Mutation Spectrum Identified by Germline Testing in a Pancreatic Cancer Cohort

Carmelina Heydrich, Cynthia L. Neben, Anjali Zimmer, Robert O'Connor, Jack Ji, Alicia Y. Zhou
Color Genomics, Burlingame, CA

Introduction

Pancreatic cancer accounts for an approximately 7% of all cancer-related deaths in the United States and has been associated with several hereditary cancer syndromes. Recent studies have estimated that between 4% and 11% of pancreatic cancer patients carry a germline pathogenic variant associated with increased risk for hereditary cancer[1,2]. The discrepancy in frequency of pathogenic variants between these two studies is likely due to differences in cohort size, ethnic background, and/or selection criteria[3]. To further investigate the frequency and spectrum of pathogenic variants found in pancreatic cancer patients, we studied a cohort of individuals with a personal history of pancreatic cancer who were referred for multi-gene next generation sequencing panel testing for hereditary cancer risk. Here, we describe the demographics and results obtained from these 107 individuals who received the Color Hereditary Cancer Test. We also present three case studies of individuals who carry pathogenic variants associated with hereditary pancreatic cancer risk, including one individual who would not have met the current recommendations for genetic testing provided by the National Comprehensive Cancer Network (NCCN).

Methods

All individuals were referred by physician order for the Color Hereditary Cancer Test which analyzes 30 genes in which pathogenic variants have been associated with increased risk for hereditary breast, ovarian, uterine/endometrial, colorectal, melanoma, pancreatic, prostate, and stomach cancer (*APC, ATM, BAP1, BARD1, BMPR1A, BRCA1, BRCA2, BRIP1, CDH1, CDK4, CDKN2A* (p14ARF and p16INK4a), *CHEK2, EPCAM, GREM1, MITF, MLH1, MSH2, MSH6, MUTYH, NBN, PALB2, PMS2, POLD1, POLE, PTEN, RAD51C, RAD51D, SMAD4, STK11,* and *TP53*). The majority of these genes were assessed for variants within all coding exons and non-canonical splice regions. Laboratory procedures were performed at the Color laboratory under CLIA and CAP compliance.

Variants were classified according to the American College of Medical Genetics and Genomics 2015 guidelines for sequence variant interpretation[4], and all variant classifications were approved by an American Board of Medical Genetics and Genomics board certified medical geneticist. Pathogenic and likely pathogenic (hereafter referred to as pathogenic) variants were confirmed by an orthogonal technology (Sanger sequencing, aCGH, or MLPA). Ethnicity assignments and personal history of cancer were based on self-reported information.

Conclusions

- Of the 7 *BRCA1* and *BRCA2* carriers identified in our cohort, one individual (14.3%) would not have met current recommendations for genetic testing provided by the NCCN.
- Excluding alleles not closely associated with pancreatic cancer, the overall frequency of pathogenic variants in the cohort was 10.3% (11/107).
- This frequency of pathogenic variants of 10.3% exceeds the often cited 10% desired diagnostic yield for genetic testing[5,6].
- Further testing of a larger number of individuals with a history of pancreatic cancer is warranted to identify genes associated with pancreatic cancer risk and determine the most appropriate testing guidelines to identify pathogenic variant carriers.

Results

Table 1. Cohort demographic details

The majority of individuals who received the Color Hereditary Cancer Test were over age 50 years and of Caucasian ethnic background. PV, pathogenic variant.

		Individuals (n)	Population	Individuals w/ PV (n)	Pathogenic Frequency
Total		107	100.0%	18	16.8%
Gender	Female	58	54.2%	12	20.7%
	Male	49	45.8%	6	12.2%
Age (Years)	31-40	4	3.7%	1	25.0%
	41-50	11	10.3%	2	18.2%
	51-65	33	30.8%	5	15.2%
	65+	59	55.1%	10	16.9%
Ethnicity	Caucasian	63	58.9%	12	19.0%
	Ashkenazi Jewish	20	18.7%	2	10.0%
	Asian	6	5.6%	1	16.7%
	Hispanic	5	4.7%	1	20.0%
	Multiple Ethnicities	3	2.8%	1	33.3%
	African	1	0.9%	1	100.0%
	Unknown	9	8.4%	1	11.1%

Figure 1. Pathogenic variant spectrum

Pathogenic variants were most frequently found in genes that have been previously associated with increased risk of hereditary pancreatic cancer (61.1%, 11/18; blue bars).

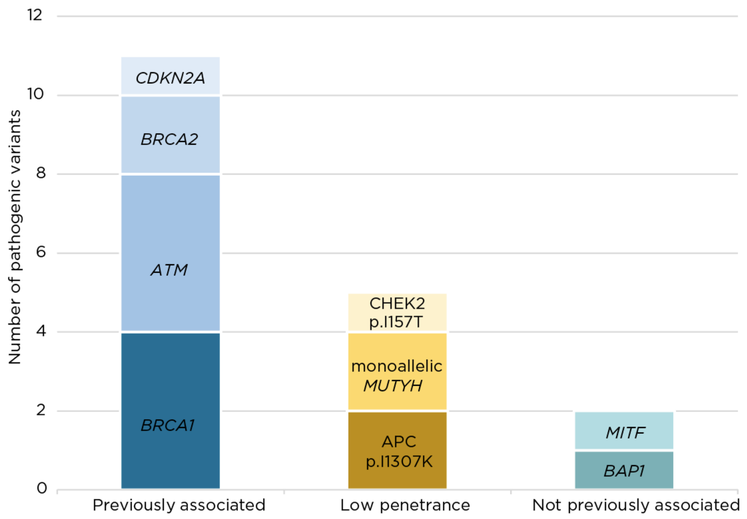


Figure 2. Pedigree of an individual with a *BRCA1* pathogenic variant

The proband is a 50-year-old female who was diagnosed with pancreatic cancer (Pan) at age 49 years. She was found to carry the pathogenic variant *BRCA1* c.181T>G (p.Cys61Gly). Pathogenic variants in *BRCA1* are associated with an increased risk of breast, ovarian, prostate, and pancreatic cancer. She would not have met current NCCN criteria for testing due to a lack of family history of cancer.

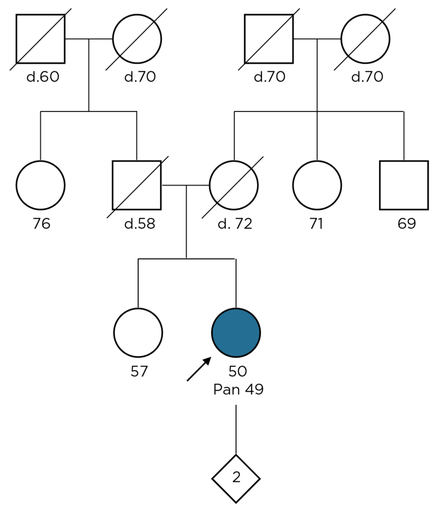


Figure 3. Pedigree of an individual with an *ATM* pathogenic variant

The proband is a 72-year-old female who was diagnosed with pancreatic cancer (Pan) at age 69 years. She was found to carry the pathogenic variant *ATM* c.4098_4099delTG (p.Cys1366*). Pathogenic variants in *ATM* are associated with an increased risk of female breast cancer (Br), pancreatic cancer, and prostate cancer (Pro).

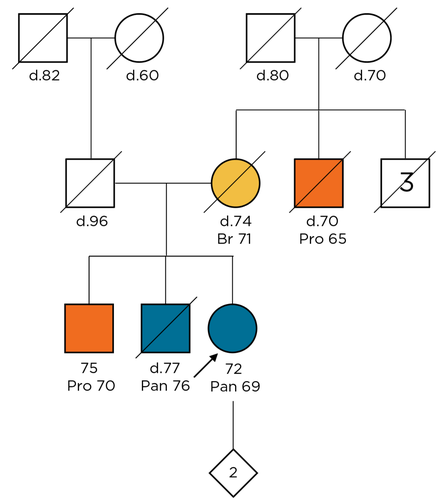
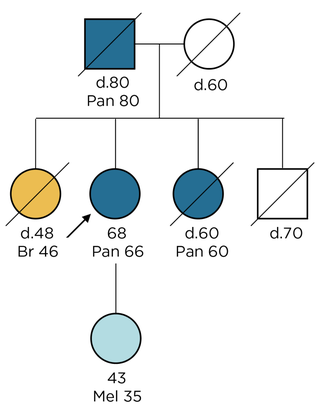


Figure 4. Pedigree of an individual with a *CDKN2A* likely pathogenic variant

The proband is a 68-year-old female who was diagnosed with pancreatic cancer (Pan) at age 66 years. She was found to carry the likely pathogenic variant *CDKN2A* c.176T>G (p.Val59Gly). Pathogenic variants in *CDKN2A* are associated with an increased risk of melanoma (Mel) and pancreatic cancer. Br, breast cancer.



References

[1] Shindo K, Yu J, Suenaga M, et al. Deleterious Germline Mutations in Patients With Apparently Sporadic Pancreatic Adenocarcinoma. *J Clin Oncol*. 2017;35(30):3382-3390.

[2] Peters MLB, Brand R, Borazanci EH, et al. Germline genetic testing in unselected pancreatic ductal adenocarcinoma (PDAC) patients. *J Clin Orthod*. 2017;35(15_suppl):1501-1501.

[3] Yurgelun MB. Germline Testing for Individuals With Pancreatic Cancer: The Benefits and Challenges to Casting a Wider Net. *J Clin Oncol*. 2017;35(30):3375-3377.

[4] Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med*. 2015;17(5):405-424.

[5] Vergote I, Banerjee S, Gerdes A-M, et al. Current perspectives on recommendations for BRCA genetic testing in ovarian cancer patients. *Eur J Cancer*. 2016;69:127-134.

[6] Bednar EM, Oakley HD, Sun CC, et al. A universal genetic testing initiative for patients with high-grade, non-mucinous epithelial ovarian cancer and the implications for cancer treatment. *Gynecol Oncol*. 2017;146(2):399-404.