

## Hereditary Pancreatic Cancer

### Identity

Other names      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-telangectasia](#) 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

**Gene Name** 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

### **Gene Name** [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

### **Gene Name** [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

### **Gene Name** 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

**Gene Name** [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 repairs

**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

**Gene Name** 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

### External links

[OMIM](#) [260350](#)

[Orphanet](#) [Pancreatic carcinoma, familial](#)

Other database [National Familial Pancreas Tumor Registry](#)

Other database [The European Registry Of Hereditary Pancreatitis And Familial Pancreatic Cancer](#)

### Bibliography

**Generalized intestinal polyposis and melanin spots of the oral mucosa, lips and digits.**

Jeghers HMD, McKusick VAMD, Katz KHMD.  
N Engl J Med 1949; 241: 992-1005.

**Pancreatic carcinoma and hereditary nonpolyposis colorectal cancer: a family study.**

Lynch HT, Voorhees GJ, Lanspa S, McGreevy PS, Lynch J.  
Br J Cancer 1985; 52: 271-273.

**Increased risk of cancer in the Peutz-Jeghers syndrome.**

. Giardiello FM, Welsh SB, Hamilton SR, Offerhaus GJA, Gittelsohn AM, Booker SV, Krush AJ, Yardley JH, Luk GD.

N Engl J Med 1987; 316: 1511-1514.

**Frequent somatic mutations and homozygous deletions of the p16 (MTS1) gene in pancreatic adenocarcinoma.**

Caldas C, Hahn SA, da Costa LT, Redston MS, Schutte M, Seymour AB, Weinstein CL, Hruban RH, Yeo CJ, Kern, SE.

Nat Genet 1994; 8: 27-32.

**Increased risk of pancreatic cancer in melanoma-prone kindreds with p16 INK4 mutations.**

Goldstein AM, Fraser MC, Struewing JP, Hussussian CJ, Ranade K, Zemetkin DP, Fontaine LS, Organic SM, Dracopoli NC, Clark WH, Tucker MA.

N Engl J Med 1995; 333: 970-974.

**A common mutation in BRCA2 that predisposes to a variety of cancers is found in both Jewish Ashkenazi and non-Jewish individuals.**

Berman DB, Costalas J, Schultz DC, Grana G, Daly M, Godwin AK.

Cancer Res 1996; 56: 3409-3414.

**Germline BRCA2 gene mutations in patients with apparently sporadic pancreatic carcinomas.**

Goggins M, Schutte M, Lu J, Moskaluk CA, Weinstein CL, Petersen GM, Yeo CJ, Jackson CE, Lynch HT, Hruban RH, Kern SE.

Cancer Res 1996; 56: 5360-5364.

**A gene for hereditary pancreatitis maps to chromosome 7q35.**

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.

Gastroenterology 1996; 110: 1975-1980.

**Hereditary pancreatitis is caused by a mutation in the cationic trypsinogen gene.**

Whitcomb DC, Gorry MC, Preston RA, Furey W, Sossenheimer MJ, Ulrich C, Martin SP, Gates LK, Amann ST, Toskes PP, Liddle R, McGrath K, Uomo G, Post JC, Ehrlich GD.

Nat Genet 1996; 14: 141-145.

**Hereditary pancreatitis and the risk of pancreatic cancer.**

Lowenfels AB, Maisonneuve EP, Dimagno YE, Gates LK, Perrault J, Whitcomb DC, and International Hereditary Pancreatitis Study Group.

J Natl Cancer Inst 1997; 89: 442-446.

**Germline BRCA2 6174delT mutations in Ashkenazi Jewish pancreatic cancer patients.**

Ozcelik H, Schmocker B, DiNicola N, Shi XH, Langer B, Moore M, Taylor BR, Narod SA, Darlington G, Andrulis IL, Gallinger S, Redston MS.

Nat Genet 1997; 16: 17-18.

**Double-strand break repair deficiency and radiation sensitivity in BRCA2**

**mutant cancer cells.**

Abbott DW, Freeman ML, Holt JT.  
J Natl Cancer Inst 1998; 90: 978-985.

**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+.**

Goggins M, Offerhaus GJA, Hilgers W, Griffin CA, Shekher M, Tang D, Sohn TA, Yeo CJ, Kern SE, Hruban RH.  
Am J Pathol 1998; 152: 1501-1507.

**A serine/threonine kinase gene defective in Peutz Jeghers syndrome.**

Hemminki A, Markie D, Tomlinson I, Avizienyte E, Roth S, Loukola A, Bignell G, Warren W, Aminoff M, Hoglund P, Jarvinen H, Kristo P, Pelin K, Ridanpaa M, Salovaara R, Toro T, Bodmer W, Olschwang S, Olsen AS, Stratton MD, de la Chapelle A, Aaltonen LA.  
Nature 1998; 391: 184-187.

**Genetics of pancreatic cancer: From genes to families.**

Hruban RH, Petersen GM, Ha PK, Kern SE.  
Surg Oncol Clin N Am 1998; 7: 1-23. (REVIEW).

**Peutz-Jeghers syndrome is caused by mutations in a novel serine threonine kinase.**

Jenne DE, Reimann H, Nezu J, Friedel W, Loff S, Jeschke R, Müller O, Back W, Zimmer M.  
Nat Genet 1998; 18: 38-43.

**Familial pancreatic cancer.**

Hruban RH, Petersen GM, Goggins M, Tersmette AC, Offerhaus GJA, Falatko F, Kern SE.  
Ann Oncol 1999; 10: S69-S73. (REVIEW).

**Pancreatic cancer - More familial than you thought.**

Tascilar M, Tersmette AC, Offerhaus GJA, Hruban RH.  
Anal Cell Pathol 1999; 19: 105-110. (REVIEW).

**Germline and somatic mutations of the STK11/LKB1 Peutz-Jeghers gene in pancreatic and biliary cancers.**

Su GH, Hruban RH, Bova GS, Goggins M, Bansal RK, Tang DT, Shekher MC, Westerman A-M, Entius MM, Yeo CJ, Kern SE.  
Am J Pathol 1999; 154: 1835-1840.

**Very high risk of cancer in familial Peutz-Jeghers Syndrome.**

Giardiello FM, Brensinger JD, Tersmette AC, Goodman SN, Petersen GM, Booker SV, Cruz-Correa M, Offerhaus JA.  
Gastroenterology 2000; 119:1447-1453.

**Inherited predisposition to pancreatic adenocarcinoma: Role of family history and germ-line p16, BRCA1, and BRCA2 mutations.**

Lal G, Liu G, Schmocker B, Kaurah P, Ozcelik H, Narod SA, Redston M, Gallinger S. Cancer Res 2000; 60: 409-416.

**Genetic counseling and testing for germ-line p16 mutations in two pancreatic cancer-prone families: Case Report.**

Lynch HT, Brand RE, Lynch JF, Fusaro RM, Smyrk TC, Goggins M, Kern SE. Gastroenterology 119:1756-1760, 2000.

**Genetic, immunohistochemical, and clinical features of medullary carcinomas of the pancreas: A Newly described and characterized entity.**

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 GJA, Hruban RH, Kern SE.

Am J Pathol 2000; 156: 1641-1651.

**Increased risk of incident pancreatic cancer among first-degree relatives of patients with familial pancreatic cancer.**

Tersmette AC, Petersen GM, Offerhaus GJA, Falatko FC, Goggins M, Rosenblum E, Wilentz RE, Yeo CJ, Cameron JL, Kern SE, Hruban RH.

Clin Cancer Res (In Press).

[REVIEW articles](#)      *automatic search in PubMed*

[Last year publications](#)      *automatic search in PubMed*

**Contributor(s)**

**Written**      12-2000 Ralph H. Hruban, Scott E. Kern

**Citation**

*This paper should be referenced as such :*

**Hruban RH, Kern SE** . Hereditary Pancreatic Cancer. Atlas Genet Cytogenet Oncol Haematol. December 2000 .

URL :

<http://www.infobiogen.fr/services/chromcancer/Tumors/HeredPancrCanID10068.html>

© *Atlas of Genetics and Cytogenetics in Oncology and Haematology*

---