

# Germline Variants and Risk for Pancreatic Cancer

## A Systematic Review and Emerging Concepts

### SUPPLEMENTAL DIGITAL CONTENT

**SUPPLEMENTARY TABLE 1.** List of All Studies With Germline Variant(s) Included

PubMed ID	Year	Title	First Author	Country	Population, Region	Genes	Included Variant(s)	Bin1	Bin2
7522998	1994	Association of pancreatic adenocarcinoma, mild lung disease, and delta F508 mutation in a cystic fibrosis patient.	Tsongalis GJ	United States	White, United States	<i>CFTR</i>	1	0	1
8644702	1996	Founding BRCA1 mutations in hereditary breast and ovarian cancer in southern Sweden.	Johannsson O	Sweden	Swedish, Sweden	<i>BRCA1</i>	1	0	0
8673089	1996	A single BRCA2 mutation in male and female breast cancer families from Iceland with varied cancer phenotypes	Thorlacius S	Iceland	Icelanders, Iceland	<i>BRCA2</i>	1	0	1
8968085	1996	Germline BRCA2 gene mutations in patients with apparently sporadic pancreatic carcinomas.	Goggins M	United States	Mixed, United States	<i>BRCA2</i>	3	1	0
9140390	1997	Germline BRCA2 6174delT mutations in Ashkenazi Jewish pancreatic cancer patients.	Ozçelik H	Canada	Ashkenazi Jewish, Canada	<i>BRCA2</i>	1	1	0
9150150	1997	BRCA2 in American families with four or more cases of breast or ovarian cancer: recurrent and novel mutations, variable expression, penetrance, and the possibility of families whose cancer is not attributable to BRCA1 or BRCA2.	Schubert EL	United States	Ashkenazi Jewish, United States	<i>BRCA2</i>	1	1	0
9150155	1997	Study of a single BRCA2 mutation with high carrier frequency in a small population	Thorlacius S	Iceland	Icelanders, Iceland	<i>BRCA2</i>	1	0	1
9973276	1999	Inherited colorectal polyposis and cancer risk of the APC I1307K polymorphism.	Gryfe R	Canada	Ashkenazi Jewish, Canada	<i>APC</i>	1	0	1
10362809	1999	Germline and somatic mutations of the STK11/LKB1 Peutz-Jeghers gene in pancreatic and biliary cancers.	Su GH	United States	Dutch, Netherland	<i>STK11</i>	1	0	0
10667595	2000	Inherited predisposition to pancreatic adenocarcinoma: role of family history and germ-line p16, BRCA1, and BRCA2 mutations.	Lal G	Canada	Mixed, Canada	<i>BRCA1, BRCA2, CDKN2A</i>	5	2	1
10719365	2000	Patients with both pancreatic adenocarcinoma and melanoma may harbor germline CDKN2A mutations.	Lal G	Canada	Unknown, Canada	<i>CDKN2A</i>	2	0	2
10956390	2000	Risk of developing pancreatic cancer in families with familial atypical multiple mole melanoma associated with a specific 19 deletion of p16 (p16-Leiden).	Vasen HF	Netherlands	Dutch, Netherland	<i>CDKN2A</i>	1	1	0
11058911	2000	A novel germline mutation, P48T, in the CDKN2A/p16 gene in a patient with pancreatic carcinoma.	Moore PS	Italy	Italian, Italy	<i>CDKN2A</i>	1	0	0
11115825	2001	Cystic fibrosis transmembrane regulator (CFTR) DeltaF508 mutation and 5T allele in patients with chronic pancreatitis and exocrine pancreatic cancer. PANKRAS II Study Group.	Malats N	Spain	Unknown, Spain	<i>CFTR</i>	1	0	1
11207041	2001	The rate of the 6174delT founder Jewish mutation in BRCA2 in patients with non-colonic gastrointestinal tract tumours in Israel.	Figer A	Israel	Ashkenazi Jewish, Israel	<i>BRCA2</i>	1	1	0
11267991	2001	A BRCA2 germ-line mutation in familial pancreatic carcinoma.	White K	Germany	German, Germany	<i>BRCA2</i>	1	1	0
11950811	2002	Family history of cancer and germline BRCA2 mutations in sporadic exocrine pancreatic cancer.	Real FX	Spain	Unknown, Spain	<i>BRCA2</i>	1	0	0

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**SUPPLEMENTARY TABLE 1.** (Continued)

PubMed ID	Year	Title	First Author	Country	Population, Region	Genes	Included Variant(s)	Bin1	Bin2
12097290	2002	Evaluation of candidate genes MAP2K4, MADH4, ACVR1B, and BRCA2 in familial pancreatic cancer: deleterious BRCA2 mutations in 17%.	Murphy KM	United States	White, United States	<i>BRCA2</i>	7	1	1
12454511	2002	CDKN2A germline mutations in familial pancreatic cancer.	Bartsch DK	Germany	German, Germany	<i>CDKN2A</i>	4	1	1
12569143	2003	BRCA2 germline mutations in familial pancreatic carcinoma.	Hahn SA	Germany	German and British, Germany	<i>BRCA2</i>	6	3	2
12649567	2003	N34S, a pancreatitis associated SPINK1 mutation, is not associated with sporadic pancreatic cancer.	Teich N	Germany	German, Germany	<i>SPINK1</i>	1	0	0
12750283	2003	Fanconi anemia gene mutations in young-onset pancreatic cancer.	van der Heijden MS	United States	Unknown, United States	<i>FANCC</i>	1	0	0
14688470	2003	Polymorphisms of SPINK1 N34S and CFTR in patients with sporadic and familial pancreatic cancer.	Matsubayashi H	United States	Unknown, United States	<i>CFTR, SPINK1</i>	2	0	1
14726700	2004	The genetics of FANCC and FANCG in familial pancreatic cancer.	Rogers CD	United States	Mixed, United States	<i>FANCC</i>	2	0	0
15017610	2004	Clinical and genetic characteristics of hereditary pancreatitis in Europe.	Howes N	United States	Mixed, Europe	<i>PRSS1</i>	3	0	1
15084977	2004	Hereditary pancreatitis as the premalignant disease: a Japanese case of pancreatic cancer involving the SPINK1 gene mutation N34S.	Masamune A	Japan	Japanese, Japan	<i>SPINK1</i>	1	0	0
15146471	2004	Familial melanoma, pancreatic cancer and germline CDKN2A mutations.	Goldstein AM	United States	Mixed	<i>CDKN2A</i>	18	5	4
15173226	2004	Prospective risk of cancer in CDKN2A germline mutation carriers.	Goldstein AM	United States	White, United States	<i>CDKN2A</i>	2	1	1
15591268	2004	Genetics of the FANCA gene in familial pancreatic cancer.	Rogers CD	United States	Mixed, United States	<i>FANCA</i>	12	0	0
15695377	2005	Germline Fanconi anemia complementation group C mutations and pancreatic cancer.	Couch FJ	United States	Mixed, United States	<i>FANCC</i>	11	0	0
15764155	2005	Mutations N34S and P55S of the SPINK1 gene in patients with chronic pancreatitis or pancreatic cancer and in healthy subjects: a report from Finland.	Lempinen M	Finland	Finnish, Finland	<i>SPINK1</i>	1	0	0
15806175	2005	Increased prevalence of the BRCA2 polymorphic stop codon K3326X among individuals with familial pancreatic cancer.	Martin ST	United States	Unselected, United States	<i>BRCA2</i>	1	0	1
16227367	2005	Cystic fibrosis transmembrane regulator gene carrier status is a risk factor for young onset pancreatic adenocarcinoma.	McWilliams R	United States	Unknown, United States	<i>CFTR</i>	3	0	2
16858628	2006	Low frequency of CHEK2 mutations in familial pancreatic cancer.	Bartsch DK	Germany	White, Germany	<i>CHEK2</i>	1	1	0
16905682	2007	Features associated with germline CDKN2A mutations: a GenoMEL study of melanoma-prone families from three continents.	Goldstein AM	United States	Mixed	<i>CDKN2A</i>	6	4	1
16996571	2006	Medullary carcinoma of the pancreas in a man with hereditary nonpolyposis colorectal cancer due to a mutation of the MSH2 mismatch repair gene.	Banville N	Ireland	Unknown, Ireland	<i>MSH2</i>	1	0	0
17072959	2006	Lack of association between UGT1A7, UGT1A9, ARP, SPINK1 and CFTR gene polymorphisms and pancreatic cancer in Italian patients.	Piepoli A	Italian	Italian, Italy	<i>CFTR, SPINK1</i>	3	0	1
17194196	2006	Palladin mutation causes familial pancreatic cancer and suggests a new cancer mechanism.	Pogue-Geile KL	United States	White, United States	<i>PALLD</i>	1	0	1
17238043	2007	Differential roles of the SPINK1 gene mutations in alcoholic and nonalcoholic chronic pancreatitis.	Masamune A	Japan	Japanese, Japan	<i>SPINK1</i>	1	0	0

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**SUPPLEMENTARY TABLE 1.** (Continued)

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17415588	2007	The P239S palladin variant does not account for a significant fraction of hereditary or early onset pancreas cancer.	Zogopoulos G	Canada	Unknown, Canada	<i>PALLD</i>	2	0	1
18184119	2008	Risk of pancreatic adenocarcinoma in patients with hereditary pancreatitis: a national exhaustive series.	Rebours V	France	French, France	<i>PRSS1</i>	2	0	1
18437078	2008	BRCA2 mutations as a universal risk factor for pancreatic cancer has a limited role in Korean ethnic group.	Cho JH	Korea	Korean, Korea	<i>BRCA2</i>	3	0	0
18439109	2008	Predominant Ashkenazi BRCA1/2 mutations in families with pancreatic cancer.	Dagan E	Israel	Ashkenazi Jewish, Israel	<i>BRCA1, BRCA2</i>	2	2	0
18714178	2008	Low prevalence of CDKN2A/ARF mutations among early-onset cancers of breast, pancreas and malignant melanoma in Poland	Debniak T	Poland	Unknown, Poland	<i>CDKN2A</i>	2	0	0
18762988	2008	Germline BRCA1 mutations predispose to pancreatic adenocarcinoma	Al-Sukhni W	Canada	Mixed, Canada	<i>BRCA1</i>	3	2	1
19064968	2009	BRCA germline mutations in Jewish patients with pancreatic adenocarcinoma.	Ferrone CR	United States	Ashkenazi Jews, United States	<i>BRCA1, BRCA2</i>	3	3	0
19147782	2009	DNA repair gene polymorphisms and risk of pancreatic cancer.	Li D	United States	Mixed, United States	<i>ATM</i>	1	0	0
19264984	2009	Exomic sequencing identifies PALB2 as a pancreatic cancer susceptibility gene.	Jones S	United States	Mixed, United States	<i>PALB2</i>	4	1	0
19454815	2009	Hereditary pancreatitis: clinical features and inheritance characteristics of the R122C mutation in the cationic trypsinogen gene ( <i>PRSS1</i> ) in six Spanish families.	de las Heras-Castaño G	Spain	Spanish, Spain	<i>PRSS1</i>	1	0	0
19635604	2009	Analysis of the gene coding for the BRCA2-interacting protein PALB2 in familial and sporadic pancreatic cancer.	Tischkowitz MD	Canada	Unknown, Canada	<i>PALB2</i>	14	0	0
19728162	2009	Germline MLH1 and MSH2 mutations in Italian pancreatic cancer patients with suspected Lynch syndrome.	Gargiulo S	Italy	Italian, Italy	<i>MLH1, MSH2</i>	5	0	0
19885835	2010	Cystic fibrosis transmembrane conductance regulator ( <i>CFTR</i> ) gene mutations and risk for pancreatic adenocarcinoma.	McWilliams RR	United States	Mixed, United States	<i>CFTR</i>	8	0	3
19896093	2009	Chronic pancreatitis and pancreatic cancer: prediction and mechanism.	Shimosegawa T	Japan	Japanese, Japan	<i>SPINK1</i>	2	1	0
19951905	2010	The variable phenotype of the p.A16V mutation of cationic trypsinogen ( <i>PRSS1</i> ) in pancreatitis families.	Grocock CJ	UK	White, United Kingdom & United States	<i>PRSS1</i>	1	0	0
20041885	2010	Clinical and genetic analysis of 18 pancreatic carcinoma/melanoma-prone families.	Bartsch DK	Germany	German, Germany	<i>BRCA2</i>	2	0	0
20110284	2010	Genotype and haplotype analysis of TP53 gene and the risk of pancreatic cancer: an association study in the Czech Republic.	Naccarati A	Czech Republic	White, Czech	<i>TP53</i>	1	0	0
20195775	2010	Prevalence of BRCA2 and CDKN2a mutations in German familial pancreatic cancer families.	Slater EP	Germany	White, Germany	<i>BRCA2</i>	18	2	1
20412113	2010	PALB2 mutations in European familial pancreatic cancer families.	Slater EP	Germany	Mixed, Europe	<i>PALB2</i>	3	1	1
20643596	2010	CHEK2 gene alterations in the forkhead-associated domain, 1100delC and del5395 do not modify the risk of sporadic pancreatic cancer.	Mohelnikova-Duchonova B	Czech Republic	White, Czech Republic	<i>CHEK2</i>	2	0	2
20711688	2011	A 67-year-old woman with BRCA 1 mutation associated with pancreatic adenocarcinoma.	Lowery M	United States	Ashkenazi Jewish, United States	<i>BRCA1</i>	1	1	0
21150883	2011	Prevalence of CDKN2A mutations in pancreatic cancer patients: implications for genetic counseling.	McWilliams RR	United States	White, United States	<i>CDKN2A</i>	8	2	3

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**SUPPLEMENTARY TABLE 1.** (Continued)

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21184274	2011	PALB2 germline mutations in familial breast cancer cases with personal and family history of pancreatic cancer.	Peterlongo P	Italy	Italian, Italy	<i>PALB2</i>	1	0	0
21468597	2011	TP53 codon 72 polymorphism is associated with pancreatic cancer risk in males, smokers and drinkers.	Sonoyama T	Japan	Japanese, Japan	<i>TP53</i>	1	0	0
21598239	2012	Prevalence of BRCA1 and BRCA2 mutations in Ashkenazi Jewish families with breast and pancreatic cancer.	Stadler ZK	United States	Ashkenazi Jewish, United States	<i>BRCA1, BRCA2</i>	4	3	1
21926548	2011	Pancreatic cancer and a novel MSH2 germline alteration.	Lindor NM	United States	Northern European, United States	<i>MSH2</i>	1	0	1
21989927	2012	Contribution of germline mutations in the BRCA and PALB2 genes to pancreatic cancer in Italy.	Ghiorzo P	Italy	Italian, Italy	<i>BRCA1, BRCA2</i>	7	0	1
22368299	2012	CDKN2A is the main susceptibility gene in Italian pancreatic cancer families.	Ghiorzo P	Italy	Italian, Italy	<i>CDKN2A</i>	6	1	1
22585167	2012	ATM mutations in patients with hereditary pancreatic cancer.	Roberts NJ	United States	Unknown, United States	<i>ATM</i>	6	1	3
23415580	2013	Cancer risk associated with STK11/LKB1 germline mutations in Peutz-Jeghers syndrome patients: results of an Italian multicenter study.	Resta N	Italy	Italian, Italy	<i>STK11</i>	1	0	0
23561644	2013	Exome sequencing identifies nonsegregating nonsense ATM and PALB2 variants in familial pancreatic cancer.	Grant RC	Canada	Unknown, Canada	<i>ATM, PALB2</i>	2	0	0
23658460	2013	High Prevalence of BRCA1 and BRCA2 Germline Mutations with Loss of Heterozygosity in a Series of Resected Pancreatic Adenocarcinoma and Other Neoplastic Lesions	Lucas AL	United States	Ashkenazi Jewish, United States	<i>BRCA1, BRCA2</i>	3	3	0
23751316	2013	Clinical and morphological characteristics of sporadic genetically determined pancreatitis as compared to idiopathic pancreatitis: higher risk of pancreatic cancer in CFTR variants.	Hamoir C	Belgium	Unknown, Belgium	<i>CFTR</i>	3	0	0
23935836	2013	Analysis of PALB2 gene in BRCA1/BRCA2 negative Spanish hereditary breast/ovarian cancer families with pancreatic cancer cases.	Blanco A	Spain	Spanish, Spain	<i>PALB2</i>	19	0	0
24737347	2014	BRCA1 and BRCA2 germline mutations are frequently demonstrated in both high-risk pancreatic cancer screening and pancreatic cancer cohorts.	Lucas AL	United States	Mixed, United States	<i>BRCA1, BRCA2</i>	4	2	1
24802709	2014	A founder MLH1 mutation in Lynch syndrome families from Piedmont, Italy, is associated with an increased risk of pancreatic tumours and diverse immunohistochemical patterns.	Borelli I	Italy	Italian, Italy	<i>MLH1</i>	1	0	1
25003218	2014	CFTR, SPINK1, PRSS1, and CTSC Mutations Are Not Associated With Pancreatic Cancer in German Patients	Schubert S	Germany	Mixed, Germany	<i>CFTR, SPINK1</i>	2	1	1
25072261	2014	Overall survival and clinical characteristics of pancreatic cancer in BRCA mutation carriers.	Golan T	Israel	Mixed, Israel	<i>BRCA1, BRCA2</i>	20	3	8
25227142	2015	Prospective risk of cancer and the influence of tobacco use in carriers of the p16-Leiden germline variant.	Potjer TP	Netherlands	Unknown, Netherlands	<i>CDKN2A</i>	1	1	0
25356972	2015	BRCA1, BRCA2, PALB2, and CDKN2A mutations in familial pancreatic cancer: a PACGENE study.	Zhen DB	United States	Mixed, United States	<i>BRCA1, BRCA2, CDKN2A, PALB2</i>	67	8	10
25479140	2015	Prevalence of germline mutations in cancer predisposition genes in patients with pancreatic cancer.	Grant RC	Canada	Unknown, Canada	<i>ATM, BRCA1, BRCA2, MLH1, MSH2, MSH6, TP53</i>	11	0	4
25675422	2015	Pancreatic mass in a young CFTR carrier with a heterozygous p.R117H CFTR gene mutation and homozygous 7T.	Hanna T	United Kingdom	Unknown, United Kingdom	<i>CFTR</i>	1	0	1

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**SUPPLEMENTARY TABLE 1.** (Continued)

PubMed ID	Year	Title	First Author	Country	Population, Region	Genes	Included Variant(s)	Bin1	Bin2
25734904	2015	Impact of TP53 codon 72 and MDM2 SNP 309 polymorphisms in pancreatic ductal adenocarcinoma.	Hori Y	Japan	Japanese, Japan	<i>TP53</i>	1	0	0
25940717	2015	Germline BRCA Mutations in a Large Clinic-Based Cohort of Patients With Pancreatic Adenocarcinoma.	Holter S	Canada	Mixed, Canada	<i>BRCA1, BRCA2</i>	12	0	4
26041759	2015	The BRCA2 polymorphic stop codon: stuff or nonsense?	Higgs JE	United Kingdom	Mixed, Europe	<i>BRCA2</i>	1	0	1
26421687	2016	The APC I1307K allele conveys a significant increased risk for cancer.	Leshno A	Israel	Unknown, Israel	<i>APC</i>	1	0	1
26483394	2016	Prevalence of Pathogenic Mutations in Cancer Predisposition Genes among Pancreatic Cancer Patients.	Hu C	United States	Mixed, United States	<i>ATM, BRCA1, BRCA2, CDKN2A, CHEK2, MLH1, MSH2, MSH6, PMS2, TP53, FANCM, BARD1, NBN</i>	27	2	3
26658419	2016	Whole Genome Sequencing Defines the Genetic Heterogeneity of Familial Pancreatic Cancer.	Roberts NJ	United States	Mixed, United States	<i>ATM, BRCA1, CDKN2A, PALB2</i>	7	4	1
27038244	2016	Do founder mutations characteristic of some cancer sites also predispose to pancreatic cancer?	Lener MR	Poland	Polish, Poland	<i>BRCA1, CHEK2, PALB2</i>	6	2	2
27106063	2016	Mutation analysis of the PALB2 gene in unselected pancreatic cancer patients in the Czech Republic	Borecka M	Czech Republic	White, Czech	<i>PALB2</i>	16	1	0
27114589	2016	Benefit of Surveillance for Pancreatic Cancer in High-Risk Individuals: Outcome of Long-Term Prospective Follow-Up Studies From Three European Expert Centers.	Vasen H	Netherlands	Mixed, the Netherlands	<i>CDKN2A</i>	1	1	0
27150568	2016	The c.657del5 variant in the NBN gene predisposes to pancreatic cancer.	Borecka M	Czech Republic	White, Czech	<i>NBN</i>	1	0	1
27358244	2016	Metastatic pancreatic adenocarcinoma associated with chronic calcific pancreatitis and a heterozygous SPINK1 N34S mutation.	Moran RA	United States	Unknown, United States	<i>SPINK1</i>	1	0	0
27449771	2016	Multiple rare variants in high-risk pancreatic cancer-related genes may increase risk for pancreatic cancer in a subset of patients with and without germline CDKN2A mutations.	Yang XR	United States	Mixed, United States & Europe	<i>APC, ATM, BRCA1, BRCA2, CFTR, FANCA, MLH1, MSH2, MSH6, PALB2, PALLD, PMS2, TP53</i>	32	1	2
27488870	2016	The Prevalence of Founder Mutations Among Individuals from Families with Familial Pancreatic Cancer Syndrome.	Lener MR	Poland	Polish, Poland	<i>BRCA1, CHEK2, PALB2</i>	7	4	2
27732944	2016	Germline mutations in Japanese familial pancreatic cancer patients.	Takai E	Japan	Unknown, Japan	<i>BRCA2, PALB2, ATM, MLH1</i>	10	0	1
27803004	2017	Mismatch-repair-deficient metastatic pancreatic ductal adenocarcinoma with a germline PALB2 mutation: unusual genetics, unusual clinical course.	Boeck S	Germany	Unknown, Germany	<i>PALB2, BRCA2, ATM</i>	3	0	0
27838800	2017	Double germline mutations in APC and BRCA2 in an individual with a pancreatic tumor.	Goehringer C	Germany	Unknown, Germany	<i>APC, BRCA2</i>	2	0	0