Identification of a Novel Kindred with Familial Pancreatitis and Pancreatic Cancer

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Key Words

Pancreatitis, hereditary • Pancreatic cancer, hereditary • Familial pancreatitis/pancreatic cancer

Abstract

Background/Aims: Hereditary pancreatic cancer comprises about 10% of pancreatic cancer cases. Multiple causative mutations have been identified. Here we describe a pancreatitis/pancreatic cancer (P/PC) family, which demonstrates pancreatitis and pancreatic cancer resulting from an uncharacterized mutation. **Methods:** Family members completed evaluations to determine signs of mutation status. Select patients were screened for mutations associated with hereditary pancreatic diseases. **Results:** In generation II, 12 siblings exhibit 6 cases of pancreatitis, 3 pancreatic cancer, and 2 obligate carrier status. The average age at pancreatitis diagnosis of enrolled members is 32.5 years; average age at pancreatic cancer diagnosis is 59 years. There is no association with known cancer syndromes. Those affected generally present with mild epigastric pain, and CT scans demonstrate characteristic fatty infiltration of the pancreatic body and tail with sparing of the head and neck. Full sequence analysis of genes associated with hereditary pancreatic disease failed to dem-

onstrate known mutations or polymorphisms. **Conclusion:** Based upon pedigree evaluation and preliminary DNA analysis, we believe that the family members with P/PC carry a novel genetic mutation resulting in hereditary pancreatitis. This mutation is autosomal dominant, expressed with high penetrance, and is part of a unique hereditary syndrome that significantly increases pancreatic cancer risk.

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Introduction

Pancreatic cancer affects nearly 33,700 patients per year, with almost uniform fatality. The median survival is 6 months, with the mortality rate remaining steady over the past 5 years [1, 2]. Currently, pancreatic cancer is the fourth leading cause of cancer mortality [3]. While little remains known about the etiology of pancreatic cancer, it is clear that its development is to some extent multifactorial. Known risk factors include tobacco use, older age, and a family history of pancreatitis and pancreatic cancer [2, 4–7]. Additional risk factors might include male gender, black ethnicity, chronic pancreatitis, diabetes mellitus (DM), prior gastrectomy, occupational

exposures, low dietary intake of fruits and vegetables, and high intake of foods that are grilled or charred. Additionally, genetic mutations in oncogenes (including *K-ras*, *HER2/neu*) and in tumor-suppressor genes (including *TP53*, *BRCA2*, *CDKN2A*) appear to be associated with pancreatic adenocarcinoma. However, at the current time the cellular and biochemical events ultimately leading to the development of pancreatic cancer are unclear [8, 9].

Recent estimates suggest that hereditary pancreatic cancer comprises up to 10% of pancreatic cancer cases [10]. Three forms of hereditary transmission have been identified: (1) hereditary pancreatic cancer (as an isolated entity); (2) pancreatic cancer in the setting of a familial cancer syndrome, and (3) hereditary pancreatitis (HP) resulting in increased risk of pancreatic cancer.

Isolated familial pancreatic cancer, defined as histologically confirmed pancreatic cancer in at least 2 first-degree relatives and in the absence of an accumulation of other cancers, is still a poorly understood disease process. Recently, Pogue-Geile et al. [11] identified a mutation in the *Palladin* gene, in the 4q32–34 susceptibility locus, which results in a proline-to-serine change at the α -actinin-binding site. This mutation appears to be responsible not only for the autosomal dominant transmission of isolated pancreatic cancer through family X but might also play a role in some sporadic pancreatic adenocarcinoma cases.

Over the last four decades, pancreatic cancer has been found with increased incidence in kindreds with certain known familial cancer syndromes [10]. In Peutz-Jeghers syndrome, *STK11/LKB1* mutations are known to result in a 36% lifetime risk of pancreatic cancer [12]; patients with familial atypical mole-malignant melanoma syndrome demonstrate a 17% lifetime risk of developing pancreatic cancer if a mutation in *CDKN2a* is present [13]. Additionally, individuals with hereditary breast and ovarian cancer/syndrome and a known *BRCA* mutation (particularly *BRCA2*), hereditary nonpolyposis colorectal cancer, and familial adenomatous polyposis have a higher lifetime risk of developing pancreatic cancer [8, 14, 15].

Finally, co-expression of HP and hereditary pancreatic cancer has also been defined, and a number of causative mutations have been identified. Comfort and Steinberg [16] first described HP, a disorder that is characterized by recurrent episodes of pancreatitis starting early in life and associated with at least two additional affected family members and an absence of other known etiologic factors [17, 18]. The incidence in males and females is

equivalent, and pancreatic calcifications are generally present. With the exception of its early onset, lack of other causative factors, and generally autosomal dominant inheritance, the clinical presentation of HP is similar to nonhereditary forms of acute and chronic pancreatitis.

In the late 1990s, two mutations in *PRSS1* were discovered and found to cause a majority of cases of HP. Whitcomb et al. [19, 20] first reported on the R122H mutation, and a year later the N29I mutation was identified [21]. Since that time a number of mutations have been identified [22], and it is believed that these result in pancreatitis via resistance to trypsin inactivation through autolysis [23]. Further studies have demonstrated that inheritance of a *PRSS1* mutation results in an 80% penetrance of HP and carries a nearly 40% lifetime risk of developing pancreatic cancer, with the risk approaching 75% if the mutation is inherited paternally [6].

Witt et al. [24] later described the first mutation in the serine protease inhibitor, Kazal type 1 (*SPINK1* or pancreatic secretory trypsin inhibitor [*PST1*]), which was also implicated in the development of HP. It is believed that *SPINK1* mutations likely fail to regulate the normal inhibition of prematurely activated trypsin in the pancreas [25, 26]. As only a few subjects with heterozygous *SPINK1* mutations develop disease, *SPINK1* might act as a disease modifier, particularly in combination with other mutations, such as *CFTR*, known to be associated with pancreatitis and possibly pancreatic adenocarcinoma [26–29].

Members of the family pancreatitis/pancreatic cancer (family P/PC) express HP with high penetrance, similar to the *PRSS1* and *SPINK1* cohorts and unlike the isolated pancreatic cancer family X cohort. Affected members appear to have a significantly increased risk of developing pancreatic cancer. Analysis of the family suggests that their phenotype is not due to a familial cancer syndrome or to known polymorphisms or mutations. Here we present the initial characterization of members of family P/PC who we believe harbor a novel, autosomal dominant mutation for HP; additionally, we describe a potential method by which those affected and unaffected may be differentiated.

Patients and Methods

Study Design and Objectives

The study consisted of a retrospective and prospective analysis of affected and unaffected members of family P/PC. The objective of the study was to characterize the clinical, hematological, radiological, endoscopic, and genetic traits of affected members of

Fig. 1. Pedigree of family P/PC. 140 members of family P/PC have been identified. Six members of the second generation developed pancreatitis, 3 developed pancreatic cancer, and 2 are obligate carriers.

family P/PC, who are believed to carry a novel, autosomal dominant gene for HP. As the locus responsible for the phenotype has not yet been identified, a second objective was to determine a method by which to risk-stratify family members who might carry mutations. The study was conducted in compliance with the institutional human research committee procedures.

Subject Identification and Enrollment

Subjects were eligible for inclusion if they were an affected or unaffected members of family P/PC and ≥ 18 years of age. Spouses of affected members were also eligible for enrollment. Potential subjects were excluded if they were younger than 18 years of age at the time of enrollment; subjects who developed symptoms prior to the age of 18 years were eligible for enrollment when they were 18 years of age. All participants were enrolled at Massachusetts General Hospital (MGH).

Clinical Evaluation

Clinical evaluation included subject completion of the Research Subject Clinical Questionnaire which presents questions related to demographics, known past and current medical problems, symptoms of pancreatic disease, details of pancreatic disease (age of onset, duration of attacks, precipitating and mitigating factors), and relevant social history (including alcohol and tobacco use and other environmental exposures). The study group completed a Researcher Questionnaire to verify the subjects' responses and to gather any missing information which was obtained from paper and electronic medical records including outside hospital records provided by the subject.

Hematological Evaluation

Subjects underwent a single blood draw; blood samples were analyzed for amylase, lipase, glucose, CEA, and CA 19-9. Blood samples were processed at the MGH Core Laboratory.

Radiologic and Endoscopic Evaluation

Affected subjects and a subset of unaffected subjects completed computed tomography (CT) scans of the pancreas according

to MGH protocol (Light Speed, 16-slice), MR cholangiopancreatography (MRCP; MGH Radiology Protocol), and endoscopic ultrasound (EUS, performed by a gastrointestinal endoscopist).

Genetic Evaluation

A subset of affected subjects underwent a genetic evaluation, including full sequence analysis for mutations and polymorphisms of genes known to be associated with HP and hereditary pancreatic cancer: *BRCA1*, *BRCA2*, *CFTR*, *PRSS1*, and *SPINK1*.

Statistical Evaluation

Unpaired t tests were used to statistically analyze the difference in laboratory values (GraphPad Prism, GraphPad Software, Inc., San Diego, Calif., USA).

Results

Characteristics of Family P/PC

Family P/PC is of Polish descent; there is no identifiable Ashkenazi Jewish descent. There are 140 known members of family P/PC spanning 4 generations (fig. 1). Family members reside in the northeast United States. Twenty-three family members (14 affected, 9 unaffected) consented to participate in the study. Six members of the second generation developed pancreatitis, 3 developed pancreatic cancer, and 2 are obligate carriers. Little is known about 2 siblings, but it is believed that they are asymptomatic and likely unaffected. Pedigree analysis reveals that the mutation responsible for the phenotype is autosomal dominant and expressed with approximately 80% penetrance.

Clinical Characteristics

The average age at diagnosis of pancreatitis in enrolled affected members was 32.5 years ($n = 12$; 1 subject was excluded from analysis due to lack of symptoms and 1 excluded for unknown date of disease onset; range 6–66 years). The youngest age at diagnosis of pancreatitis was 6 years in an enrolled subject. To date only 1 enrolled member has developed pancreatic cancer, the average age at pancreatic cancer onset was calculated from all family members diagnosed with pancreatic cancer. There are 4 cases of pancreatic cancer diagnosed in generations II and III. The average age at diagnosis of pancreatic cancer is 58.7 years, with the earliest diagnosis in the proband at 45 (range 45–71) years. Information regarding staging of pancreatic cancer at the time of diagnosis is available on 2 of the affected family members; the remaining 2 family members were diagnosed with pancreatic adenocarcinoma, and they were deemed unresectable (TNM staging not available). One member on whom staging data are available underwent a total pancreatectomy for diffuse involvement of the gland. A T3N1 (1/21) moderately differentiated tumor of the pancreatic tail was identified. Foci of intraductal carcinoma were identified in the head. Chronic pancreatitis was identified throughout the gland. The 2nd affected member was found to have a T3N1 poorly differentiated, pancreatic ductal adenocarcinoma at the pancreatic head. He underwent a Whipple procedure with intraoperative radiation therapy. Two months after his resection, he was found to have metastatic disease to the liver and succumbed to his disease shortly thereafter. All 4 individuals with pancreatic cancer were identified as having chronic pancreatitis, 2 by histologic confirmation and 2 by clinical history.

Of the 14 enrolled members with pancreatic disease, details on symptoms are available for 12. Of these, 2 members deny any history of abdominal pain and the remaining 10 have mild abdominal pain. Pain is most frequent at the epigastrium ($n = 9$) and less commonly in the right upper quadrant ($n = 2$), left upper quadrant ($n = 1$), and back ($n = 3$). Nausea is associated with disease in 5 affected members. The 2 members who lack abdominal pain are characterized as affected, as both have diabetes and CT confirmation of fatty infiltration of the pancreas, consistent with affected status. Additionally, 1 of the 2 is an obligate carrier.

Comparison of comorbid conditions was completed in enrolled members in whom clinical data were available (affected $n = 12$; unaffected $n = 8$). Six of 12 affected members (50.0%) developed DM, while 0 of 8 of those unaffected (0%) were diagnosed with DM at the time of en-

rollment. One of 8 unaffected members (12.5%) was diagnosed with inflammatory bowel disease (Crohn's disease), and 2 of 12 affected (16.7%) were diagnosed (1 with Crohn's and 1 with ulcerative colitis). Three extra-pancreatic cancers were diagnosed in the affected enrolled subjects (25.0%), with 1 case of prostate cancer, 1 case of breast cancer, and 1 case of uterine cancer; 1 case of uterine cancer (12.5%) was identified in an unaffected enrolled member. Only 1 affected member (8.3%) was found to have an anatomic anomaly (pancreas divisum). No cases of Peutz-Jeghers syndrome, atypical moles or melanoma, colorectal cancer, or cystic fibrosis were identified in any members of the family.

Alcohol and tobacco are common among both affected and unaffected family members. Of the 8 unaffected members for whom social history is available, all (100%) use alcohol regularly (range 0.03–2.3 drinks/day). Of the 12 affected members for whom social history is available, 7 consume alcohol regularly (58.3%, range 0.006–3.1 drinks/day). In terms of tobacco use, 4 of 8 unaffected members (50%) used tobacco compared to 7 of 12 affected members (58.3%).

Laboratory Characteristics

There was no significant difference between the means of laboratory values: amylase (mean of affected members [$n = 13$] 87.2 U/l; mean of unaffected members [$n = 4$] 39.0 U/l; $p = 0.10$), lipase (mean of affected members [$n = 13$] 11.2 U/dl; mean of unaffected members [$n = 4$] 3.2 U/dl; $p = 0.08$), glucose (mean of affected members [$n = 9$] 134.7 mg/dl; mean of unaffected members [$n = 4$] 92.0 mg/dl; $p = 0.32$), CA 19-9 (mean of affected members [$n = 10$] 57.0 U/ml; mean of unaffected members [$n = 4$] 4.2 U/ml; $p = 0.53$), and CEA (mean of affected members [$n = 10$] 1.0 ng/ml; mean of unaffected members [$n = 4$] 1.0 ng/ml; $p = 0.98$). The data are summarized in table 1. Though the mean values for amylase, lipase and glucose were not significantly different between those affected and unaffected, the laboratory values of unaffected members fell within the normal range set by the MGH Core Laboratory, while affected individuals were noted to have low but elevated amylase and lipase levels.

Radiologic and Endoscopic Characteristics

Eight affected family members and 4 unaffected members completed CT scans of the pancreas. CT images of the pancreas in affected members revealed characteristic fatty infiltration of the body and tail, with sparing of the head and neck (fig. 2a and c). In contrast, unaffected members failed to demonstrate the same fatty infiltration (fig. 2b).

Fig. 2. CT images of the pancreata of affected and unaffected members of family P/PC. A proband of family P/PC demonstrates a pancreatic ductal adenocarcinoma of the pancreatic head (a). Sibling 1 of the proband, who is asymptomatic, has a normal pancreas and is believed to be an unaffected member (b). Sibling 2 of the proband is asymptomatic but demonstrates a characteristic fatty infiltration of the body and tail of the pancreas (c). Sibling 2 is believed to be a mutation carrier.

Table 1. Comparison of laboratory values of enrolled affected and unaffected members of family P/PC

Laboratory values	Unaffected subjects	Affected subjects	p value
Amylase, U/l	39.0	87.2	0.10
Lipase, U/l	3.2	11.2	0.08
Glucose, mg/dl	92.0	134.7	0.32
CA 19-9, U/l	4.2	57.0	0.53
CEA, ng/ml	1.0	1.0	0.98

Though only a limited number of CT scans are available of subjects prior to their onset of symptoms (i.e., childhood and teenage years), subjects who are thought to be affected did not demonstrate characteristic fatty infiltration of the pancreas until their 4th decade of life.

Six affected family members completed MRCPs. MRCP findings were unremarkable and failed to demonstrate ductal dilation or mass lesions.

Five affected family members underwent EUS. In 1, an irregular mass in the head of the pancreas was identified. The remaining 3 subjects had pancreata with diffusely hyperechoic parenchyma consistent with fatty infiltration. There were also hyperechoic ductal margins without ductal dilation.

Genetic Characteristics

Three affected subjects underwent genetic evaluation. Full sequence analysis for mutations and polymorphisms

of genes known to be associated with HP and hereditary pancreatic cancer – *BRCA1* (n = 1), *BRCA2* (n = 1), *CFTR* (n = 2), *PRSS1* (n = 3), and *SPINK1* (n = 2) – failed to demonstrate any known mutations or polymorphisms in both affected and unaffected subjects. It is believed that the mutation responsible for disease in family P/PC is novel and previously unidentified.

Discussion

For those affected with HP, the diagnosis not only carries with it a lifetime of debilitating abdominal symptoms but also portends a significantly increased risk of developing pancreatic cancer. For the greater than 200 HP kindreds identified worldwide, most carry known mutations of *PRSS1* and *SPINK1*. For these subjects, screening guidelines will ideally allow early diagnosis of pancreatic cancer at a curable stage. However, for approximately 30% of HP subjects, the cause of disease is not known, and prevention, screening, and treatment strategies are still a work in progress.

Members of family P/PC fall into this latter category. Like HP kindreds with identifiable mutations causing disease, members of family P/PC develop acute and chronic forms of pancreatitis at an early age with symptoms that are virtually indistinguishable from non-hereditary forms of pancreatitis. Additionally, their disease is the result of a gene, transmitted in an autosomal dominant fashion, which carries what is believed to be an 80% penetrance. It is clear that the presence of this HP muta-

tion carries with it a significant risk of developing pancreatic cancer at an age much younger than patients who develop sporadic pancreatic cancer. However, at this time, the progression of disease is not fully defined, and additional data collection may help identify pre-neoplastic lesions that serve as intermediates between the two phenotypes: pancreatitis and pancreatic cancer.

Unlike kindreds with an identifiable mutation contributing to disease, the affected members of family P/PC do appear to have identifiable signs of mutation status that will aid in identification of members who require more intensive screening measures. Mutation carriers, both with and without symptoms, demonstrate characteristic CT findings that appear to be unique to this family: fatty infiltration of the body and tail of the pancreas, with relative sparing of the head and neck. While mutation identification is ongoing, CT findings, in combination with symptoms, will help guide screening and treatment strategies in this family.

In studies of other HP kindreds, tobacco use by HP patients has been shown to cause pancreatic cancer with increased incidence (154-fold) and decreased latency (pancreatic cancer develops 20 years earlier than in non-smokers) [30]. While it appears that exposure to environmental factors such as alcohol and tobacco is not the cause of disease, it does appear that exposure to these environmental factors facilitates or augments the development of symptomatic disease in mutation carriers. As with preventive recommendations for other HP kindreds, we also recommend abstinence from environmental factors, such as alcohol or tobacco, which accelerate disease.

Prior studies in *PRSSI* kindreds have demonstrated that paternal inheritance results in a significantly greater risk of developing pancreatic cancer: the risk of cancer increases to 75 from 40% in patients with HP [6]. Similarly prior studies have demonstrated that kindreds with

HP likely demonstrate genetic anticipation, with offspring of affected members developing disease an average of 20 years earlier [31]. While we do observe 4 children who have been affected with disease prior to the age of 20, and while 75% of these children inherited their mutation from a paternal source, it is too early to determine whether this family demonstrates genetic anticipation or increased risk due to paternal inheritance.

Studies to identify the locus responsible for family P/PC's phenotype are currently under way. While the gene responsible remains unknown, the need for close, early surveillance in this family is clear. At the current time, our screening protocol involves CT pancreas protocol, EUS, and MRI/MRCP at presentation. Subsequent surveillance is by MRI/MRCP and EUS every year but staggered by 6-month intervals. Although no members have developed pancreatic cancer since the introduction of this screening protocol, and although the benefit of the screening still remains to be determined, as with all established screening protocols, our hope is to detect pancreatic cancer in members of family P/PC in its earliest, treatable stages.

In conclusion, members of family P/PC carry a novel mutation for HP. This mutation is transmitted in an autosomal dominant fashion, expressed with 80% penetrance, and places affected subjects at a significantly greater risk of developing pancreatic cancer. Investigations into the mutated locus are under way, but in the interim, early aggressive screening of family members may allow early detection and treatment of pancreatic cancer while it is curable.

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