA
- Rare pathogenic or likely pathogenic (P/LP) variants were identified using the American College of Medical Genetics and Genomics (ACMG) guidelines for 12 PDAC susceptibility genes (*APC*, *ATM*, *BRCA1*, *BRCA2*, *CDKN2A*, *MLH1*, *MSH2*, *MSH6*, *PALB2*, *PMS2*, *STK11*, *TP53*) and another 6 genes implicated in pNET (*MEN1*, *MEN2/RET*, *NF1*, *TSC1*, *TSC2*, *VHL*).
- Statistical analysis: Logistic regression was used, adjusting for age, sex, and top four principal components. Odds ratios (ORs), 95% confidence intervals (CIs), and p-values were computed using gene-burden test with Robust SKAT-O. Bonferroni correction was used to adjust for multiple testing.

WORKFLOW FOR IDENTIFYING P/LP VARIANTS



RESULTS

TABLE 1. DESCRIPTIVE STATISTICS OF STUDY PARTICIPANTS

	Case n=842	Control n=52760	Total n=53602
Age at Recruitment			
Mean (SD)	59.4 (12.6)	60.0 (15.4)	59.9 (15.3)
Q1, Q3	51.0, 68.0	51.0, 71.0	51.0, 71.0
Sex			
Male	462 (54.9%)	21730 (41.2%)	22192 (41.4%)
Ethnicity			
Non-Hispanic White	814 (96.7%)	50943 (96.6%)	51757 (96.6%)
Non-Hispanic Black	9 (1.1%)	608 (1.2%)	617 (1.2%)
American Indian/Alaska Native	4 (0.5%)	143 (0.3%)	147 (0.3%)
Native Hawaiian/Pacific Islander	0 (0.0%)	9 (0.0%)	9 (0.0%)
Non-Hispanic Asian	8 (1.0%)	569 (1.1%)	577 (1.1%)
Other	7 (0.8%)	488 (0.9%)	495 (0.9%)
BMI at Enrollment			
Mean (SD)	28.5 (5.6)	28.8 (6.0)	28.8 (6.0)
Q1, Q3	24.4, 31.7	24.6, 32.1	24.6, 32.1
Current Smoking Status			
Never	472 (57.1%)	30403 (58.2%)	30875 (58.2%)
Current	46 (5.6%)	2556 (4.9%)	2602 (4.9%)
Former	309 (37.4%)	19295 (36.9%)	19604 (36.9%)
Missing	15	506	521
Type 2 Diabetes	186 (24.4%)	9359 (17.7%)	9545 (17.8%)
Personal Hx. of Breast Cancer	24 (2.9%)	2913 (5.6%)	2937 (5.6%)
Personal Hx. of Ovarian Cancer	5 (0.6%)	321 (0.6%)	326 (0.6%)
Personal Hx. of Colorectal Cancer	11 (1.3%)	742 (1.4%)	753 (1.4%)
Personal Hx. of Other Cancer	148 (17.6%)	8957 (17.2%)	9105 (17.2%)
FDR of Pancreas Cancer	57 (7.2%)	2100 (4.4%)	2157 (4.4%)

Abbreviations: FDR, first-degree relative; Hx., history

TABLE 2. ASSOCIATION BETWEEN RARE PATHOGENIC GERMLINE VARIANTS AND RISK OF PNET

Gene	Cases n=842		Controls n=52760		Association Results	
	P/LP variants	Carrier Freq., %	P/LP variants	Carrier Freq., %	OR (95% CI)	Adjusted p-value ^a
<i>MEN1</i>	28	3.325	32	0.061	56.7 (34.0-94.6)	3.6E-38
<i>TSC2</i>	3	0.356	3	0.006	62.9 (12.7-312.0)	3.8E-05
<i>ATM</i>	24	2.850	581	1.101	2.6 (1.7-4.0)	1.1E-04
<i>MSH2</i>	3	0.356	21	0.040	9.0 (2.7-30.2)	0.0026
<i>MLH1</i>	3	0.356	31	0.059	6.1 (1.8-19.9)	0.0047
<i>VHL</i>	5	0.594	87	0.594	3.6 (1.5-8.9)	0.0107
<i>MEN2/RET</i>	3	0.356	46	0.356	4.1 (1.3-13.2)	0.0297
<i>MSH6</i>	2	0.238	54	0.238	2.3 (0.6-9.5)	0.0792
<i>CDKN2A</i>	1	0.119	18	0.119	1.3 (0.4-4.2)	0.1248
<i>BRCA1</i>	3	0.356	140	0.356	2.1 (0.5-8.7)	0.1507
<i>PALB2</i>	2	0.238	59	0.238	3.5 (0.5-26.1)	0.1598
<i>APC</i>	3	0.356	106	0.356	1.8 (0.6-5.6)	0.3854
<i>BRCA2</i>	4	0.475	204	0.475	1.2 (0.5-3.3)	0.6806
<i>PMS2</i>	1	0.119	88	0.119	0.7 (0.1-5.1)	0.9035

^aAdjusted for age, sex, and top four principal components of genetic ancestry

OTHER FINDINGS

- P/LP variants carrier frequency was 10% in cases and 3% in controls.
- Variants in these genes were not found in cases:
 - *TP53* (case n=0, control n=29)
 - *NF1* (case n=0, control n=19)
 - *TSC1* (case n=0, control n=1)
 - *STK11* (case n=0, control n=0)

CONCLUSIONS

- We have performed the largest study to date on genetic risk assessment for pNET, examining associations for 18 cancer susceptibility genes.
 - We found that pNET cases had a higher frequency of germline P/LP variants in these genes than did the control patients.
 - Our study establishes *MEN1*, *TSC2*, *ATM*, and *MSH2* as pNET predisposition genes, as carriers of a P/LP variant in the genes had a higher risk of pNET.
 - We did not find associations for these genes: *APC*, *BRCA1*, *BRCA2*, *CDKN2A*, *MLH1*, *MSH6*, *PALB2*, *PMS2*, *STK11*, *TP53*, *MEN2/RET*, *NF1*, *TSC1*, and *VHL*.
- The findings are important for identifying individuals genetically susceptible to pNET for genetic counseling and closer surveillance toward early cancer detection.
 - Our findings may also have implications for therapy selection for patients who carry pathogenic germline variants in certain genes and might respond better to targeted treatment based on their genetic background. This is an important goal for future research.
 - Currently, there are no recommendations for germline genetic testing for all pNET patients, but this might be necessary for identifying high-risk families for screening to enhance early detection.

REFERENCES

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