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 were identified.
- Genetic testing could be

  Invitae® Common Hereditary Cancers Panel (42-47 genes)

  OR Invitae® Multi-Cancer Panel (80-84 genes)

  with the option to add on genes associated with chronic pancreatitis

  CFTR CASR CTRC CPA1 PRSS1 SPINK1

- Demographic data were collected and assessed retrospectively.

  Age Gender Ancestry Family history Cancer stage

- The incidence of PGVs in PDAC and 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.

Table 1. Incidence of pathogenic germline variants (PGVs) of interest in PDAC, PNEN

	PDAC (N=1203)	PNEN (N=129)	p value
Germline PV	245 (20.4%)	19 (14.7%)	0.12
# mutated genes			0.46
1	218 (18.1%)	18 (14.0%)	
2/3	27 (2.3%)	1 (0.8%)	
CFTR	53 (11.9%)	2 (5.1%)	0.30
BRCA2	29 (2.4%)	0 (0.0%)	0.10
ATM	28 (2.3%)	1 (0.8%)	0.35
MUTYH	21 (1.8%)	5 (3.9%)	0.10
CHEK2	20 (1.7%)	1 (0.8%)	0.71
Pancreatitis genes	66 (14.8%)	3 (7.7%)	0.22
CFTR	53 (11.9%)	2 (5.1%)	
SPINK1	8 (1.8%)	0 (0.0%)	
CTRC	5 (1.1%)	0 (0.0%)	
PRSS1	1 (0.2%)	1 (2.6%)	
DNA Repair genes	80 (6.7%)	3 (2.3%)	0.05
BRCA2	29 (2.4%)	0 (0.0%)	
CHEK2	20 (1.7%)	1 (0.8%)	
BRIP1	9 (0.8%)	0 (0.0%)	
BRCA1	7 (0.6%)	0 (0.0%)	
PALB2	7 (0.6%)	0 (0.0%)	
FANCC	4 (0.4%)	0 (0.0%)	
BARD1	2 (0.2%)	0 (0.0%)	
RAD50	2 (0.2%)	1 (0.8%)	
RAD51C	1 (0.1%)	0 (0.0%)	
FANCA	0 (0.0%)	1 (11.1%)	

All PGVs identified are monoallelic.

Conclusion

- 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.

References

1. Rahib L, Smith BD, Aizenberg R, Rosenzweig AB, Fleshman JM, Matrisian LM. Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. Cancer Res 2014;74:2913-21.
2. American Cancer Society. Cancer Facts & Figures 2022. Atlanta: American Cancer Society; 2022.
3. Hu C, Hart SN, Polley EC, et al. Association Between Inherited Germline Mutations in Cancer Predisposition Genes and Risk of Pancreatic Cancer. Jama 2018;319:2401-9.
4. Salo-Mullen EE, O'Reilly EM, Kelsen DP, et al. Identification of germline genetic mutations in patients with pancreatic cancer. Cancer 2015;121:4382-8.
5. Yin L, Wei J, Lu Z, et al. Prevalence of Germline Sequence Variations Among Patients With Pancreatic Cancer in China. JAMA Netw Open 2022;5:e2148721.
6. Hefferon TW, Groman JD, Yurk CE, Cutting GR. A variable dinucleotide repeat in the CFTR gene contributes to phenotype diversity by forming RNA secondary structures that alter splicing. Proc Natl Acad Sci U S A 2004;101:3504-9.
7. Muller N, Sarantitis I, Rouanet M, et al. Natural history of SPINK1 germline mutation related-pancreatitis. EBioMedicine 2019;48:581-91.
8. McWilliams R, Highsmith WE, Rabe KG, et al. Cystic fibrosis transmembrane regulator gene carrier status is a risk factor for young onset pancreatic adenocarcinoma. Gut 2005;54:1661-2.
9. Neglia JP, FitzSimmons SC, Maisonneuve P, et al. The risk of cancer among patients with cystic fibrosis. Cystic Fibrosis and Cancer Study Group. N Engl J Med 1995;332:494-9.
10. Robinson PS, Thomas LE, Abascal F, et al. Inherited MUTYH mutations cause elevated somatic mutation rates and distinctive mutational signatures in normal human cells. Nature Communications 2022;13:3949.