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Novel pathogenic germline variants (PGV) identified in pancreatic neuroendocrine neoplasm (PNEN) patients during genetic testing

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BACKGROUND

Poor outcomes in pancreatic cancer are in part due to the inability to identify patients with early-stage disease. Prevention strategies have focused on identifying high risk patients through genetic susceptibility genes associated with the development of pancreatic cancer. Invitae® initiated The Detect Hereditary Pancreatic Cancer program through which patients diagnosed with pancreatic ductal adenocarcinoma (PDAC) or pancreatic neuroendocrine neoplasm (PNEN) were offered no charge genetic testing. Approximately 10% of PNENs are due to germline mutations often as part of an inherited genetic syndrome. Here we report the incidence of pathogenic germline variants (PGVs) in PNEN patients enrolled in the program.

METHODS

Patients diagnosed with PDAC or PNEN seen at Cedars-Sinai and underwent genetic testing between 9/5/2019 and 2/15/2022 with either the Invitae® Common Hereditary Cancers Panel (42-47 genes) or Multi-Cancer Panel (80-84 genes) with the option to add on genes associated with chronic pancreatitis (CFTR, CASR, CTRC, CPA1, PRSS1, SPINK1) were identified. Demographic data including age, gender, ancestry, family history and cancer stage were collected and assessed retrospectively. The incidence of PGVs in PNEN patients was evaluated.

RESULTS

A total of 129 PNEN patients (median age, 58 years; 47.3% female; 75.4% white; 81.3% with family history of cancer; 52.8% stage IV) had germline testing performed. PGVs were found in 14.7% (19/129) of PNEN. The pancreatitis panel was added to 39 PNEN and PGVs in these genes were detected in 7.7% (3/39) of PNEN. CFTR alterations, identified in 5.1% (2/39) of PNEN, were the most common pancreatitis-associated gene in which PGVs were found in PNEN. Alterations in MUTYH, associated with polyposis syndrome, were the most frequently detected in PNEN (3.9%, 5/129) and were less prevalent in PDAC (1.8%, 21/1203). DNA or base repair PGVs were found in 7% (9/129) of PNEN.

Prevalence of PGVs in PNEN

	Variable	PNEN (N=129)
Patients with PGVs		19 (14.7%)
Pancreatitis gene PGVs (N=39)	CFTR	2 (5.1%)
	PRSS1	1 (2.6%)
DNA/Base Repair gene PGVs (N=129)	ATM	1 (0.8%)
	CHEK2	1 (0.8%)
	FANCA	1 (0.8%)
	MUTYH	5 (3.9%)
	RAD50	1 (0.8%)

All PGVs identified are monoallelic.

CONCLUSIONS

PGVs in PNENs were more common than previously reported. This suggests that germline testing for pancreatic NENs may play a role in standard of care management of these patients. Although biallelic loss of MUTYH is associated with colorectal polyposis and risk of colorectal cancer, this study suggests further evaluation into monoallelic pathogenic MUTYH alterations as a potential risk factor for PNEN.

ABSTRACT ID 28488