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ORIGINAL ARTICLE

Genomic analysis of familial pancreatic cancers and intraductal papillary mucinous neoplasms: A cross-sectional study

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Abstract

Environmental and genetic factors play a critical role in the pathogenesis of pancreatic cancer, which is likely to follow a multistep process that includes intraductal papillary mucinous neoplasm. The pathogenesis of familial pancreatic cancer has been reported; however, epidemiological characteristics and causative genes remain unclear. This study aimed to determine the relationship between the family history of pancreatic cancer and tumor malignancy and identify novel susceptible germline variants of pancreatic cancer. We performed an epidemiologic study at our institute on a cohort of 668 patients with intraductal papillary mucinous neoplasm and 242 with pancreatic cancer but without associated intraductal papillary mucinous neoplasm stratified by family history of pancreatic cancer. Whole-exome sequencing was conducted for 10 patients from seven families with familial pancreatic cancer and intraductal papillary mucinous neoplasm. We found that patients who had intraductal papillary mucinous neoplasm with positive family history of pancreatic cancer within first-degree relatives were more likely to develop malignancy in a shorter period than those without family history. Duplicate frameshift variants in *TET2* c.3180dupG (p.Pro1061fs) and *ASXL1* c.1934dupG (p.Gly646fs) in one family and *POLN* c.1194dupT (p.Glu399fs) in another were identified as pathogenic truncating germline variants which were previously recognised susceptibility genes. Moreover, *PDIA2* c.1403C>T (p.Pro468Leu) and *DPYSL4* c.926C>A (p.Pro309Gln) were shared in four and two patients, respectively. In particular, *PDIA2* was identified as a novel candidate for one of the deleterious variants of familial pancreatic cancer.

KEYWORDS
cancer susceptibility genes, cross-sectional study, familial pancreatic cancer, germline variant, intraductal papillary mucinous neoplasm

Abbreviations: EUS, endoscopic ultrasound; IPMC, intraductal papillary mucinous carcinoma; IPMN, intraductal papillary mucinous neoplasm; MPD, main pancreatic duct; MRCP, magnetic resonance cholangiopancreatography.

1 | INTRODUCTION

Pancreatic cancer is a malignant tumor with a poor prognosis, partly because of difficulty in detecting the cancer in early stages. Delineation of risk factors for pancreatic cancer could help initiate surveillance targeting a subpopulation at greater risk. Previous studies have shown that both environmental and genetic factors play important roles in the pathogenesis of pancreatic cancers. Known environmental risk factors include obesity, diabetes, smoking, and alcohol consumption.[1]

Documentation of familial aggregation of pancreatic cancer in the literature points to the influence of genetic factors. A prospective epidemiological study of pancreatic cancer conducted by Klien et al.[2] in 2004 showed that the lifetime risk of pancreatic cancer was 6.4 times higher in family members with two first-degree relatives with pancreatic cancer than in those without first-degree relatives with pancreatic cancer. In addition, the risk was 32 times higher in family members with three first-degree relatives with pancreatic cancer. Sequencing analysis of germline variants of families with pancreatic cancer unraveled the critical role of *ATM*, *BRCA1*, *BRCA2*, and *CHEK2*.[3-6] Besides studies on familial clusters, genome-wide association studies demonstrated that the single-nucleotide variants rs13303010 in *NOC2L* at 1p36.33 and rs78193826 in *GP2* at 16p12.3 are associated with pancreatic cancer even among patients without apparent family histories.[7,8]

Similar to other cancers, the pathogenesis of pancreatic cancers is likely a multistep process. The observation that familial pancreatic cancer was more likely to have earlier onset and mortality supports the multistep progression of pancreatic cancers. Intraductal papillary mucinous neoplasm (IPMN) has been regarded as the critical precancerous lesion of pancreatic cancers. A recent whole-exome analysis of 350 patients with IPMN showed that germline variants in *ATM* and *BRCA2* are associated with the progression of IPMN to pancreatic cancer.[9] However, whether genetic factors play a role in the development of IPMN remains unclear.

In this study, we performed epidemiologic and genetic studies on 668 patients with IPMN and 242 patients with pancreatic cancer but without associated IPMN. Among these two groups, we identified 18 patients with two or more affected family members, excluding the proband. Among these 18 patients, 10 patients from seven families underwent genomic studies. Identification of new risk genes for pancreatic cancer may facilitate genomic screening for early detection and treatment of pancreatic cancer.

2 | MATERIALS AND METHODS

2.1 | Study design and ethical approval

This retrospective and genome-sequencing study was conducted according to the Declaration of Helsinki after approval from the Institutional Review Board of the Keio University School of Medicine (approval numbers: 20120443 and 20190042; date of approval: October 30, 2019).

2.2 | Patients and data collection

We retrospectively reviewed the clinical characteristics and environmental factors of all patients who underwent endoscopic ultrasound (EUS) and endoscopic retrograde cholangiopancreatography between 2012 and 2020 and identified 668 patients with IPMN and 242 patients with non–IPMN-associated pancreatic cancer (Figure S1). We defined non–IPMN-associated pancreatic cancer as pancreatic cancer with no evidence of pancreatic cysts or IPMN based on magnetic resonance cholangiopancreatography (MRCP) or EUS scan interpreted by the radiologist and endoscopist.

The patients' clinical backgrounds were collected from medical records, and a questionnaire was provided during the first visit. Data collected included age, sex, body mass index (BMI), history of smoking and habitual alcohol consumption, medical history, family history of diabetes and cancer within first- or second-degree relatives, and imaging findings of pancreatic lesions. Habitual alcohol consumption was defined as the consumption of more than 100 g of alcohol per week. History of diabetes was defined as receiving antidiabetic treatment before the diagnosis of pancreatic tumors. The clinical characteristics of all patients (668 IPMN and 242 non–IPMN-associated pancreatic cancer) are shown in Table S1.

Patients with IPMN were classified as high risk or low risk according to the IPMN International Clinical Practice Guidelines 2017.[10,11] The high-risk IPMN group included those who met the criteria for "worrisome features (imaging findings include cyst of ≥3 cm, enhancing mural nodule <5 cm, thickened enhanced cyst walls, main pancreatic duct [MPD] 5–9 mm, lymphadenopathy, an elevated serum level of carbohydrate antigen, and a rapid rate of cyst growth >5 mm per 2 years)" and "high-risk stigma (obstructive jaundice, enhanced mural nodule ≥5 mm, MPD ≥10 mm)." Furthermore, those with intraductal papillary mucinous carcinoma (IPMC)-, IPMN-concomitant, and IPMN-derived pancreatic cancer were included in the high-risk IPMN group. The low-risk IPMN group comprised patients with IPMN who did not meet the criteria defined above.

2.3 | Whole-exome sequencing of germline samples

After obtaining written informed consent, whole-exome sequencing was performed on peripheral blood samples of 10 patients from seven families using the NovaSeq platform (Illumina) and Sure Select XT Human All Exon V6 (Agilent Technologies). Mapping of the sequenced reads to the reference human genome (GRCh37) and variant calling were performed according to the best practice guidelines

of the Burrows-Wheeler Aligner[12] and the Genome Analysis Tool Kit,[13] as packaged in the integrated analysis suite variant tools.[14] The variants were annotated with SnpEff.[15]

2.4 | Annotation of variants

To characterize potential functional significance of the variants revealed by whole-exome analysis, the allele frequencies of the variants among Japanese patients were evaluated from epidemiological standpoints. Any variant for which the allele frequency among >7000 normal Japanese individuals was larger than 0.03 as per the ToMMo database was excluded from further consideration.[16] Thus, only variants for which the allele frequency was between 40% and 60% were retained. When two or more affected members including the proband were tested, only the shared variants were retained. Among the 10 patients from seven families, 4148 variants were retained according to these criteria.

2.4.1 | Search for pathogenic variants in previously recognized susceptibility genes

We extracted frameshift, nonsense, and splicing variants and filtered them by previously reported pancreatic cancer–related genes (Table S2). Variants corresponding to a combined annotation-dependent depletion (CADD) score of >20 were extracted.[17]

2.4.2 | Comparison with molecular epidemiological data from Japan

We further evaluated these filtered (nonsynonymous) variants based on our previous work on whole-genome analysis of samples from Biobank Japan. We analyzed the table of variants and their allele count, allele number, and allele frequency of 6206 samples derived from patients with noncancer polygenic disorders and 1521 samples from patients with various kinds of cancer excluding pancreatic cancer.[18,19] Nonsynonymous variants with increased frequency among cancers were considered as candidate susceptibility variants. Filtered variants from familial pancreatic cancers and IPMN were identified from the table of candidate variants.

2.5 | Statistical analyses

Categorical variables were compared between the two groups using the chi-squared and Fisher's exact tests. The Mann-Whitney U test was used to compare quantitative variables. Statistical analyses were performed using SPSS for Mac (version 25.0; IBM). Statistical significance was set at $p < 0.05$, and all tests were two-sided. Kaplan-Meier analysis was used to assess differences in survival between cohorts.

3 | RESULTS

3.1 | Clinical characteristics of patients with IPMN and pancreatic cancer with a strong family history of pancreatic cancer

Among the 668 patients with IPMN and the 242 with non–IPMN-associated pancreatic cancer, we identified 15 patients with IPMN and three patients with non–IPMN-associated pancreatic cancer who had two or more affected family members excluding the proband (i.e., two first-degree relatives or one first-degree and one second-degree relative with pancreatic cancer; Figure S2). These patients were arbitrarily defined as "patients with a strong family history."

The clinical characteristics of patients with IPMN and pancreatic cancer with a strong family history of pancreatic cancer ($n = 18$) are shown in Table 1. Seven patients with IPMN had branch-type IPMN, two had high-grade IPMN, three had IPMN-derived pancreatic cancer, three had IPMN concomitant with pancreatic cancer, and three had non–IPMN-related pancreatic cancer.

3.2 | Malignant progression of IPMN with positive family history of pancreatic cancer

We compared the clinical backgrounds of the patients with IPMN and those with non–IPMN-related pancreatic cancer by categorizing them into those with positive family history of pancreatic cancer (more than one first-degree relative with pancreatic cancer) and those without (Table 2). Patients with IPMN-related pancreatic cancer with positive family history of pancreatic cancer were more likely to be female and to have a personal history of cancer; however, this finding was not statistically significant (Table 2).

Progression to malignant pancreatic cancer or high-risk IPMN (including high-grade IPMN, IPMC, and IPMN-related pancreatic cancer) was evaluated in these subgroups using Kaplan-Meier analysis (Figure 1). We observed 242 patients with high-risk IPMN during the study period, of which 23 had a positive family history of pancreatic cancer and 219 had no family history of pancreatic cancer. We found that patients with IPMN and positive family history were more likely to develop malignancy in a shorter period than those with no family history of pancreatic cancer (log-rank test, $p = 0.006$).

3.3 | Families with truncating variants in known pancreatic cancer–related genes

Of the 18 patients with a strong family history, 11 patients underwent genomic analysis, five patients died, and two did not wish to undergo testing.

One patient (#7) underwent commercial testing for multiple cancer genes, and a heterozygous *PALB2* pathogenic variant

TABLE 1 Characteristics of patients with a strong family history of pancreatic cancer ($N = 18$)

Patient	Pedigree	Age	Sex	Disease	Family history of pancreatic cancer	Past cancer history	Genome sequencing	Outcome
#1	#A	41	Female	Branch duct–type IPMN	Mother and grandmother	None	–	Alive
#2	#B	79	Female	Branch duct–type IPMN	Older brother and younger sister	None	Whole-exome sequencing	Alive
#3	#B	82	Female	Branch duct–type IPMN	Younger brother and younger sister	None	Whole-exome sequencing	Alive
#4	#C	52	Female	Branch duct–type IPMN	Father, younger brother, and father's aunt	None	Gene panel testing	Alive
#5	#D	73	Female	Branch duct–type IPMN	Older brother, mother, and mother's uncles	None	Whole-exome sequencing	Alive
#6	#E	62	Female	Branch duct–type IPMN	Father, father's aunt, and grand father	None	–	Alive
#7	#F	72	Female	Branch duct–type IPMN	Father, older brother, and younger brother	Breast cancer	Whole-exome sequencing	Alive
#8	#G	78	Female	High-grade IPMN	Younger sister and daughter	Cervical cancer	Whole genome sequencing	Alive
#9	#G	51	Female	High-grade IPMN	Mother and mother's aunt	None	Whole genome sequencing	Alive
#10	#H	54	Female	IPMN-derived pancreatic cancer	Father and father's grandmother	Breast cancer	–	Dead
#11	#I	75	Male	IPMN-derived pancreatic cancer	Older brothers, father, and mother	None	Whole-exome sequencing	Alive
#12	#J	69	Male	IPMN-concomitant pancreatic cancer	Older sister and younger sister	Rectal cancer	–	Dead
#13	#K	72	Male	IPMN-concomitant pancreatic cancer	Older brother and younger brother	None	Whole-exome sequencing	Alive
#14	#L	79	Female	IPMN-derived pancreatic cancer	Mother and older sister	Lung cancer	–	Dead
#15	#M	82	Female	IPMN-concomitant pancreatic cancer	Father and older sister	None	–	Dead
#16	#G	72	Female	Non–IPMN-related pancreatic cancer	Older sister and sister's daughter	None	Whole genome sequencing	Alive
#17	#N	71	Male	Non–IPMN-related pancreatic cancer	Father and father's uncle	Gastric cancer	Whole-exome sequencing	Alive
#18	#O	53	Male	Non–IPMN-related pancreatic cancer	Father and father's aunt	None	–	Dead

Abbreviation: IPMN, intraductal papillary mucinous neoplasm.

TABLE 2 Clinical backgrounds of patients with intraductal papillary mucinous neoplasm (IPMN) and pancreatic cancer stratified by family history of pancreatic cancer ($N = 668$)

Characteristics	Positive family history of pancreatic cancer ($n = 46$)	No family history of pancreatic cancer ($n = 622$)	p
Age, years, median (range)	68 (41–83)	70 (28–90)	0.384
Age >70 years	20 (43.5)	312 (50.2)	0.382
Sex (male/female)	18/28	316/306	0.127
BMI (kg/m^2)	21.0 (16.7–31.6)	21.8 (12.8–34.2)	0.313
BMI >25	7 (15.2)	105 (16.9)	0.704
Smoking (Ex/Cur)	15 [13/2] (32.6)	216 [177/39] (34.7)	0.765
Alcohol consumption	13 (28.3)	119 (19.1)	0.134
History of diabetes	5 (10.9)	75 (12.1)	0.889
History of cancer	7 (15.2)	159 (25.6)	0.117

Note: Data are presented as *n* (%) unless otherwise indicated.

Abbreviations: BMI, body mass index; Cur, current smoker; Ex, ex-smoker.

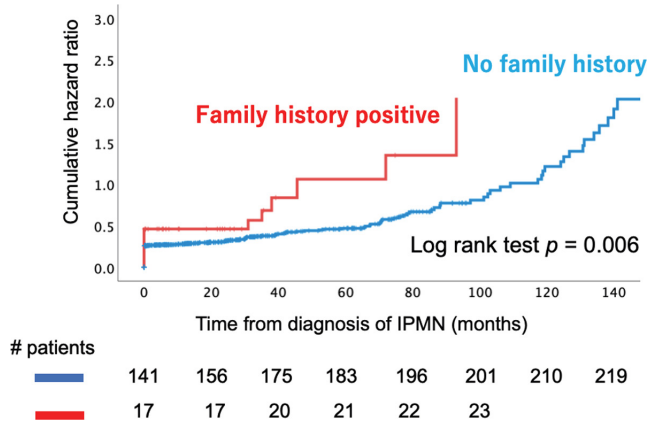

FIGURE 1 Cumulative risk of malignancy and overall survival of patients with intraductal papillary mucinous neoplasm (IPMN) stratified by family history of pancreatic cancer. The cumulative hazard ratio for malignant transformation in patients with IPMN with a family history of pancreatic cancer is shown. Malignant transformation includes intraductal papillary mucinous carcinoma and IPMN-concomitant pancreatic cancer. The red line represents those with family history, whereas the blue line represents those without. $p = 0.006$ (analyzed by log rank test)

(c.1675_1676inv [p. Gln559*]) and a heterozygous *NBN* pathogenic variant (c.265C>T [p. Arg89*]) were identified that has been reported elsewhere.[20]

Whole-exome sequencing was performed for 10 patients from seven families. The summary of the whole-exome sequencing results is shown in Table 3. Truncating variants of genes already implicated in the pathogenesis of pancreatic cancer (Table S1) were identified in two families. Heterozygous frameshift variants of NM_017628.4 (*TET2*; c.3180dupG, p. Pro1061fs) and NM_015338.6 (*ASXL1*; c.1934dupG, p. Gly646fs) were identified in patient #16 (Table 3a and Figure 2A), and a frameshift variant of NM_181808.4 (*POLN*; c.1194dupT, p. Glu399fs) was identified in patient #10 (Table 3b and Figure 2B).

3.4 | Comparison with molecular epidemiological data from Japan

We then compared the 4148 variants extracted from the analyzed patients to the allele frequencies of the whole-genome sequencing data from cancer ($n = 1521$) and noncancer patients ($n = 6206$). Of these variants, 172 variants with odds ratios >1.0 and *P*-values <0.05 were extracted. We further tested whether any of the variants were recurrent among the 10 families in which the proband underwent whole-exome analysis.

Two were common among families and deleterious according to the PROVEAN, SIFT (http://provean.jcvi.org/protein_batch_submit.php?species=human), and PolyPhen-2 scores (http://genetics.bwh.harvard.edu/pph2/): NM_006849.4 (*PDIA2*; c.1403C>T, p. Pro468Leu) was common to patients #1, #10, #11, and #12 (Table 3b and Figure 2B), and NM_006426.3 (*DPYSL4*; c.926C>A, p. Pro309Gln) was common to patients #2 and #14 (Table 3b and Figure 2C).

In most families, only the probands were tested. Intrafamilial segregation was confirmed in two families.

4 | DISCUSSION

In this study, we found deleterious variants in cancer susceptibility genes, including *TET2*, *ASXL1*, and *POLN*, which are known susceptibility genes, and *PDIA2* and *DPSYL4*, which are novel risk factors.

Premature truncating germline variants in *TET2* and *ASXL1* have been identified in patients with familial pancreatic cancer.[5,6] Tet methyl cytosine dioxygenase 2 (TET2) is involved in DNA demethylation, and its loss-of-function mutations result in hypermethylation.[21] Meanwhile, ASXL1 is a histone modifier, and gain-of-function mutations are associated with tumorigenesis.[22] Somatic variants in *TET2* and *ASXL1* represent poor prognostic indicators in hematological tumors.[23] It is notable that a patient with strong family

TABLE 3 Susceptible germline variants of pancreatic cancer and intraductal papillary mucinous neoplasm. (a) Susceptible frameshift variants of familial pancreatic cancer. (b) Susceptible single-nucleotide variants of familial pancreatic cancer

(a)

Gene	NM	Patients	Codon change	Amino acid change	AF of cancer	AF	AF of non-cancer	CADD score	Category
TET2	NM_017628.4	#13	c.3180dupG	p. Pro1061fs		-	0.0265	32.0	Cancer driver gene
ASXL1	NM_015338.6	#13	c.1934dupG	p. Gly646fs		0.00084	0.0220	34.0	Cancer driver gene
POLN	NM_181808.4	#5	c.1194dupT	p. Glu399fs		0.001	0.0220	24.8	DNA polymerase gene

(b)

Gene	NM	Patients	Codon change	Amino acid change	AF of cancer	OR (95%CI)	*p*	PROVEAN score	SIFT score	Polyphen-2
PDIA2	NM_006849.4	#5, #8, #9, #16	c.1403C>T	p. Pro468Leu	0.0377	1.48	0.005	Deleterious (−8.50)	Damaging (0.003)	Possibly damaging
DPYSL4	NM_006426.3	#11, #17	c.926C>A	p. Pro309Gln	0.0301	1.45	0.019	Deleterious (−7.62)	Damaging (0.013)	Probably damaging

Abbreviations: AF, allele frequency; CADD, combined annotation-dependent depletion; CI, confidence interval; OR, odds ratio; PROVEAN, protein variation effect analyzer; SIFT, sorting intolerant from tolerant.

history was a double heterozygote for truncating germline variants of *TET2* and *ASXL1*. The two genes could have an additive effect in tumorigenesis.

POLN gene is a member of the DNA polymerase family and is responsible for repairing DNA damage.[24] Truncating variants of *POLN* have been previously reported as causative genes of germline variants in pancreatic cancer. To our knowledge, this is the first study to report that a truncating variant (i.e., a frameshift variant) of *POLN* could be associated with both IPMN and pancreatic cancer.[5,25]

Two variants observed in patients with a strong family history were previously reported to have a significantly higher frequency in patients with various cancers than in the general population. First, the protein disulfide-isomerase A2 (PDIA2), a protein expressed in the pancreas, is involved in the regulation of cellular levels and biological functions of estrogen and has been identified as an autoantibody for autoimmune pancreatitis in vivo.[26,27] Although the association between a pathogenic *PDIA2* variant and pancreatic cancer has not yet been reported, all four patients in the two families with this variant were females with a strong family history, which could lead to pancreatic cancer or cystic changes. Second, DPYSL4 is an intracellular metabolic regulator induced by p53, a known tumor suppressor, and is found in mitochondria of mast cells.[28] However, its relatively high allele frequency among Southeast Asians (0.098) makes the candidacy of variants less likely.

This study has some limitations. First, protein functions by candidate gene variants obtained from our analysis have only been investigated using in silico analysis. According to the American College of Medical Genetics and Genomics/the Association for Molecular Pathology (ACMG/AMP) guideline 2015, NM_006849.4 (*PDIA2*: c.1403C>T, p. Pro468Leu) and NM_015338.6 (*DPYSL4*: c.926C>A, p. Pro309Gln) are classified as variants of uncertain significance, suggesting the need for functional and segregation analysis.[29] Second, only subsets of the affected family members and obligate carriers underwent genomic analysis. The segregation analysis is incomplete because of the limited availability of samples from family members.

Nevertheless, even among families who were not shown to have relevant variants in known cancer susceptibility genes, IPMN and strong family history were demonstrated as significant factors predictive of progression to IPMC or pancreatic cancer. Furthermore, patients with IPMN and strong family history tended to be negative for known environmental risk factors for pancreatic cancer. Patients with IPMN and a strong family history of pancreatic cancer could benefit from surveillance using EUS and/or MRCP regardless of the known environmental risk factors.[30,31]

The identification of novel pancreatic cancer or IPMN susceptibility genes, including *PDIA2*, could advance the genomic screening of patients who would benefit from regular imaging studies for IPMN and pancreatic cancers and provide a better understanding of the multistep pathogenic progression of pancreatic cancer.[32]

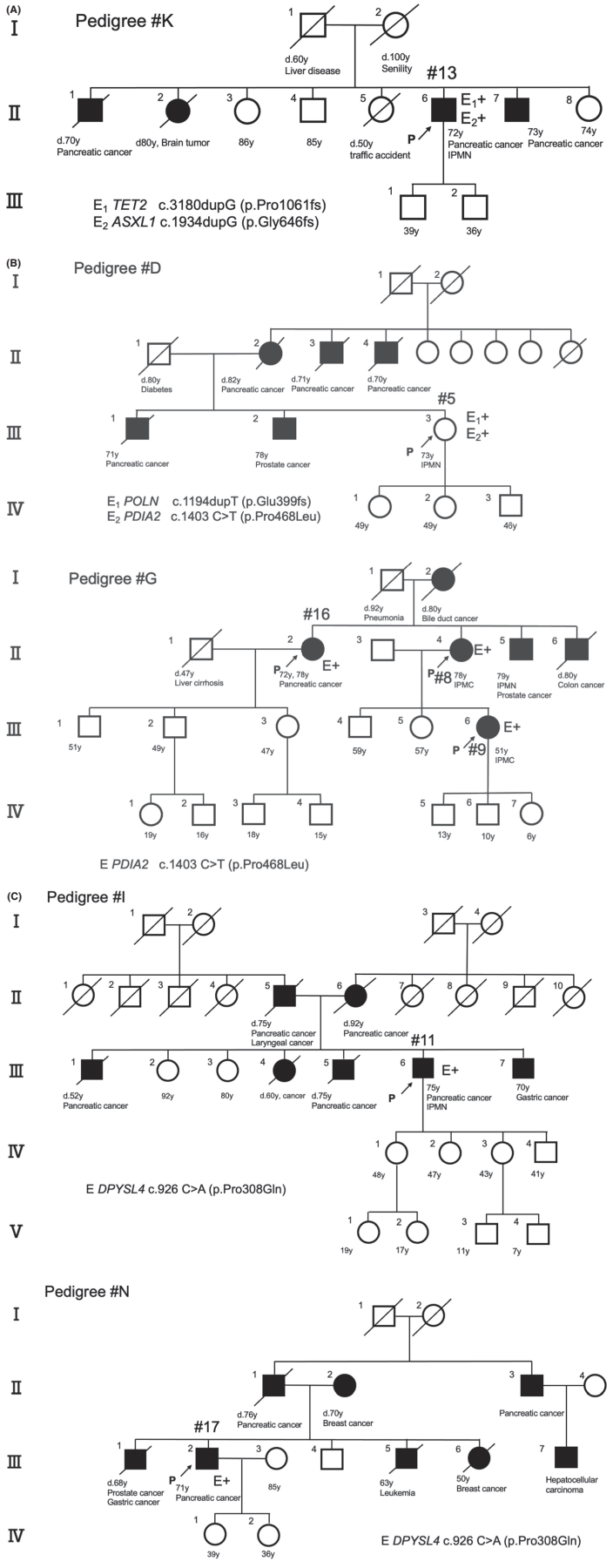

FIGURE 2 Family tree of patients who underwent whole-exome sequencing analysis. A, Patient #13 (pedigree #K; pancreatic cancer) was identified to have *TET2* and *ASXL1* frameshift overlapped variants. B, Patient #5 (pedigree #D; branch duct–type intraductal papillary mucinous neoplasm [IPMN]) has a *POLN* frameshift variant and a *PDIA2* missense variant, similar to pedigree #G of patients #16 (pancreatic cancer), #8 (high-grade IPMN), and #9 (high-grade IPMN). C, Patient #11 (pedigree #I; IPMN-related pancreatic cancer) and patient #17 (pedigree #N; pancreatic cancer) have a common missense variant *DPYSL4*

In conclusion, in our cohort of 668 patients with IPMN and 244 with pancreatic cancer, we identified 18 patients with a strong family history who are at high risk of progression to pancreatic cancer. Genomic analysis of these patients identified three previously recognized susceptibility genes and a novel potential candidate, *PDIA2*.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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