Short Communication

Cancer Epidemiology, Biomarkers & Prevention

Prevalence of Pathogenic Mutations in Cancer Predisposition Genes among Pancreatic Cancer Patients

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Abstract

The prevalence of germline pathogenic mutations in a comprehensive panel of cancer predisposition genes is not well-defined for patients with pancreatic ductal adenocarcinoma (PDAC). To estimate the frequency of mutations in a panel of 22 cancer predisposition genes, 96 patients unselected for a family history of cancer who were recruited to the Mayo Clinic Pancreatic Cancer patient registry over a 12-month period were screened by next-generation sequencing. Fourteen pathogenic mutations in 13 patients (13.5%) were identified in eight genes: four in *ATM*, two in *BRCA2*, *CHEK2*, and *MSH6*, and one in *BARD1*, *BRCA1*, *FANCM*, and *NBN*. These included nine mutations (9.4%) in established pancreatic cancer genes. Three mutations were found in patients with a first-degree relative with PDAC, and 10 mutations were found in patients with first- or second-degree relatives with breast, pancreas, colorectal, ovarian, or endometrial cancers. These results suggest that a substantial proportion of patients with PDAC carry germline mutations in predisposition genes associated with other cancers and that a better understanding of pancreatic cancer risk will depend on evaluation of families with broad constellations of tumors. These findings highlight the need for recommendations governing germline gene-panel testing of patients with pancreatic cancer. *Cancer Epidemiol Biomarkers Prev; 25(1); 207–11. ©2015 AACR.*

Introduction

Pancreatic ductal adenocarcinoma (PDAC), which constitutes the vast majority of pancreatic cancer, has a poor prognosis with an overall 5-year survival rate of 6% (1). In the United States, pancreatic cancer is the fourth most common cause of cancer death (2). Pancreatic cancer is a component of hereditary breast–ovarian cancer syndrome (HBOC; refs. 3, 4), Lynch syndrome (5, 6), familial adenomatous polyposis (7), familial atypical multiple mole melanoma syndrome (8), hereditary pancreatitis (9), Peutz–Jeghers syndrome (10), and Li–Fraumeni syndrome (11). These syndromes have been well-defined in guidelines for care from the National Comprehensive Cancer Network (NCCN). Epidemiologic studies have suggested that 10% to 20% of pancreatic cancers are associated with an inherited component, with familial pancreatic cancer (FPC), defined as kindreds containing at least two affected first-degree relatives, an established entity of inherited disease (12). Although germline studies have focused on single cancer predisposition genes (13), the prevalence of pathogenic mutations in *BRCA1*, *BRCA2*, *PALB2*, and *CDKN2A* has recently been estimated at 8% among patients with FPC and 3.5% among families with less pancreatic cancer history (14). The first panel-based study of 13 cancer predisposition genes among patients with pancreatic cancer identified 11 pathogenic mutations (3.8%) in *ATM*, *BRCA1*, *BRCA2*, *MLH1*, *MSH2*, *MSH6*, and *TP53* (15). Thus, determination of the contributions of predisposition genes to pancreatic cancer has important ramifications for patients and their relatives. Here, we report on mutation screening of 96 patients with PDAC, recruited to the Mayo Clinic pancreatic cancer patient registry over a 12-month period, with a 22-gene panel to determine the prevalence of mutations in these genes.

Materials and Methods

Subjects

Patients with pancreatic cancer were identified at time of first presentation with a possible pancreatic cancer, often prior to a documented diagnosis through pancreatology, surgery, and oncology clinics and consented to a Mayo Clinic Institutional Review Board–approved prospective pancreas patient registry (13). PDAC was confirmed by medical record review and pathologic diagnosis. Patients with other diagnoses or nonadenocarcinoma histologies were excluded. Blood samples, risk factor, family history questionnaires, and access to medical records were requested. Approximately 80% of patients with confirmed PDAC participated in the registry. A sequential series of 96 patients with

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PDAC enrolled between June 1, 2013, and June 1, 2014, was included in this study.

Panel-based mutation analysis

Germline DNA samples underwent custom capture (Agilent eArray) for all coding sequences, intron/exon boundaries, and partial nonrepetitive intronic regions from 21 cancer predisposition genes (*BRCA1*, *BRCA2*, *PALB2*, *ATM*, *BARD1*, *BRIP1*, *RAD51C*, *RAD51D*, *CHEK2*, *MRE11A*, *NBN*, *RAD50*, *MLH1*, *MSH2*, *MSH6*, *PMS2*, *CDH1*, *TP53*, *PTEN*, *STK11*, and *FANCM*). *CDKN2A* was also screened because the gene has been implicated in pancreatic cancer (16). Products from each capture were sequenced on a HiSeq2000 (Illumina) and likely pathogenic variants were validated by Sanger sequencing.

Bioinformatic and data analysis

Paired end reads (100 bp) were aligned to the hg19 reference human genome using Novoalign (Novocraft Technologies). Realignment and recalibration were performed with GATK (https://www.broadinstitute.org/gatk). Germline variants were called with GATK Unified Genotyper. Copy-number variation (CNV) was assessed by "PatternCNV" (17). Coverage was evaluated by Integrative Genomics Viewer (IGV; ref. 18). The χ^2 test, *t* test, and Fisher exact test were used for association studies.

Results

Patient characteristics

Table 1 displays the baseline characteristics of the 96 patients in the study. Ninety-three of 96 (97%) were non-Hispanic white. No patients reported Ashkenazi Jewish ancestry. The mean age of diagnosis of PDAC was 66.7 years (range, 41–90 years), and 53% of patients reported a history of smoking. Of the 96 patients, approximately 5% had a personal history of breast, 2% colorectal, and 2% endometrial cancer, whereas 7% had first-degree relatives with pancreatic cancer and met the criteria for FPC. Another 10% had second-degree relatives with the disease. Breast cancer was observed in first-degree relatives for 14% and first- or second-degree relatives of 21%. Colorectal (8%), ovarian (3%), or endometrial cancers (6%) were also reported among first-degree relatives.

Table 1. Characteristics of 96 patients with pancreatic cancer

Characteristic	(*n* = 96) *N* (%)
Sex	
Male	51 (53)
Female	45 (47)
Race	
White/Caucasian	93 (97)
American Indian/Alaskan Native	1 (1)
Black	1 (1)
Multiracial	1 (1)
Smoking	
Never	33 (47)
Ever	37 (53)
Unknown	26 (27)
Age at diagnosis of pancreatic cancer	
Mean (±SD)	66.7 (±9.9)
Range	41–90
Family history of cancer	
Pancreas	16 (17)
Breast	20 (21)
Personal history of cancer	
No	74 (78)
Yes	21 (22)
Unknown	1 (1)

Inactivating mutations

A total of 14 likely pathogenic mutations were identified and confirmed by Sanger sequencing in 13 patients (14%; Table 2). Two frameshift and two nonsense mutations were detected in *ATM*. Two truncating mutations were observed in *BRCA2*, but the K3326X (c.9976A>T) variant that is associated with a low risk of cancer was excluded (19). One frameshift and one splicing defect were detected in *MSH6*, and two 1100delC mutations were found in *CHEK2*. Protein truncating mutations were also detected in *BRCA1*, *BARD1*, and *FANCM*. Two mutations had not previously been reported (*ATM* c.6012_6013insA and *FANCM* c.2586_2589delAAAA). One patient had mutations in both *NBN* and *CHEK2* (Table 2). Nine of 96 (9%) patients had mutations in established pancreatic cancer predisposition genes. Interestingly, no mutations were identified in the *PALB2* pancreatic cancer susceptibility gene (14). The youngest age at diagnosis for patients with likely pathogenic mutations was 51 years (*BRCA2*: c.6373dupA). There was no difference in mean age at diagnosis between 83 noncarriers [66.2 years; 95% confidence interval (CI), 63.9–68.3] and either the 13 mutation carriers (69.5 years; 95% CI, 63.9–74.9; $P = 0.27$) or carriers of nine mutations in established predisposition genes ($P = 0.93$).

Family history

Mutation carriers displayed a marginal association with FPC ($P = 0.056$) and a significant association with breast cancer in first-degree relatives ($P = 0.018$; Table 3). Including first- and second-degree relatives with cancer yielded associations with family history of breast ($P = 0.002$) and pancreatic cancers ($P = 0.023$; Table 3). Furthermore, breast and pancreatic cancers combined ($P = 0.003$); breast/pancreatic/ovarian/colorectal combined ($P = 0.037$); and breast/pancreatic/ovarian/colorectal/endometrial cancer combined ($P = 0.05$) all showed associations with mutation status (Table 3). However, there was no significant association between mutations and personal history of these cancers ($P = 0.167$; Table 3).

Missense mutations and CNV analysis

No large deletions or rearrangements were identified in the 22 genes. However, 161 missense variants and in-frame deletions were identified (Supplementary Table S1). Each variant was evaluated for potential pathogenic effects with Veste3 (score > 0.5), MetaSVM (score > 0.5), and MetaLR (score > 0.5) *in silico* prediction models that exhibit approximately 90% sensitivity and specificity for known pathogenic missense variants in ClinVar. Fourteen variants were consistently predicted to disrupt protein activity, but two of these were classified as benign (Supplementary Table S2). Carriers of 10 of the 12 remaining variants of uncertain significance (VUS) did not have a family history of breast or pancreatic cancer. However, *CDKN2A* c.350T>C was associated with a family history of breast cancer and *CDKN2A* c.272T>A from the same patient, as *MSH6* c.3040_3042delAAG was associated with a family history of pancreatic cancer. In addition, the *MLH1* c.1832T>C and *MSH2* c.905T>C carriers both had a family

Table 2. Phenotypic characteristics associated with deleterious mutations

Gene	Position[a]	Nucleotide	Codon	Age, y	Personal history of other cancer (age at diagnosis)	Cancer in first- and second-degree relatives[b]	Hereditary syndrome by NCCN criteria
ATM	108,141,828	c.2880delC		64	None	3 colorectal	
ATM	108,183,151	c.5932G>T	p.Glu1978X	83	Breast (67)	1 breast	
ATM	108,186,555	**c.6012_6013insA**		66	Liver (66)	None	
ATM	108,200,960	c.7327C>T	p.Arg2443X	67	Unknown (67)	1 pancreatic	
BARD1	215,595,215	c.1921C>T	p.Arg641X	71	None	1 pancreatic	
BRCA1	41,258,472	c.212+1G>A		59	None	2 breast, 1 pancreatic	Yes (HBOC V2.2015)
BRCA2	32,914,356	c.5864C>A	p.Ser1955X	69	None	1 breast	Yes (HBOC V2.2015)
BRCA2	32,914,859	c.6373dupA		51	None	2 pancreatic, 2 breast, 1 endometrial	Yes (HBOC V2.2015)
CHEK2	29,091,856	c.1100delC		79	None	None	
FANCM	45,644,539	**c.2586_2589delAAAA**		76	Melanoma	2 breast, 1 pancreatic	
MSH6	48,033,592	c.3804dupA		63	Endometrial (43)	2 breast, 2 colorectal	Yes (Lynch syndrome V 1.2015)
MSH6	48,033,791	c.4001+11_4001+35del25		75	None	1 breast	No (Lynch syndrome V1.2015)
NBN/CHEK2	90,983,441	c.657_661del5/1100delC		80	None	None	

NOTE: Novel deleterious mutations are in bold.

[a]The reference sequence for variant position is Hg19.

[b]Only breast cancer, pancreatic cancer, colorectal cancer, and endometrial cancer in relatives were counted.

history of colorectal cancer and the *CDH1* variant carrier had a family history of endometrial cancer. In addition, the *MLH1* c.1832T>C and *MSH2* c.905T>C carriers had a family history of colorectal cancer and the *CDH1* variant carrier had a family history of endometrial cancer. Thus, up to 12 additional missense variants may predispose to pancreatic and other cancers.

Discussion

Panel-based mutation screening of 22 known cancer predisposition genes identified 14 likely pathogenic mutations in eight genes among 13.5% of patients with PDAC. Of these, nine (9.4%) were in the established *ATM*, *PALB2*, *BRCA1*, *BRCA2*, and *MSH6* high- and moderate-risk pancreatic cancer genes. Another 12 missense variants were predicted pathogenic by *in silico* models in 11 patients. These results suggest that 9.4% to 25% of patients with pancreatic cancer in the Mayo Clinic registry may carry predisposing alleles. This contrasts with 11 (3.8%) mutations in 13 genes identified by the Ontario Pancreas Cancer Study (OPCS) of PDAC with family history of breast, ovarian, or pancreatic cancer and a subset without a family history of these cancers (15). The enrichment of mutations in the Mayo Clinic patient registry may reflect the ascertainment of the patients, although the rapid ascertainment approach coupled with screening of a sequential series of patients enrolled from June 2013 to June 2014 ensures that the study population is representative of PDAC cases seen at Mayo Clinic. In addition, the 96 selected cases were not enriched for family history of breast or pancreatic cancer relative to OPCS (21% vs. 19.7% breast; 12% vs. 13.9% pancreas). However, 33% of the Mayo cases with family history of breast cancer had mutations, whereas only 10.7% of similar cases in OPCS had mutations. The reason for the higher mutation rate is unclear.

Table 3. Personal and family history of related cancers by mutation status (deleterious vs. no mutation)

Cancer history	No mutation ($n = 83$) *n* (%)	Deleterious mutation ($n = 13$) *n* (%)	*P*
Family history (first-degree relatives)			
Breast			
No	71 (90)	8 (62)	0.018
Yes	8 (10)	5 (38)	
Pancreas			
No	75 (95)	10 (77)	0.056
Yes	4 (5)	3 (33)	
Family history (first- and second-degree relatives)			
Breast			
No	70 (84)	6 (46)	0.002
Yes	13 (16)	7 (54)	
Pancreas			
No	72 (87)	8 (62)	0.023
Yes	11 (13)	5 (38)	
Breast/pancreas			
No	60 (72)	4 (31)	0.003
Yes	23 (28)	9 (69)	
Breast/pancreas/colorectal/ovarian			
No	45 (54)	3 (23)	0.037
Yes	38 (46)	10 (77)	
Breast/pancreas/colorectal/ovarian/endometrial			
No	43 (52)	3 (23)	0.05
Yes	40 (48)	10 (77)	
Personal history of second cancer			
No	66 (80)	8 (62)	0.167
Yes	17 (20)	5 (38)	

The finding that mutations in the Mayo Clinic registry were significantly associated with family history of breast/pancreatic cancer and breast/pancreatic/colorectal/ovarian/endometrial cancer in first- and second-degree relatives strongly suggests that the current definition of FPC, which focuses on pancreatic cancer among first-degree relatives only, excludes many of the individuals with mutations in cancer predisposition genes that account for a significant proportion of pancreatic cancer cases. Identification of other pancreatic cancer predisposition genes may be better served by studies of families with a broader, clinically relevant definition of FPC and a wide spectrum of cancers.

BRCA2 is an important pancreatic cancer predisposition gene with 6% to 10% of patients with FPC carrying *BRCA2* mutations (13). The relative risk of pancreatic cancer among *BRCA2* mutation carriers has been estimated at 3.5 to 5 (20). However, the two patients with *BRCA2* mutations in this study did not fit FPC criteria. Few studies have implicated *BRCA1* in pancreatic cancer (3, 4). Here, one mutation in *BRCA1* (c.212+1G>A) that disrupts normal splicing was observed. *ATM* pathogenic mutations are frequent (1%) in the general population (21) and among patients with FPC (2.4%; ref. 22). Four of 14 mutations (31%) in the 96

sequential cases were likely pathogenic *ATM* mutations. Three carriers had a family history of breast, pancreatic, or colorectal cancer. Consistent with the link between predisposition genes and double-strand DNA break repair signaling, single mutations were also identified in *BARD1* and *NBN*. Neither gene has been established as a pancreatic cancer predisposition gene, but both have been implicated in breast and ovarian cancer. Further studies are needed to define the role of these genes in pancreatic cancer.

DNA mismatch repair (MMR) genes have been associated with an elevated risk of pancreatic cancer (23). Here, two likely pathogenic mutations in *MSH6* and seven predicted pathogenic missense VUS in MMR genes were identified, suggesting that germline MMR gene mutations may be as common as *ATM* mutations among pancreatic cancer cases. *CHEK2* mutations have been implicated in multiple cancers and may contribute to FPC (24). Neither of the *CHEK2* mutation carriers identified in this study, one with an *NBN* inactivating mutation, had a family history of breast, pancreatic, ovarian, or colorectal cancer. Thus, the contribution of *CHEK2* to pancreatic cancer risk needs further exploration. Fanconi anemia complementation gene M (*FANCM*) was recently implicated in cancer susceptibility (25). Whether the *FANCM* c.2586_2589delAAAA mutation detected here confers an increased risk of cancer remains to be determined.

Overall, a high proportion of patients with pancreatic cancer with a family history of a variety of solid tumors carry likely pathogenic mutations in known cancer predisposition genes. The suggestion is that pancreatic cancer is part of a constellation of tumors resulting from mutations in these genes and that studies focused on rare families predominantly enriched for pancreatic cancer may underestimate the contribution of predisposition genes to this disease. Importantly, relatives of individuals with pancreatic cancer who are found to carry mutations in high-risk predisposition genes such as *BRCA1*, *BRCA2*, *MMR* genes, *ATM*, and *PALB2* may also benefit from clinical testing for family mutation/s and subsequent awareness, screening, and perhaps prevention options for several types of cancer.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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