Cancer Genetics 208 (2015) 559–563

Cancer Genetics

ORIGINAL ARTICLE

Identification of genetic risk for pancreatic adenocarcinoma

Kendra Flores [a,*], Kate Dinh [b], Erin Rouleau [a], Giles Whalen [b], Wahid Wassef [c], Jennifer LaFemina [b]

[a] *Department of Pediatrics, Division of Genetics, University of Massachusetts Medical School, Worcester, MA, USA;*
[b] *Department of Surgery, Division of Surgical Oncology, University of Massachusetts Medical School, Worcester, MA, USA;*
[c] *Department of Medicine, Division of Gastroenterology, University of Massachusetts Medical School, Worcester, MA, USA*

Recent consortium guidelines support research-based screening for those at high risk of pancreatic cancer (pancreatic ductal adenocarcinoma (PDAC)). Genetic testing plays an important role in the establishment of high-risk PDAC research clinics by delineating those individuals who would benefit from screening protocols. We retrospectively examined patients referred for PDAC-related genetic testing from January 2009 to June 2014. Patients were referred for a personal and/or family history of PDAC or a questioned diagnosis of hereditary pancreatitis (HP). Of the 75 referred patients, 36 underwent testing, of which 11 (31%) were mutation-positive. In total, 36% of patients with chronic pancreatitis carried a mutation, 11% of patients with a family history of PDAC carried a mutation, and 20% of patients with a personal history of PDAC carried a mutation. The most common barrier to testing was lack of insurance coverage. Genetic testing yields a suitable number of mutation-positive individuals who may benefit from increased screening. Subjects with possible HP yielded the highest positive rate. Individuals with idiopathic pancreatitis, onset of pancreatitis before the age of 30 years, and those with a family history of PDAC should be considered for testing. Sub-optimal insurance coverage remains a major deterrent to obtaining testing.

Keywords Genetic testing, Pancreatic cancer, Pancreatitis

It is estimated that as many as 1 in 10 pancreatic ductal adenocarcinomas (PDACs) have a hereditary component (1). High-risk screening is suggested for individuals at increased risk of PDAC (2), a key factor in the identification of inherited genetic predisposition. High-risk breast and colon cancer clinics rely heavily on genetic identification of risk and have been shown to reduce morbidity and mortality (3,4). In order to establish the same benefit within PDAC cohorts, genetic testing is essential to determine who should be considered "high risk."

Genetic risk of PDAC is typically separated into three risk categories, the first of which is hereditary pancreatitis (HP). HP is primarily caused by mutations to the cationic trypsinogen gene (*PRSS1*), with genetic contributions from other genes such as *SPINK1*, *CTRC*, and the cystic fibrosis gene, *CFTR* (5–7). Evidence suggests that individuals with HP have an up to 40% risk of PDAC, and possibly as high as a 75% risk when HP is paternally inherited (8). Indications for genetic testing for HP include unexplained pancreatitis, especially <30 years of age, a family history of pancreatitis, or the occurrence of pancreatitis in a child (9).

Several hereditary cancer predisposition syndromes include an increased risk of PDAC. A high risk of pancreatic malignancy (>10%) has been reported for conditions such as *CDKN2A*-mediated familial atypical malignant melanoma syndrome (FAMMM) (10), Peutz-Jeghers syndrome (11), and von Hippel-Lindau disease (12). Moderate risk of PDAC (a 5–10% risk) is seen in Li-Fraumeni syndrome (13), hereditary breast and ovarian cancer syndrome (HBOC) mediated by mutations to *BRCA1* and *BRCA2* (14), adenomatous polyposis coli (APC) (15), and Lynch syndrome (16). Finally, newly implicated genes, such as *PALB2* and *ATM*, have been identified with increased frequency in PDAC family cohorts. However,

Received July 22, 2015; received in revised form August 30, 2015; accepted September 1, 2015.
* Corresponding author.
E-mail address: kendra.flores@umassmemorial.org

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http://dx.doi.org/10.1016/j.cancergen.2015.09.002

recent studies have not completely elucidated how the presence of these latter mutations influences the risk of developing PDAC (17,18).

Finally, in the absence of a known or described hereditary cancer syndrome, the occurrence of two or more first-degree relatives with PDAC meets criteria for the diagnosis of familial pancreatic cancer syndrome (19). Although a single gene causation has not yet been discovered, several empirical studies have suggested that even without a known familial mutation, an increased risk of PDAC is seen with increasing numbers of affected first-degree relatives (20–22).

Current data is inconclusive regarding the benefit of radiologic and endoscopic screening for pancreatic cancer. The International Cancer of the Pancreas Screening (CAPS) Consortium suggests screening patients confirmed to be high risk, preferably on a research protocol (23–26). The first dilemma, however, remains with the identification and referral of high-risk patients. The aims of the current study were to determine referral indications, identify mutations, and identify reasons for declination of genetic testing in an enriched population referred to genetic counseling for PDAC risk.

Patients and methods

All patients were referred for PDAC-related genetic counseling from January 2009 to June 2014 at a tertiary care center, and were retrospectively identified from an existing clinical care database. A total of 75 unrelated individuals were identified. The referral indication for genetic counseling was categorized as personal history of PDAC, family history of PDAC, or a potential diagnosis of HP. Patients were referred for a potential diagnosis of HP in cases where cause had been ruled out and chronic pancreatitis has been deemed idiopathic in nature, childhood chronic pancreatitis, or chronic pancreatitis in an individual with a family history of pancreatitis or PDAC. All patients referred received counseling by a licensed genetic counselor.

Genetic testing was offered on the basis of clinical discretion in accordance with National Comprehensive Cancer Network guidelines. All testing was performed at a Clinical Laboratory Improvement Amendments (CLIA)-certified genetics laboratory. The genes included in analysis by indication are summarized in Table 1. Records of which, if any, genetic syndrome was suspected and for which testing was offered was documented. If the patient did not elect genetic testing, the stated reason for declination was recorded. If genetic testing was elected, the results of that testing were noted. The study was conducted according to institutional human research committee procedures.

Results

Of the 75 patients, 43 (57%) were referred for questioned HP, 27 (36%) were referred because of a family history of PDAC, and five (7%) were referred due to a personal history of PDAC. Of the 75 total referrals, 65 met the criteria for genetic testing, of which 36 (55%) elected genetic testing. The 10 patients who did not meet the criteria were excluded from further analysis, but are depicted in Figure 1 to summarize their indication for referral. Of these 36 tested individuals, 11 (31%) were found to carry a mutation that contributed to their risk of PDAC. The rate of mutation identification and type of mutation seen varied within these three referral categories. Within the questioned HP cohort (n = 43), all patients had documented chronic pancreatitis; 23 had no family history of pancreatic disease and were referred on the basis of diagnosis of chronic pancreatitis < 30 years old or a lack of an apparent etiology; 12 had a family history of PDAC in a third-degree relative or closer; and 8 had a family history of pancreatitis in a third-degree relative or closer (Figure 2).

In the individuals without a family history of pancreatic disease (n = 23), all patients were offered genetic testing of the *PRSS1*, *SPINK1*, *CTRC*, and *CFTR* genes, of which 12 elected testing; 4 (33%) were found to be mutation carriers; 2 were *CFTR* heterozygous; 1 was *CFTR* homozygous; and 1 was *SPINK1* homozygous. In patients with questioned HP on the basis of a family history of chronic pancreatitis (n = 8), five individuals elected genetic testing, of which one was identified as a *SPINK*1 heterozygote, which resulted in a positive mutation rate of 20% tested. In the group with a family history of PDAC, one family history prompted suspicion of HBOC, which, when tested, identified a *BRCA1* mutation carrier. Of the remaining 11 patients, 7 elected genetic testing for HP. Of these, three were found to carry a single *CFTR* mutation, which yielded a total of four identified mutations (33% of those tested). Overall, of the 43 patients referred for a potential diagnosis of HP, 25 (58%) elected genetic testing, and 9 of the 25 tested (36%) were found to carry a genetic mutation.

Within the cohort referred due to a family history of PDAC (n = 27), 10 individuals did not have a family history that was readily suggestive of a described hereditary cancer syndrome and, therefore, were not offered genetic testing. These patients were excluded from analysis. Three individuals had a family history indicative of Lynch syndrome, nine had family histories consistent with HBOC, and five had family histories suggestive of multiple cancer predisposition syndromes (Figure 1).

Of those cases in which Lynch syndrome was implicated, genetic testing was elected in two cases—both of which were negative for analysis of the *MLH1*, *MSH2*, *MSH6*, *EPCAM*, and *PMS2* genes. In the nine HBOC suggestive families, five

Table 1 Genes included in analysis on the basis of indication

Hereditary pancreatitis	Causative: *PRSS1* Contributing: *SPINK1*, *CFTR*, *CTRC*
Lynch syndrome	*MLH1*, *MSH2*, *MSH6*, *PMS2*, *EPCAM*
Hereditary breast and ovarian cancer syndrome	*BRCA1*, *BRCA2*
Ambry Genetics (Aliso Viejo, CA) PancNext multi-gene panel	*ATM*, *APC*, *BRCA1*, *BRCA2*, *CDKN2A*, *MLH1*, *MSH2*, *MSH6*, *EPCAM*, *PMS2*, *PALB2*, *STK11*, *P53*