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The spectrum of genetic variants in hereditary pancreatic cancer includes Fanconi anemia genes

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Abstract

Approximately 5–10% of all pancreatic cancer patients carry a predisposing mutation in a known susceptibility gene. Since >90% of patients present with late stage disease, it is crucial to identify high risk individuals who may be amenable to early detection or other prevention. To explore the spectrum of hereditary pancreatic cancer susceptibility, we evaluated germline DNA from pancreatic cancer participants (n= 53) from a large hereditary cancer registry. For those without a

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflicts of interest.

ETHICAL APPROVAL

All procedure performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

INFORMED CONSENT

Informed consent was obtained from all individual participants included in the study.

known predisposition mutation gene (n=49), germline next generation sequencing was completed using targeted capture for 706 candidate genes. We identified 16 of 53 participants (30%) with a pathogenic (P) or likely pathogenic (LP) variant that may be related to their hereditary pancreatic cancer predisposition; seven had mutations in genes associated with well-known cancer syndromes (13%) [*ATM*(2), *BRCA2* (3), *MSH2* (1), *MSH6*(1)]. Many had mutations in Fanconi anemia complex genes [*BRCA2* (3 participants), *FANCF*, *FANCM*]. Eight participants had rare protein truncating variants of uncertain significance with no other P or LP variants. Earlier age of pancreatic cancer diagnosis (57.5 vs 64.8 years) was indicative of possessing a P or LP variant, as was cancer family history (p-values <0.0001). Our multigene panel approach for identifying known cancer predisposing genetic susceptibility in those at risk for hereditary pancreatic cancer may have direct applicability to clinical practice in cases with mutations in actionable genes. Future pancreatic cancer predisposition studies should include evaluation of the Fanconi anemia genes.

Keywords

pancreatic cancer; germline; hereditary; susceptibility; *BRCA2*

INTRODUCTION

The Projected burden of pancreatic cancer in 2016 is 53,070 new cases and 41,780 deaths in the United States [1]. Only 7.7% of individuals will be expected to survive five years [1]. The significant mortality rate is due to limitations in effective screening and detection, with resultant late stage diagnoses. It is thus crucial to have clinical tools that identify individuals at high risk and who may be amenable to early detection strategies or other preventative measures.

Approximately 5–10% of all pancreatic cancers are due to a known specific hereditary cancer syndrome [2,3]. Hereditary cancer susceptibility syndromes such as Familial Atypical Multiple Mole Melanoma (*CDKN2A*), Hereditary Breast and Ovarian Cancer (HBOC; *BRCA1*, *BRCA2*), Lynch Syndrome (*MLH1*, *MSH2*, *MSH6*, *PMS2*, *EPCAM*), hereditary pancreatitis (*PRSS1*, *SPINK1*), Peutz-Jeghers (*STK11*), von Hippel-Lindau (*VHL*), and *ATM* and *PALB2*-related cancer syndromes, all predispose individuals to pancreatic cancer [4,5].

Currently, there is limited consensus to guide genetic counseling and gene selection in genetic cancer risk assessment for those with a personal and/or family history of pancreatic cancer. The prevailing clinical guidelines include those from the genetic/familial high-risk assessment for breast and ovarian cancer from the National Comprehensive Cancer Network (NCCN) [6]. However, the referral guidelines place pancreatic cancer in the context of testing for HBOC due to *BRCA1* or *BRCA2* mutations, and only ambiguously address susceptibility from other genetic etiologies.

Our goal was to determine the type and frequency of germline variants in patients with pancreatic cancer who were enrolled to a large hereditary cancer research registry; the

Clinical Cancer Genomics Cancer Research Network (CCGCRN) registry. We identified mutations in known cancer predisposition genes and candidate susceptibility genes.

MATERIALS AND METHODS

Setting

Since 1996, probands and their family members at risk for hereditary cancers have been recruited into a prospective human subjects Institutional Review Board (IRB; COH IRB# 96144) approved cancer genetics registry through City of Hope Comprehensive Cancer Center (COH) and a collaborative network of 48 community-based practices across the United States and Latin America [7,8] (Figure 1, Supplementary Table 1). Those enrolled in the >16,000 participant CCGCRN registry, were enrolled to explore hereditary cancer predisposition, largely in the context of genetic cancer risk assessment. The most common referrals are for hereditary predisposition to breast, ovarian, or colorectal cancer. A personal history of pancreatic cancer is much rarer referral indication and comprised less than 0.01% of registry participants at the time of study selection. Each participant is given the option to provide a DNA sample, complete baseline and follow-up questionnaires, and allow for future re-contact and return of actionable research findings that can be used for commercial laboratory validation. A major administrative, data coordinating, and laboratory infrastructure, including a HIPAA-compliant database, has been developed at COH to house the clinical data and biospecimens. Lab specimens include blood, serum, plasma, white blood cells, DNA, and tumor samples.

Case accrual and selection

Individuals enrolled prior to May 17, 2016 with a history of pancreatic cancer were retrospectively selected for study. Those with pancreatic ductal adenocarcinomas were included. Individuals with neuroendocrine or mixed endocrine tumors were excluded. Pathology was missing from a subset of tumors, they were still considered pancreatic ductal adenocarcinomas as other histologies are rare [9]. Participants with previously identified pathogenic or likely pathogenic results were excluded from sequencing but were included in the overall analyses (n = 4; see Results). Extracted blood or saliva DNA from participants without prior clinical testing, or with uninformative testing were selected and sequenced (n = 49) (Table 1). See Supplementary Table 1 for the list of institutions within the CCGCRN and the enrollment site origin of the participants for the study.

Sequencing

For preparing the sequencing libraries, we used KAPA Hyper Preparation Kits (Kapa Biosystems, Inc., Wilmington, MA) and hybridized bar-coded samples to a custom Agilent SureSelect (Santa Clara, CA) targeted 706 gene capture kit with full exon coverage for candidate hereditary cancer susceptibility genes involved in DNA repair and damage response, cell cycle regulation, apoptosis, and the Fanconi anemia, mTOR, JAK-STAT, and RAS-MAPK pathways (gene list provided in Supplemental Table 2). Genes included candidate genes with little, unclear, or no known hereditary cancer susceptibility, known pancreatic susceptibility genes (e.g., *BRCA2*, *PALB2*, *CDKN2A*), and tumor suppressor and oncogenes frequently mutated in pancreatic tumors from the Catalog of Somatic Mutations

in Cancer (COSMIC) database. The panel included both the 5' and 3' untranslated regions as well as sequencing extending 10 base pairs into all of the introns.

Each sample was assigned a 6-digit DNA barcode sequence and linked to a unique patient identifier. 100 base-pair paired-end sequencing on the HiSEQ 2500 Genetic Analyzer (Illumina Inc., San Diego, CA) was performed in the COH Integrative Genomics Core (IGC) to an average fold coverage of 100x. Paired-end reads from each sample were aligned to human reference genome (hg19) using the Burrows-Wheeler Alignment Tool (BWA, v0.7.5a-r405) under default settings, the aligned binary format sequence (BAM) files were sorted and indexed using SAMtools [10,11]. The sorted and indexed BAMs were then processed by Picard MarkDuplicates (<http://broadinstitute.github.io/picard/>) to remove duplicate sequencing reads. Following local realignment of reads around in-frame insertions and deletions (indels) and base quality score recalibration by The Genome Analysis Toolkit (GATK), GATK HaplotypeCaller was utilized to call variants.

Variant calling

Variant call format files were evaluated using Ingenuity Variant Analysis (IVA) version 4 (Qiagen Inc, Alameda, CA). IVA used the following content versions: Ingenuity Knowledge Base (Hogwarts 160211.000), the Human Gene Mutation Database (HGMD, 2015.4), the Catalogue of Somatic Mutations in Cancer (COSMIC, v75) [12], dbSNP Build 146 (12/04/2015) [13], 1000 Genome Frequency (v5b) [14], Exome Variant Server (EVS, ESP6500SI-V2) [15], JASPAR (2010) [16], PhyloP hg18 and hg19 (11/2009) [17,18], Vista Enhancer hg18 and hg19 [19], CGI Genomes (08/2012) [20], Sorting Intolerant from Tolerant (SIFT, 01/2013) [21], bidirectional SIFT (BSIFT, 01/2013) [21], The Cancer Genome Atlas (TCGA, 09/05/2013) [22], PolyPhen-2 (v2.2.2, 2012) [23], Clinvar (01/04/2016), Allele Frequency Community (01/09/2016), and the Exome Aggregation Consortium [24] data set (ExAC, release0.3). In brief, variants with a call quality less than 20, read depth of less than 10, allele fraction ratio less than 40% or over 60%, or alleles with a frequency greater than 3% in the 1000 genomes project, National Heart, Lung, and Blood Institute (NHLBI) Exome Sequencing Project (ESP) exome, or ExAC databases were excluded.

American College of Medical Genetics and Genomics (ACMG) guidelines were applied to remaining variants using the ACMG calling algorithm in IVA [25]. IVA categorizes variants based on standard ACMG variant calling recommendations (i.e., PVS1, BS2, etc.) by searching available databases and literature for known information for each particular variant in addition to running in silico models as described above. All ACMG-called pathogenic (P) or likely pathogenic (LP) variants, as well as the remaining frameshift or nonsense variants, or variants that disrupt a splice site up to two bases into the intron, were individually evaluated by the research team using the available literature and ClinVar to make a final call [26]. The team included a member who was board certified in Molecular Diagnostics through the American Board of Clinical Chemistry (TPS). Homopolymer variants or poor quality presumed to be sequencing errors were excluded.

Data Analyses

Participants with P and LP variants from Table 2 were compared to participants without P or LP variants for the age of pancreatic cancer diagnosis and first and second degree cancer family history; family histories of non-melanoma skin cancer and cervical cancer were excluded. Those with only protein truncating variants of uncertain significance (PTVUS) (see Table 2) were excluded from the analyses. Due to small sample numbers, 1000 bootstrap repetitions were completed (SAS software, Cary, NC) for statistical analyses. The age of pancreatic cancer diagnosis comparison was completed using the T-test. The family history comparison was completed using a Chi-Square test. A p-value <0.05 was considered statistically significant. Pathway analysis for sequenced genes was completed using IVA version 4 (Qiagen Inc, Alameda, CA), which accesses the Ingenuity Knowledge Base.

RESULTS

Participants with no, or previously uninformative genetic testing

Forty-nine participants with no prior germline testing (n=15; 31%) or past uninformative testing (n=34; 69%) were sequenced and analyzed. Results of their ACMGG [25] P, LP, or remaining PTVUS are shown in Table 2. Four variants were frameshift/nonsense/splicing mutations in the last exon. Three of these were listed as PTVUS (*WRN*, p.R1406*; *RNF6*, p.R661*; *POLN*, p.S883fs). One was listed as a LP variant *LIG4*, p.I712fs*5 as nonsense mutations distally have been described as pathogenic in CLINVAR (i.e., *LIG4*, p.R814 [26]*). The average ExAC frequency for all variants reported in this study was 0.12%, the variant identified in *CARD6* had the highest frequency at 1.97%.

Of note, three participants (Table 2, highlighted in gray, without the notation ¥ after the participant number) were identified with mutations in actionable cancer predisposition genes that could impact clinical care for the patient and/or family members. We are in process of contacting the patients with the ATM p.R248fs*6 and BRCA2 p.S1982fs*22 variants so updated genetic counseling and Clinical Laboratory Improvement Amendments (CLIA)-lab validation may be completed [27]. The individual with the BRCA2p.K2162fs*5 variant had CLIA testing completed in the interim confirming the identified research finding. Poly ADP-ribose polymerase (PARP) inhibitor therapy for her advanced pancreatic cancer is now being considered by her treating oncologist.

Participants with previously identified pathogenic or likely pathogenic results

Four participants in the dataset had previously been identified with P or LP variants from clinical testing. These included two diagnosed with Lynch syndrome (*MSH2* and *MSH6*), one with HBOC syndrome (*BRCA2*), and one with an ATM mutation [Tables 1 and 2].

Significant clinical characteristics

Our study cohort was ethnically diverse, with 11% Hispanic and 9% Asian representation. Nearly all participants had a family history of cancer in a first or second degree family member (83%; see Table 1). Twenty-three families met criteria for familial pancreatic cancer (FPC) (43% of the cohort) (Table 1). FPC kindreds were defined as those with at least one pair of first-degree relatives with pancreatic adenocarcinoma (or presumed adenocarcinoma)

[28]. Therefore, all participants with a first-degree relative with pancreatic cancer in this study met criteria for familial pancreatic cancer (Table 1). One other participant in the study had two relatives with pancreatic cancer who were first-degree relatives of one another.

Participants with a P or LP variant had a younger mean age of pancreatic cancer diagnosis than those without a P or LP variant (57.5 vs 64.8 years, p-value <0.0001). Having a family history of cancer was associated with having a P or LP variant (p-value <0.0001). A family history of pancreatic cancer alone did not show significant association. Those with only PTVUS were excluded from the above analyses.

Pathway analysis

Ten of 54 participants (19%) had P or LP variants in the hereditary breast cancer signaling pathway [*ATM* (x2), *ATR*, *BRCA2* (x3), *FANCF*, *FANCM*, and *RAD50* (x2)]. Multiple variants were found in other pathways (Table 2). These pathways included the: DNA double-strand break repair by non-homologous end joining pathway (*ATM* (x2), *LIG4*, *RAD50* (x2), *WRN*) and the p53 signaling pathway (*ATM* (x2), *ATR*, *PLAG1*, *SCO2*).

Pancreatic adenocarcinoma tumor correlations

We evaluated genes with variants in Table 2, as well as, remaining known Fanconi anemia genes for their mutation profile in pancreatic adenocarcinomas. The 49 gene list included: *ATM*, *ATR*, *BRCA1* (*FANCS*), *BRCA2* (*FANCD1*), *BRIPI* (*FANCI*), *CARD6*, *CDC14A*, *CFTR*, *CLPTMIL*, *DLEC1*, *EME2*, *ERCC4* (*FANCF*), *ERCC6*, *FANCA*, *FANCB*, *FANCC*, *FANCD2*, *FANCE*, *FANCF*, *FANCG*, *FANCI*, *FANCL*, *FANCM*, *LIG4*, *MCM7*, *MSH2*, *MSH6*, *MUC6*, *NEIL1*, *ORC2*, *PALB2* (*FANCN*), *PLAGL1*, *POLN*, *RAD50*, *RAD51* (*FANCR*), *RAD51C* (*FANCO*), *RAD54L*, *RECQL4*, *RNF168*, *RNF6*, *SCO2*, *SLX4* (*FANCP*), *SPINK1*, *UBE2T* (*FANCT*), *WRN*, and *XPA*. Data from 777 pancreatic adenocarcinomas was accessed through www.cbioportal.org (May 22, 2017). Queried data sets included: 1) The Cancer Genome Atlas (TCGA) provisional study [22], 2) University of Texas Southwestern Medical Center [29], 3) Queensland Centre for Medical Genomics [30], and 4) the International Cancer Genome Consortium [31]. Given limited control datasets, RNA expression data was not evaluated. Results showed truncating mutations in all genes except the following, which had missense mutations only: *BRIPI*, *CARD6*, *CDC14A*, *DLEC1*, *ENDOV*, *FANCC*, *FANCF*, *FANCG*, *MCM7*, *NEIL1*, *PLAGL1*, *POLN*, *RAD54L*, *RECQL4*, *RNF6*, *SLX4*, and *WRN*. *ERCC6* and *FANCE* had splicing variants only; *CLPTMIL* and *EME2* had in-frame variants only. No mutations of any kind were identified in the following genes: *FANCI*, *FANCL*, *SCO2*, *SPINK1*, *XPA*, or *RAD51*.

Regarding specific germline variants identified (Table 2), three have been previously seen in neoplasms in the COSMIC database (accessed May 22, 2017). COSMIC evaluates the literature as well as TCGA and notates specific somatic variants that have been found previously across a wide tumor spectrum. The *BRCA2* variant, p.S1982fs*22, identified in the germline of participant 3 (Table 2) with pancreatic adenocarcinoma, also has been previously seen in a pancreatic adenocarcinoma [32]. The *RNF6* variant, p.R661*, identified in participant 14, was previously seen in one large intestine carcinoma sample. The *ERCC6*

variant in participant 24, p.R735*, has been previously reported in a lymphoid neoplasm and a stomach carcinoma.

DISCUSSION

We have detailed the spectrum of germline variants identified in those with pancreatic cancer from a large hereditary cancer cohort. Our results identified 16 of 53 participants (30%) with a P or LP variant. Many of these variants are in genes that previously have not been associated with pancreatic cancer. Therefore, more research will be needed to understand their potential roles in pancreatic cancer predisposition. Of note, seven (13%, Table 2, highlighted in gray) had mutations in actionable cancer predisposition genes. All of the participants with mutations in actionable genes met HBOC NCCN testing criteria or Lynch syndrome Amsterdam II criteria except participant 9 [6,33]. This participant had an *MSH6* mutation associated with Lynch syndrome (Table 2). Although they did not meet testing criteria, their personal history of both colorectal and pancreatic cancer was provocative for Lynch syndrome. All of the participants (or a member of their family) with actionable gene findings have been (n=5), or will be (n=2), notified of their results through genetic counseling as part of the study. Recommendations are to test all first-degree relatives for individualized cancer risk assessments and appropriate management. Unaffected first-degree family members carrying mutations in *BRCA2* have been recommended to consider pancreatic surveillance after the age of 50 years per recent guidelines [34]. Given her current diagnosis and recent advancements in targeted treatment, participant 24 is now being considered for PARP inhibitor therapy [35].

The most significant pathway disrupted by P or LP variants was the hereditary breast cancer signaling pathway which included many Fanconi anemia complex genes: *FANCF*, *FANCM*, and *BRCA2* (*FANCD1*; in 3 participants). The Fanconi anemia family is comprised of 19 genes that encode proteins involved in distinct functional complementation groups (A, B, C, D1, D2, E, F, G, I, J, L, M, N, O, P, Q, R, S, T) [36]. The proteins help control DNA interstrand crosslink sensitivity [36]. Germline homozygous or compound heterozygous mutations in these genes lead to Fanconi anemia, characterized by chromosomal instability and inefficient DNA regulation and repair, leading to bone marrow failure and cancer predisposition in affected individuals [36]. Genes in this pathway have already been strongly linked to cancer predisposition in the carrier state. For instance, heterozygous (haplo-insufficient) *BRCA1*, *BRCA2*, and *PALB2* carriers are well known to be at a substantially increased risk for breast, ovarian, and/or pancreatic cancer [37–39]. A recent publication by Roberts et al., 2016, also found multiple Fanconi anemia protein truncating variant carriers [5 *BRCA2*, 5 *PALB2* (*FANCN*), 3 *FANCC*, 4 *FANCG*, and 3 *FANCM*] out of 638 individuals with familial pancreatic cancer (defined as families with two or more relatives with pancreatic cancer) [40]. Smith et al., 2016 also noted *FANCG* and multiple *FANCL* protein truncating variants in 109 individuals with pancreatic cancer (eight with pancreatic cancer onset < 50 years, and 101 individuals from 85 families with > 2 individuals affected with pancreatic cancer) [41]. Multiple other studies have also reported Fanconi anemia gene mutations in familial pancreatic cancer, young onset pancreatic cancer cases, or in pancreatic tumors [42–46]. A publication by Witkiewicz et al. evaluated the University of Texas Southwestern Medical Center [29] data set and specifically noted that multiple Fanconi

anemia genes were mutated or deleted in relatively high frequency (35%) along with other DNA repair genes in pancreatic adenocarcinomas [29]. This demonstrates the need for further exploration of the role of Fanconi anemia genes in pancreatic cancer susceptibility and tumor progression.

We compared our findings (Table 2) and remaining Fanconi anemia genes to known somatic genetic variants found in pancreatic adenocarcinomas. Twenty-seven out of 49 genes (55%) had truncating variants identified in pancreatic cancer. Not all Fanconi anemia genes had truncating variants in the pancreatic adenocarcinomas examined, or any variants in the case of *FANCI*, *FANCL*, and *RAD51* (*FANCR*). Substantial limitations exist for evaluating this data. In particular, healthy pancreatic control datasets are currently limited. Therefore, RNA-expression analyses could not be completed. Of note, although the *BRCA2* variant, p.S1982fs*22, has been previously identified in a pancreatic adenocarcinoma in the COSMIC database, this is a common *BRCA2* Ashkenazi Jewish mutation, also known as c. 6174delT, and therefore has a high carrier frequency [47]. The participant carrying the mutation in the study herein was Ashkenazi Jewish.

Novel variants with no associated findings in the literature were identified in multiple genes in this study including those in *EME2*, *NEIL1*, *RAD50*, *CLPTMIL*, *ATM*, *SCO2*, *ATR*, *PLAGL1*, *CDC14A*, *MUC6*, *MCM7*, *POLN*, *LIG4*, *RAD54L*, and *ORC2*. All of these variants were nonsense or frameshift variations and the majority were categorized as PTVUS. Family segregation data was available only for participant 11 with the *ORC2* variant. The proband's mother also had pancreatic cancer (diagnosed at age 74). The *ORC2* variant was not identified in the proband's mother, however, the proband's father had small bowel cancer at 50 and a paternal grandfather had pancreatic or colorectal cancer and passed away at age 46. Therefore, *ORC2* should remain a candidate cancer predisposition gene. More research will be necessary to better understand the effect of these variants on protein production and whether they predisposed to pancreatic cancer susceptibility.

No participants in Table 2 were found to have variants in *PALB2*, *CDKN2A*, *STK11*, or *BRCA1*. Mutations in these genes have all been strongly associated with pancreatic cancer predisposition [4]. The absence of variants in these genes in this study is likely due to the low prevalence of variants in these genes in pancreatic cancer susceptibility and the small numbers of participants in our study.

CFTR and *SPINK1* LP variants were found in participants 17 and 22 (Table 2). Both of these participants also had other variants identified (*RNF168*, and *LIG4*). *RNF168* and *LIG4* are associated with rare radiosensitivity associated autosomal recessive disorders, RIDDLE Syndrome and LIG4 syndrome, respectively [48,49]. *LIG4* has been associated with risk for pancreatic cancer in one study [50]. It is unclear if multifactorial effects could be additive, leading to pancreatic cancer susceptibility in these individuals.

Of the PTVUS identified, only homozygous or compound heterozygous mutations in *WRN* (participant 26) have been associated with pancreatic cancer susceptibility in the literature [51]. Werner's Syndrome is an autosomal recessive disorder of accelerated aging caused by gene disruption of *WRN* [51]. The individual was found to only be a carrier for this disorder,

and therefore, it is unclear if monoallelic carriers would be at an increased risk for pancreatic cancer. The same participant also had an *ATRLP* variant. Eight participants had rare allele frequency PTVUS in candidate cancer susceptibility genes with no other P or LP variants identified.

There are multiple limitations to this study that should be considered when evaluating the results. The first limitation is that caution must be taken in correlating findings, particularly in PTVUS, with disease. The small sample size prevented a larger case control analysis that could begin to explore associations. The small sample size was due to infrequent referrals; since there are uneven guidelines regarding which individuals with pancreatic cancer need genetic cancer risk assessment and participants recruited into the CCGCRN registry were largely from unsolicited referrals from oncology practices. The study was therefore biased towards participants with young cancer onset, multiple primary cancers, and/or significant family histories of cancer. Only one enrollment came from outside of the United States (from Colombia; no variants identified), since resources are lacking even for hereditary breast and ovarian cancer syndrome assessments (i.e., *BRCA1*) [52]. Copy number variation and large insertion/deletion analysis using target capture panels through next-generation sequencing technology remains a challenge. Therefore, some participants may have an undetectable large copy number variations or insertion-deletions using our approach. Hereditary susceptibility was studied using a targeted gene panel including known and candidate pancreatic cancer susceptibility genes. Although cost-effective, this limited the extent of discovery. The thousands of non-protein truncating variants of uncertain significance identified in this study (not shown) should also not be discounted as many could be clinically relevant, via a Mendelian single gene model, or as part of multifactorial cancer predisposition.

Regarding the cases of familial pancreatic cancer, only cases enrolled in the research registry had medical record and/or histology report confirmation. Although we do not know of any studies specific to the accuracy of first-degree relative reports of pancreatic cancer family history diagnoses, it has been shown in a general clinic setting that family cancer history of first-degree relatives is fairly reliable for breast (99%), ovarian (100%), prostate (85%), and colorectal cancers (93%) [53]. In our study, only one familial pancreatic cancer was not a first-degree relative.”

In conclusion, using a relatively small hereditary cancer cohort we uncovered multiple variants that may lead to new genotype-phenotype correlations. Our multigene panel approach for identifying known cancer predisposing genetic susceptibility in patients at risk for hereditary pancreatic cancer may have direct applicability to clinical practice in cases with mutations in actionable genes. Future pancreatic cancer genetic epidemiology studies should include evaluation of the hereditary breast cancer signaling pathway and particularly the Fanconi anemia genes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Clinical Cancer Genomics Cancer Research Network Participating Site Locations
 Markers represent Clinical Cancer Genomics Community Research Network participating site locations. See Supplemental Table 1 for a complete site list and site origin for enrolled participants from this study.

Table 1

Clinical characteristics

Characteristic	n (%)
Study participants	
Previous pathogenic or likely pathogenic clinical testing	4
Sequenced	49
Total analyzed in study	53
Gender	
Female	30 (57)
Male	23 (43)
Mean age at pancreatic cancer diagnosis, years	61.8 (range 20-90)
Racial and Ethnic Categories *	
White (Non-Hispanic Caucasian)	41 (77)
Hispanic or Latino	6 (11)
Asian	5 (9)
American Indian	1 (2)
Family history	
First degree relative (FDR) with Pancreatic cancer	22 (42)
More than one FDR with Pancreatic cancer	6 (11)
At least one FDR or second degree relative (SDR) with Pancreatic cancer **	24 (45)
FDR and/or SDR with one or more of the following cancers: breast, colorectal, ovarian, thyroid, uterine, leukemia, sarcoma, and/or pancreatic	44 (83)
Participants with other primary cancers (detailed counts provided below)	17 (32)
Breast (6), Renal (3), Colorectal (2), Prostate (2), Lung (2), Seminoma (1), Bladder (1)	

* Per <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-089.html>,

** 23 of these were Familial Pancreatic Cancer kindreds (see results, significant clinical characteristics).

Table 2

Germline DNA sequencing results for participants with variants identified.

Pt #	Gene	Protein Variant	Call	Variant Impact	1st Diagnosis & Age	2nd Diagnose & Age	3rd Diagnosis & Age	FDR with Pan	SDR with Pan
1	<i>ATM</i>	p.R248fs*6	P	frameshift	Pan	50		1	0
2 [†]	<i>ATM</i>	c.1065+1G>T	LP	Splicing	Lung	53	Pan	0	0
3	<i>BRCA2</i>	p.S1982fs*22	P	frameshift	Pan	57		0	0
4 [†]	<i>BRCA2</i>	p.N1784Hfs	P	frameshift	Pan	66		0	1
5	<i>DLEC1</i>	p.E1605fs*44	PTVUS	frameshift	Pan	58		0	0
6	<i>FANCM</i>	p.R1931*	LP	stop gain	Br	45	Pan	0	0
7	<i>MCM7</i>	p.A74fs*6	PTVUS	frameshift	Bladder	68	Pan	0	0
8 [†]	<i>MSH2</i>	p.N596del	P	in-frame	CRC	57	Pan	1	0
9 [†]	<i>MSH6</i>	p.Y1038*	P	stop gain	CRC	67	Pan	0	0
10	<i>MUC6</i>	p.V2170fe*40	PTVUS	frameshift	Pan	66		2	1
11	<i>ORC2</i>	p.E538*	PTVUS	stop gain	Pan	50		2	0
12	<i>POLN</i>	p.S883fe	PTVUS	frameshift	Pan	59		1	0
13	<i>RAD50</i>	p.M11	LP	missense	Pan	72		1	0
14	<i>RNF6</i>	p.R661*	PTVUS	stop gain	Pan	37		0	0
15	<i>SCO2</i>	p.D252fs	PTVUS	frameshift	Pan	70		1	0
16	<i>XPA</i>	p.H244R	LP	missense	Br	46	Pan	1	0
17	<i>SPINK1</i> <i>LIG4</i>	c.147A>G p.I712fs*5	LP LP	5'UTR error frameshift	Pan	63		0	0
18	<i>FANCF</i> <i>RAD54L</i>	p.L162fs*103 p.Y227*	LP PTVUS	frameshift stop gain	Pan	68		0	0
19	<i>RAD50</i> <i>CLPTMIL</i>	p.V892fs*5 p.Q44*	P PTVUS	frameshift step gain	Br	56	Pan	0	0
20	<i>ATR</i> <i>WRN</i>	p.V1297fs*11 p.R1406*	LP PTVUS	frameshift stop gain	Pan	43		0	0
21	<i>CARD6</i> <i>EME2</i>	p.L30fs*11 p.Q322*	PTVUS PTVUS	frameshift stop gain	Pan	60		0	0
22	<i>CFTR</i> <i>RNF168</i>	p.Q1352H p.R131*	LP P	missense stop gain	Pan	20		0	0

Pt #	Gene	Protein Variant	Call	Variant Impact	1st Diagnosis & Age	2nd Diagnose & Age	3rd Diagnosis & Age	FDR with Pan	SDR with Pan
23	<i>RECOL4</i>	p.Q757*	LP	frameshift	Pan	45		0	0
	<i>CDC14A</i>	p.R376*	PTVUS	stop gain					
	<i>PIAGLI</i>	p.F448*46	PTVUS	stop gain					
24	<i>BRCA2</i>	p.K2162fs*5	P	frameshift	Pan	48		0	0
	<i>ERCC6</i>	p.R735*	P	stop gain					
	<i>NEIL1</i>	p.G25fs*14	PTVUS	frameshift					

Clinically tested positive† participants (Pt). No pathogenic variants (P), likely pathogenic variants (LP), or protein truncating variants of unknown significance (PTVUS) were seen more than once. Gray rows indicate variants in actionable genes. Cancer diagnoses including pancreatic ductal adenocarcinomas (Pan), breast cancer (Br), colorectal cancer (CRC) and first degree relatives (FDR) and second degree relatives (SDR) with pancreatic cancer are shown.