

Cancer Prone Disease Section

Review

Hereditary pancreatic cancer

Ralph H Hruban, Scott E Kern

The Johns Hopkins University School of Medicine, Baltimore, MD 21205, USA (RHH, SEK)

Published in Atlas Database: December 2000

Online updated version : <http://AtlasGeneticsOncology.org/Kprones/HeredPancrCanID10068.html>

DOI: 10.4267/2042/37717

This work is licensed under a Creative Commons Attribution-Noncommercial-No Derivative Works 2.0 France Licence.

© 2001 Atlas of Genetics and Cytogenetics in Oncology and Haematology

Identity

Alias: Familial pancreatic cancer

Inheritance

It has been estimated that as many as 10% of pancreatic cancers have a hereditary basis; five genetic syndromes have been identified that are associated with the familial aggregation of pancreatic cancer; these include:

The second breast cancer syndrome (BRCA2), the familial atypical multiple mole melanoma (FAMMM), the Peutz-Jeghers Syndrome, the hereditary pancreatitis and the hereditary non-polyposis colorectal cancer (HNPCC) syndrome.

Most kindreds with familial pancreatic cancer, however, do not fall into one of these well-defined syndromes and these are referred to simply as "family pancreatic cancer."

Clinics

Note

a generally accepted definition of familial pancreatic cancer is a kindred in which at least a pair of first-degree relatives (sibling-sibling or parent-child) have been diagnosed with pancreatic cancer; several large registries have been established to define the patterns of inheritance and genetic basis for the familial aggregation of pancreatic cancer in these kindreds, the National Pancreas Tumor Registry (NFPTR) is the largest such registry; over 260 familial pancreatic cancer kindreds have enrolled in this registry and studies of these kindreds has revealed that when followed prospectively, apparently healthy, first-degree relatives of patients with familial pancreatic cancer have an 18-fold increased risk of developing pancreatic cancer; when there are three or more family members with pancreatic cancer in a kindred, the first-degree relatives of the index patient with pancreatic cancer

have a 56-fold increased risk of developing pancreatic cancer.

Each of the five clinically recognized syndromes associated with the familial aggregation of pancreatic cancer has its own unique clinical findings.

Second breast cancer syndrome: the BRCA2 tumor suppressor gene is located on chromosome 13q and carriers of germline BRCA2 mutations have a significant lifetime risk of developing breast cancer (30-85%) at a young age; they are also at risk for bilateral breast cancer; BRCA2 is also associated with an increased risk of male breast cancer, ovarian cancer, prostate cancer and pancreatic cancer; the lifetime risk of pancreatic cancer in carriers of germline BRCA2 mutations is approximately 10%; germline BRCA2 mutations are particularly common amongst individuals of Ashkenazi Jewish heritage because of a founder effect.

Familial atypical multiple mole melanoma (FAMMM) syndrome has an autosomal dominant mode of transmission; most cases are caused by germline mutations in the p16 tumor suppressor gene on chromosome 9p; individuals affected with FAMMM develop multiple melanocytic nevi, some of which can be atypical; they also are at increased risk of developing melanoma and pancreatic cancer; the lifetime risk of pancreatic cancer in individuals with germline p16 mutations is about 20%.

The Peutz-Jeghers Syndrome is inherited in an autosomal dominant mode; it has recently been shown to be caused by germline mutations in the STK11/LKB1 gene on chromosome 19p; individuals with this syndrome typically develop multiple mucocutaneous melanin macules, hamartomatous gastrointestinal polyps and they have an increased risk of developing cancers of the gastrointestinal tract; it has been estimated that the lifetime risk of pancreatic cancer in patient with the Peutz-Jeghers Syndrome is approximately 30%.

Hereditary pancreatitis has an autosomal dominant mode of transmission; it is caused by germline mutations in the cationic trypsinogen gene (called PRSS1) on chromosome 7q35; affected individuals develop recurrent episodes of pancreatitis at a young age and they have an elevated lifetime risk of developing pancreatic cancers that approaches 40%.

The hereditary nonpolyposis colorectal cancer (HNPCC) syndrome is caused by germline mutations in one of the DNA mismatch repair genes (such as hMLH1 on chromosome 3 p and hMSH2 on chromosome 2p); in addition to colorectal neoplasia, affected family members have an increased risk of developing pancreatic cancer; the pancreatic cancers that arise in patients with HNPCC often have a distinct histologic appearance referred to as "medullary" histology.

The ataxia-telangiectasia and familial adenomatous polyposis syndromes have also been associated with an increased risk of developing pancreatic cancer, however, these associations are not well-established.

Treatment

Currently, there are no effective methods to screen individuals at-risk for early pancreatic cancer; several studies are underway to examine the effectiveness of endoscopic ultrasound (EUS) in the early detection of pancreatic cancer.

Prognosis

Prognosis will depend on the stage of the disease at diagnosis more than it does on hereditary susceptibility.

Genes involved and proteins

BRCA2

Location: 13q12.3

DNA/RNA

Description: gene spanning more than 70kb of genomic DNA; the coding sequence comprises 27 exons (11 395 nucleotides).

Protein

Description: the corresponding protein has 3 418 amino acid residues (384 kDa).

Function: the Brca2 protein binds to Rad51 and serves as an important co-factor in the Rad51 -dependent DNA repair of double strand breaks; the Brca2 protein may also have transcription activation potential.

Mutations

Germinal: more than 300 unique germ-line mutations have been reported; the 6174 delT mutation is particularly common in Jewish subjects

Somatic: acquired mutations in BRCA2 rare in pancreatic cancer.

p16

Location: 9p21

DNA/RNA

Description: the coding sequence comprises 3 exons; this locus gives rise to 2 distinct transcripts from different promoters (p16 and p16(ARF)).

Protein

Description: the corresponding protein, called cyclin-dependent kinase inhibitor-2A, has 156 amino acid residues.

Function: cyclin-dependent kinase inhibitor 2A binds to CDK4 and inhibits the ability of CDK4 to interact with cyclinA thereby inducing a G1 cell cycle arrest.

Mutations

Germinal: germline mutations are associated with the FAMMM Syndrome.

Somatic: virtually all invasive pancreatic carcinomas show inactivation of the p16 gene; forty percent by homozygous deletion, 40% by an intragenic mutation coupled with loss of heterozygosity (LOH) and 15% by hypermethylation of the p16 promoter.

STK11

Location: 19p13.3

DNA/RNA

Description: gene Spanning 23kb of genomic DNA, the coding sequence comprises 9 exons (1446bp).

Protein

Description: the corresponding protein has 433 amino acid residues.

Function: serine threonine protein kinase 11.

Mutations

Germinal: almost all germline mutations are predicted to disrupt the function of the kinase domain.

Somatic: approximately 4% of sporadic pancreatic cancers have somatic inactivation of STK11.

PRSS1

Location: 7q35

DNA/RNA

Description: the coding sequence comprise 5 exons (800bp).

Protein

Description: trypsin, which is active in the pancreas, is inactivated by cleavage; mutations which abrogate this cleavage site can result in autodigestion and pancreatitis.

Mutations

Germinal: the arg117-to-his mutation (R117H) is the most common mutation identified to date.

hMLH1

Location: 3p21.3

DNA/RNA

Description: the coding sequence comprises 2484b.

Protein

Description: MLH1 forms a complex with other DNA mismatch repair gene; functions in DNA mismatch repairs2.

Mutations

Germinal: one of at least 5 known human mismatch repair genes associated with the hereditary non-polyposis colorectal cancer syndrome: the neoplasms that develop in these patients typically show microsatellite instability.

hMSH2

Location: 2p22-p21

DNA/RNA

Description: the MSH2 locus covers approximately 73kb and contains 16 exons.

Protein

Description: MSH2 functions in DNA mismatch repair.

Mutations

Germinal: one of at least 5 known human mismatch repair genes associated with the hereditary non-polyposis colorectal cancer syndrome; the neoplasms that develop in these patients typically show microsatellite instability.

References

JEGHERS H, MCKUSICK VA, KATZ KH. Generalized intestinal polyposis and melanin spots of the oral mucosa, lips and digits; a syndrome of diagnostic significance. *N Engl J Med.* 1949 Dec 22;241(25):993, illust; passim

Lynch HT, Voorhees GJ, Lanspa SJ, McGreevy PS, Lynch JF. Pancreatic carcinoma and hereditary nonpolyposis colorectal cancer: a family study. *Br J Cancer.* 1985 Aug;52(2):271-3

Giardiello FM, Welsh SB, Hamilton SR, Offerhaus GJ, Gittelsohn AM, Booker SV, Krush AJ, Yardley JH, Luk GD. Increased risk of cancer in the Peutz-Jeghers syndrome. *N Engl J Med.* 1987 Jun 11;316(24):1511-4

Caldas C, Hahn SA, da Costa LT, Redston MS, Schutte M, Seymour AB, Weinstein CL, Hruban RH, Yeo CJ, Kern SE. Frequent somatic mutations and homozygous deletions of the p16 (MTS1) gene in pancreatic adenocarcinoma. *Nat Genet.* 1994 Sep;8(1):27-32

Goldstein AM, Fraser MC, Struewing JP, Hussussian CJ, Ranade K, Zemetkin DP, Fontaine LS, Organic SM, Dracopoli NC, Clark WH Jr. Increased risk of pancreatic cancer in melanoma-prone kindreds with p16INK4 mutations. *N Engl J Med.* 1995 Oct 12;333(15):970-4

Berman DB, Costalas J, Schultz DC, Grana G, Daly M, Godwin AK. A common mutation in BRCA2 that predisposes to a variety of cancers is found in both Jewish Ashkenazi and non-Jewish individuals. *Cancer Res.* 1996 Aug 1;56(15):3409-14

Goggins M, Schutte M, Lu J, Moskaluk CA, Weinstein CL, Petersen GM, Yeo CJ, Jackson CE, Lynch HT, Hruban RH, Kern SE. Germline BRCA2 gene mutations in patients with apparently sporadic pancreatic carcinomas. *Cancer Res.* 1996 Dec 1;56(23):5360-4

Whitcomb DC, Gorry MC, Preston RA, Furey W, Sossenheimer MJ, Ulrich CD, Martin SP, Gates LK Jr, Amann

ST, Toskes PP, Liddle R, McGrath K, Uomo G, Post JC, Ehrlich GD. Hereditary pancreatitis is caused by a mutation in the cationic trypsinogen gene. *Nat Genet.* 1996 Oct;14(2):141-5

Whitcomb DC, Preston RA, Aston CE, Sossenheimer MJ, Barua PS, Zhang Y, Wong-Chong A, White GJ, Wood PG, Gates LK Jr, Ulrich C, Martin SP, Post JC, Ehrlich GD. A gene for hereditary pancreatitis maps to chromosome 7q35. *Gastroenterology.* 1996 Jun;110(6):1975-80

Lowenfels AB, Maisonneuve P, DiMaggio EP, Elitsur Y, Gates LK Jr, Perrault J, Whitcomb DC. Hereditary pancreatitis and the risk of pancreatic cancer. International Hereditary Pancreatitis Study Group. *J Natl Cancer Inst.* 1997 Mar 19;89(6):442-6

Ozcelik H, Schmock B, Di Nicola N, Shi XH, Langer B, Moore M, Taylor BR, Narod SA, Darlington G, Andrulis IL, Gallinger S, Redston M. Germline BRCA2 6174delT mutations in Ashkenazi Jewish pancreatic cancer patients. *Nat Genet.* 1997 May;16(1):17-8

Abbott DW, Freeman ML, Holt JT. Double-strand break repair deficiency and radiation sensitivity in BRCA2 mutant cancer cells. *J Natl Cancer Inst.* 1998 Jul 1;90(13):978-85

Goggins M, Offerhaus GJ, Hilgers W, Griffin CA, Shekher M, Tang D, Sohn TA, Yeo CJ, Kern SE, Hruban RH. Pancreatic adenocarcinomas with DNA replication errors (RER+) are associated with wild-type K-ras and characteristic histopathology. Poor differentiation, a syncytial growth pattern, and pushing borders suggest RER+. *Am J Pathol.* 1998 Jun;152(6):1501-7

Hemminki A, Markie D, Tomlinson I, Avizienyte E, Roth S, Loukola A, Bignell G, Warren W, Aminoff M, Höglund P, Järvinen H, Kristo P, Pelin K, Ridanpää M, Salovaara R, Toro T, Bodmer W, Olschwang S, Olsen AS, Stratton MR, de la Chapelle A, Aaltonen LA. A serine/threonine kinase gene defective in Peutz-Jeghers syndrome. *Nature.* 1998 Jan 8;391(6663):184-7

Hruban RH, Petersen GM, Ha PK, Kern SE. Genetics of pancreatic cancer. From genes to families. *Surg Oncol Clin N Am.* 1998 Jan;7(1):1-23

Jenne DE, Reimann H, Nezu J, Friedel W, Loff S, Jeschke R, Müller O, Back W, Zimmer M. Peutz-Jeghers syndrome is caused by mutations in a novel serine threonine kinase. *Nat Genet.* 1998 Jan;18(1):38-43

Mattson K. Docetaxel (Taxotere) in the neo-adjuvant setting in non-small-cell lung cancer. *Ann Oncol.* 1999;10 Suppl 5:S69-72

Su GH, Hruban RH, Bansal RK, Bova GS, Tang DJ, Shekher MC, Westerman AM, Entius MM, Goggins M, Yeo CJ, Kern SE. Germline and somatic mutations of the STK11/LKB1 Peutz-Jeghers gene in pancreatic and biliary cancers. *Am J Pathol.* 1999 Jun;154(6):1835-40

Tascilar M, Tersmette AC, Offerhaus GJ, Hruban RH. Pancreatic cancer--more familial than you thought. *Anal Cell Pathol.* 1999;19(3-4):105-10

Giardiello FM, Brensinger JD, Tersmette AC, Goodman SN, Petersen GM, Booker SV, Cruz-Correa M, Offerhaus JA. Very high risk of cancer in familial Peutz-Jeghers syndrome. *Gastroenterology.* 2000 Dec;119(6):1447-53

Lal G, Liu G, Schmock B, Kaurah P, Ozcelik H, Narod SA, Redston M, Gallinger S. Inherited predisposition to pancreatic adenocarcinoma: role of family history and germ-line p16, BRCA1, and BRCA2 mutations. *Cancer Res.* 2000 Jan 15;60(2):409-16

Lynch HT, Brand RE, Lynch JF, Fusaro RM, Smyrk TC, Goggins M, Kern SE. Genetic counseling and testing for germline p16 mutations in two pancreatic cancer-prone families. *Gastroenterology*. 2000 Dec;119(6):1756-60

Wilentz RE, Goggins M, Redston M, Marcus VA, Adsay NV, Sohn TA, Kadkol SS, Yeo CJ, Choti M, Zahurak M, Johnson K, Tascilar M, Offerhaus GJ, Hruban RH, Kern SE. Genetic, immunohistochemical, and clinical features of medullary carcinoma of the pancreas: A newly described and characterized entity. *Am J Pathol*. 2000 May;156(5):1641-51

Tersmette AC, Petersen GM, Offerhaus GJ, Falatko FC, Brune KA, Goggins M, Rozenblum E, Wilentz RE, Yeo CJ, Cameron JL, Kern SE, Hruban RH. Increased risk of incident pancreatic cancer among first-degree relatives of patients with familial pancreatic cancer. *Clin Cancer Res*. 2001 Mar;7(3):738-44

This article should be referenced as such:

Hruban RH, Kern SE. Hereditary pancreatic cancer. *Atlas Genet Cytogenet Oncol Haematol*. 2001; 5(1):72-75.
