Review Article

Inherited pancreatic cancer

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Abstract: Pancreatic cancers arise through a series of genetic events both inherited and acquired. Inherited genetic changes, both high penetrance and low penetrance, are an important component of pancreatic cancer risk, and may be used to characterize populations who will benefit from early detection. Furthermore, pancreatic cancer patients with inherited mutations may be particularly sensitive to certain targeted agents, providing an opportunity to personalized treatment. Family history of pancreatic cancer is one of the strongest risk factors for the disease, and is associated with an increased risk of caners at other sites, including but not limited to breast, ovarian and colorectal cancer. The goal of this chapter is to discuss the importance of family history of pancreatic cancer, and the known genes that account for a portion of the familial clustering of pancreatic cancer.

Keywords: Familial pancreatic cancer (FPC); genetic syndromes; genome-wide association

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Family history and risk of pancreatic cancer

Family history is a long-recognized risk factor for pancreatic cancer and an important predictor of disease risk. Studies have suggested that approximately 5–10% of pancreatic cancer patients report a close relative with pancreatic cancer (1,2). Most epidemiological studies have demonstrated a 2- to 3-fold increase in risk of pancreatic cancer among individual with affected first-degree relatives (FDRs) (3-12). However, some studies have shown even higher risk. A Swedish study reported a standardized incidence ratios (SIRs) for pancreatic cancer of 1.73 (95% CI: 1.13–2.54) in offspring with at least one parent presented with pancreatic ductal adenocarcinoma (PDAC) (13). In a prospective study from the National Familial Pancreas Tumour Registry (NFPTR), the SIRs for pancreatic cancer in comparison to the Surveillance, Epidemiology, and End Results (SEER) rates were 6.4 (95% CI: 1.8–16.4) and 32.0 (95% CI: 10.2–74.7) in individuals with two and three FDRs with pancreatic cancer (14).

Familial clustering was considered the first evidence supporting the genetic predisposition to pancreatic cancer. Reports of multiple siblings in one generation and individuals in three consecutive generations affected by pancreatic cancer are strong evidence of a hereditary form of the disease following the Mendelian inheritance (15-19). This was later supported by segregation analyses, which favored a major gene model that was predicted to follow an autosomal dominant pattern of a rare allele (20). As demonstrated in the observational epidemiologic studies, individuals with a family history of pancreatic cancer are at an increased risk of developing the disease themselves. In addition, a population-based twin study in Europe has estimated the heritability for pancreatic cancer to be 36%

Table 1 Pancreatic cancer predisposing genes

Genes	Predisposition syndromes	Risk of pancreatic cancer
BRCA2	Hereditary breast and/or ovarian cancer	SIR =2.20–5.90
BRCA1		SIR =1.60–4.73
PALB2	Familial breast cancer	Increased
ATM		Increased
STK11	Peutz-Jeghers syndrome	SIR =76.2–139.7
PRSS1	Hereditary Pancreatitis	SIR =53–87
CDKN2A	Familial atypical multiple mole and melanoma syndrome	SIR =14.8–80.8
Mismatch repair genes (*MLH1*, *MSH2*, *MHS6* and *PMS2*)	Hereditary non-polyposis colorectal cancer	No effect up to SIR =10.68

SIR, standardized incidence ratio.

(95% CI: 0–53%) (21). As more evidence of the genetic basis of pancreatic cancer has emerged, an operational definition of familial pancreatic cancer (FPC) was proposed to facilitate investigations of the inherited components of the disease. FPC is defined as kindreds with at least a pair of FDRs diagnosed with PDAC. Comparing to the general population, FPC kindred members have a 7- to 9-fold increased risk of pancreatic cancer (14,22). Risk is even higher among members of FPC kindreds with a young-onset case (<50 years; SIR =9.31; 95% CI: 3.42–20.28) than those without (SIR =6.34; 95% CI: 4.02–9.51) (22).

Both prospective and retrospective studies have found increased risks of other cancers in relatives of pancreatic cancer patients, particularly breast cancer (23,24), melanoma (24), ovarian (25), and colorectal cancer (24,26). Study from NFPTR reported an increased risk of dying from cancer of the breast [weighted standardized mortality ratio (wSMR) =1.66; 95% CI: 1.15–2.34], ovarian (wSMR= 2.05; 95% CI: 1.10–3.49), bile duct (wSMR =2.89; 95% CI: 1.04–6.39) and bladder (wSMR =1.90; 95% CI: 1.00–3.30) in FDRs of FPC probands (27). Elevated mortality of colon cancer (wSMR=2.31; 95% CI: 1.30–3.81) and prostate cancer (wSMR=2.31; 95% CI: 1.14–4.20) were also observed among the relatives of young-onset (<50 years old) pancreatic cancer probands (27). These findings suggest a shared genetic etiology between pancreatic cancer and several other cancers, and the potential benefits of surveillance at-risk relatives for cancers with established screening guidelines.

Pancreatic cancer genes

Pancreatic cancer is more prevalent in families with several hereditary syndromes, for which the predisposing genes have been identified, including *BRCA1* and *BRCA2* associated with hereditary breast and ovarian cancer (HBOC), *STK11* associated with Peutz-Jeghers syndrome (PJS), *CDKN2A/p16* associated with familial atypical mole and multiple melanoma (FAMMM), mismatch repair (MMR) genes associated with Lynch syndrome, and *PRSS1* associated with hereditary pancreatitis (HP). These genetic syndromes are reported to be associated with a substantially higher risk of pancreatic cancer. The recent discovery of germline mutations in *PALB2* and *ATM* gene in FPC kindreds has extended the list of established high- and moderate-risk pancreatic cancer genes (*Table 1*).

BRCA1/2

BRCA1 and *BRCA2* gene are well-known high-penetrant predisposing genes for HBOC. These genes are involved in the DNA damage response and DNA double-strand breaks repair. Pancreatic cancer is the third most common cancer associated with *BRCA1/2* mutations, though the penetrance at age 70 is much lower (28-31). The prevalence of *BRCA2* mutations in pancreatic cancer patients is 1.4–8.2% for patients unselected for family history (32-36), about 6–16% among FPC patients (37-42), and up to 17.2% in families with 3 or more pancreatic cancers (38,41,43). Comparing to the general population, the risk of pancreatic cancer is about 2–6 fold in *BRCA2* carriers (28,44) and 2–5 fold in *BRCA1* carriers (29,30,44). Several studies had reported a higher risk of pancreatic cancer in *BRCA2* carriers than in *BRCA1* carriers (28,31,44-46). *BRCA1/2* mutation carriers are at particularly high risk (SIR =4–10) for early onset

pancreatic cancer (28-30,44). FDRs of *BRCA1/2* carriers, regardless of their carrier status, have a significantly higher risk of pancreatic cancer than the general population (44,46).

PALB2

PALB2 gene is a tumor suppressor that interacts closely with both *BRCA1* and *BRCA2* during double-strand DNA repair. Mutations of *PALB2* had previously been associated with familial breast cancer (47). Jones *et al.* first reported the discovery of truncating mutations of *PALB2* gene in four FPC probands from the NFPTR (48). Since then, pathogenic mutations of *PALB2* gene have been found in 0.4–4% FPC families, majority of which were families with history of both pancreatic cancer and breast/ovarian cancer (49-55).

ATM

ATM is a breast cancer susceptibility gene that coordinates the DNA double-strand breaks repair. Deleterious mutations of *ATM* gene were first reported by Roberts and his colleagues in two FPC families with at least three members affected by pancreatic cancer (56). In the subsequent analysis, four additional *ATM* mutations were found in 166 FPC patients compared to none in 190 spouse controls (56). To date, *ATM* mutations are found in 1–5% patients with pancreatic cancer (35,36,42,57-59).

STK11

PJS is caused by germline mutations in the *STK11* gene (60-62). PJS patients are at very high risk of developing cancer during their lifetimes, particularly gastrointestinal cancer and gynecological cancer. The cumulative risk of developing any gastrointestinal cancer is 38–66% at age 70 (63). Compared to the general population, PJS patients have a 76- to 140-fold elevated risk for pancreatic cancer (64-66). The cumulative risk of developing pancreatic cancer at age 70 in PJS patients is 11–55% (64-67).

CDKN2A

CDKN2A is a tumor suppressor gene that is considered a major cause of familial melanoma. In melanoma-prone families of European ancestry, pancreatic cancer is the second most common type of cancers associated with *CDKN2A* mutations. Longitudinal studies in these families have found a 15- to 80-fold increased risk of pancreatic cancer in carriers of *CDKN2A* mutations comparing to the general population (68-73). The risk of developing pancreatic cancer is also higher in FDRs of carriers than in FDRs of non-carriers (RR =7.4; 95% CI: 2.3–18.7) (74).

MMR genes

Hereditary non-polyposis colorectal cancer (HNPCC), also known as Lynch Syndrome, accounts for 2–5% of all colorectal cancer. It is caused by inactivating mutations of DNA MMR genes: *MLH1*, *MSH2*, *MSH6* and *PMS2*. While several studies found no increase in risk of pancreatic cancer in Lynch Syndrome patients (75-78), others reported an approximately 7- to 10-fold elevated risk of developing pancreatic cancer in carriers of MMR gene mutations (79-82). The relative risk of pancreatic cancer is higher at younger age (79,80). The cumulative risk of developing pancreatic cancer at age 70 among mutation carriers was estimated to be 3.68% (95% CI: 1.45–5.88%) (80).

PRSS1

HP is autosomal-dominant disorder characterized by recurrent episodes of acute pancreatitis in childhood and frequent progression to chronic pancreatitis. Germline mutations in *PRSS1* are responsible for the majority of HP cases. Comparing to the general population, the risk of pancreatic cancer is about 69-fold higher in HP patients, and the median age of cancer onset was at least 15 years earlier (83-86). About 20–50% HP patients would develop pancreatic cancer at age 70 (83-85,87). The risk is even higher among smokers with HP who tend to develop pancreatic cancer 20 years before non-smokers (85,88).

Germline mutations in sporadic cases

Inherited genetic alterations are not restricted to patients with FDRs affected by pancreatic cancer. While current guidelines recommend germline genetic testing for pancreatic cancer patients with a first degree relative with pancreatic cancer or pancreatic cancer patients with a family history indicative of one of the above mentioned genetic syndromes, patients with apparently sporadic pancreatic cancer may also harbor mutation in a pancreatic cancer susceptibility gene. In fact, the discovery of the role of *BRCA2* in pancreatic cancer was based upon the observation of Three germline mutations in *BRCA2* was

found in 41 (7.3%) sporadic pancreatic cancer patients (32). Subsequent studies have showed that in a series of 306 unselected PDAC patients, 14 carried mutations in *BRCA1* or *BRCA2* while only 2 of the 14 had a family history of PDAC (33). Salo-Mullen *et al.* reported a 7.4% prevalence of *BRCA* mutations in 27 PDAC patients of Ashkenazi Jewish ancestry without a family history of breast, ovarian or pancreatic cancer (34). Studies have reported 0–3% sporadic or unselected pancreatic cancer patients carrying *PALB2* mutations, leading to an aggregated prevalence of 0.75% (55). Recently, in an evaluation of 854 pancreatic cancer patients, twelve of them had germline *BRCA2* mutations, ten with *ATM*, three with *BRCA1*, and two with *PALB2 (*36). Larger scale studies are currently underway to evaluate the mutation prevalence in apparently sporadic pancreatic cancer and expanding genetic testing beyond the current guidelines.

Targeted therapy

Understanding genetic predisposition of pancreatic cancer has important implication for the development and translation of targeted therapies. Tumors with mutations in *BRCA1/2*, *PALB2*, and *ATM* are highly sensitive to DNA-damaging related treatments such as crosslinking agents (89-91) and poly(ADP-ribose) polymerase inhibitors (PARPi) (92-95). Preclinical studies have demonstrated improved sensitivity to chemotherapeutic agents and ionizing radiation in pancreatic cancer cells treated by these agents (96-98). The clinical benefits of using crosslinking agents and PARPi in patients with pancreatic cancer are currently being investigated. Preliminary results have shown promising efficacy of these agents, particularly in patients with *BRCA2*-associated pancreatic cancer (99-102).

Common low-risk susceptibility loci

Genome-wide association studies (GWAS) allow for the unbiased evaluation of common genomic variants associated with pancreatic cancer. To identify common susceptibility variants, five pancreatic cancer GWAS have been conducted by the Pancreatic Cancer Cohort Consortium (PanScan) and the Pancreatic Cancer Case Control Consortium (PanC4) in populations of European ancestry, including PanScan I in 2009 (103), PanScan II in 2010 (104), PanScan III in 2014 (105), PanC4 in 2015 (106) and a recent imputation analysis of GWAS data from PanScan I–III (107). A total of 16 pancreatic cancer susceptibility loci located in 13 genomic regions have been discovered in European populations (*Table 2*).

PanScan I

PanScan I was a two-stage GWAS including 1,896 patients with incidence pancreatic cancer and 1,939 controls in the discovery stage, as well as 2,457 cases and 2,654 controls in the replication stage. The most significant variant (rs505922) on chromosome 9q34.2 was mapped to the first intron of *ABO* blood group gene (103). The association of ABO loci with pancreatic cancer has been robustly replicated in studies of European (105,106,108,109) and Asian populations (110-112). These findings are consistent with the observation that individuals with blood group O had a lower risk of pancreatic cancer than those with groups A or B. About 17% to 19.5% of all pancreatic cancers in populations of European descent was attributable to the inheritance of a non-O blood group (113,114).

PanScan II

From 3,851 pancreatic cancer cases and 3,934 controls, PanScan II identified three novel genomic regions on chromosome 13q22.1 (a large non-genic region), chromosome 1q32.1 (*NR5A2*) and chromosome 5p15.33 (*TERT-CLPTM1L*) to be significantly associated with pancreatic cancer (104). The locus on chromosome 13q22.1 (rs9543325) was mapped to a large gene desert flanked by the *KLF5* and *KLF12* genes. Both genes encode a transcription factor involved in cell transformation, proliferation, and carcinogenesis. Several studies have reported the overexpression of the *KLF5* gene in pancreatic cancer (115-118). The *KLF2* gene, on the other hand, was found to be downregulated in PDAC tumor tissues, and its expression may suppress the malignant transformation of PDAC cancer cells through its regulation of beta-catenin/TCF signaling (119).

Two variants on chromosome 1q32.1 are associated with pancreatic cancer independently. The first significant variant (rs3790844) identified in PanScan II is located in the first intron of the *NR5A2* gene (104). Imputation analysis of PanScan I–III detected the second variant in the upstream of *NR5A2* (rs2816938). *NR5A2* encodes the nuclear receptor subfamily 5 group A member 2, a transcription factor that activates or inhibits transcription of specific target genes. Overexpression of *NR5A2* was observed in resected PDAC tumor tissues and was associated with reduced

Table 2 Genetic susceptibility loci for pancreatic cancer identified in European populations

Chr†	Nearest Gene(s)	Top SNP	Minor/major alleles	Consequence type	Allelic OR (95% CI)	P
1q32.1	*NR5A2*	rs3790844	T/C	Intron	0.77 (0.71–0.84)	2.45×10^{-10}
1q32.1	*NR5A2*	rs2816938	A/T	Upstream	1.20 (1.15–1.25)	4.88×10^{-15}
2p13.3	*ETAA1*	rs1486134	G/T	Downstream	1.14 (1.09–1.19)	3.36×10^{-9}
3q29	*TP63*	rs9854771	A/G	Intron	0.89 (0.85–0.93)	2.35×10^{-8}
5q15.33	*TERT, CLPTM1L*	rs401681	C/T	Intron	1.19 (1.11–1.27)	3.66×10^{-7}
5p15.33	*TERT, CLPTM1L*	rs2736098	T/C	Synonymous	0.80 (0.76–0.85)	9.78×10^{-14}
5p15.33	*TERT, CLPTM1L*	rs35226131	T/C	Upstream	0.71 (0.63–0.80)	1.70×10^{-8}
7p13	*SUGCT*	rs17688601	A/C	Intron	0.88 (0.84–0.92)	1.41×10^{-8}
7q32.3	*LINC-PINT*	rs6971499	C/T	Intron	0.79 (0.74–0.84)	2.98×10^{-12}
8q24.21	*MYC*	rs10094872	T/A	Intron	1.15 (1.10–1.20)	3.22×10^{-9}
9q34	*ABO*	rs505922	T/C	Intron	1.20 (1.12–1.28)	5.37×10^{-8}
13q12.2	*PDX1*	rs9581943	A/G	Upstream	1.15 (1.10–1.20)	2.35×10^{-9}
13q22.1	*None*	rs9543325	T/C	Intergenic	1.26 (1.18–1.35)	3.27×10^{-11}
16q23.1	*BCAR1, CTRB1, CTRB2*	rs7190458	A/G	Synonymous	1.46 (1.30–1.65)	1.13×10^{-10}
17q25.1	*LINC00673*	rs11655237	T/C	Non-coding transcript exon	1.26 (1.19–1.34)	1.42×10^{-14}
22q12.1	*ZNRF3*	rs16986825	T/C	Intron	1.18 (1.12–1.25)	1.18×10^{-8}

†, Chromosomal location in NCBI genome build 37. SNP, single nucleotide polymorphisms; OR, odds ratio; CI, confidence interval.

survival time in PDAC patients (120). Heterozygous Nr5a2 mice exhibit increased rates of pancreatic acinar to ductal metaplasia and impaired recovery after chemically induced acute pancreatitis (121,122). Loss of Nr5a2 accelerates the development of oncogenesis driven by Kras (121,122). These findings suggest a tumor suppressor role of *NR5A2* that protects the pancreas from KRAS driven pre-neoplastic changes.

Four independent pancreatic cancer risk loci have now been identified in the multi-cancer *TERT-CLPTM1L* region on chromosome 5p15.33. The first pancreatic cancer risk locus identified in PanScan II is located in the intron 13 of *CLPTM1L* (rs401681). PanScan III reported a second independent risk locus on chromosome 5p15.33, tagged by a synonymous variant within the second exon of *TERT* (rs2736098) (105). A third independent risk locus located in the first intron of *TERT* gene (rs2853677) was discovered through a candidate gene analysis in 5,550 pancreatic cancer cases and 7,585 control subjects from PANDoRA (PANcreatic Disease ReseArch) consortium and PanScan (123). Recently, imputation of PanScan I–III and replication in PANDoRA and PanC4 found a fourth risk locus for pancreatic cancer in this genomic region (rs35226131), which is located about 200bps upstream of the transcriptional start site of *TERT* (107). The chromosome 5p15.33 region contains two plausible candidate genes: *TERT*, which encodes the catalytic subunit of telomerase reverse transcriptase and *CLPTM1L*, which encodes the cleft lip and palate-associated transmembrane 1 like protein. TERT is a component of the protein and RNA complex that maintains telomere ends. Mutations in TERT promoter region were frequent in multiple tumor types and were correlated with increased TERT expression and telomerase activation (124). Common variants in the *TERT* region were associated with leukocyte telomere length in patients with breast and ovarian cancer (125). A recent study had reported an association between the minor allele of rs401681 and shorter telomere length in pancreatic cancer patients, which was consistent with the observation that telomere shortening occurs as an early event in pancreatic tumorigenesis (126-128). Overexpression of *CLPTM1L* gene are observed in lung and pancreatic

cancer tissues (129-131). CLPTM1L protects tumor cells from genotoxic apoptosis and is required for Ras-induced oncogenic transformation (129,130,132). It's also found that overexpression of CLPTM1 may lead to an abrogation of normal cytokinesis and promote cell proliferation in pancreatic cancer cells (131).

PanScan III

The PanScan III study population combined 1,582 newly genotyped pancreatic cancer cases and 5,203 control subjects with PanScan I cohort and sought replication in 2,576 cases and 6,662 controls from the PANDoRA consortium. Four new risk loci for pancreatic cancer was identified on chromosome 7q23.2 (*LINC-PINT*), 16q23.1 (*BCAR1*), 13q12.2 (*PDX1*) and 22q12.1 (*ZNRF3*). The signal on 7q32.3 was marked by an intronic variant (rs6971499) in *LINC-PINT*, a long intergenic p53-induced non-protein coding RNA located between muskelin 1 *(MKLN1*) and Kruppel-like factor 14 *(KLF14*). Muskelin is an intracellular protein that mediates cell adhesive and cytoskeletal responses to the extracellular matrix (133). KLF14 is a member of the Kruppel-like family of transcription factors that may act as a suppressor of KRAS-mediated cell growth through regulation of the cyclin A promoter (134). Loss of KLF14 may also trigger centrosome amplification, aneuploidy and spontaneous tumorigenesis (135). KLF14 has also been associated with several metabolic phenotypes including type-2 diabetes mellitus (T2DM), a known risk factor for pancreatic cancer (136-139).

A synonymous variant residing in the last exon of *BCAR1* was noted on 16q23.1 (rs7190458). Breast cancer anti-estrogen resistance 1 (BCAR1), also known as p130Cas is a member of the Cas (Crk-associated substrate) family of adaptor proteins with important regulatory roles in migration, cell cycle control and apoptosis (140). Altered expression and activity of p130Cas is known to promote metastasis and drug resistance in multiple cancers (140,141). In addition, two chymotrypsinogen genes, *CTRB1* and *CTRB2* are also located closely to the detected signal. As important members of a family of serine proteases secreted by the pancreas into the gastrointestinal tract (142), these two genes are plausible target for susceptibility variants at this locus. The detected signal for pancreatic cancer is also in proximity of a susceptibility locus (rs7202877) for type-I and type-II diabetes (143,144) that was found to impair beta-cell function (145) and influences expression of CTRB1/2 in pancreas tissues (146).

The top ranked variant on chromosome 13q12.2 (rs9581943) is located in the promoter region of the *PDX1* (pancreatic and duodenal homeobox1 protein 1) gene. Pathway analysis of GWAS data identified *PDX1*, along with *NR5A2*, *HNF1A*, and *HNF4G*, as important genes for pancreatic development (147). The protein encoded by *PDX1* is a transcriptional activator of several genes. It is essential in the early development of pancreas (148), and plays a major role in beta-cell function and glucose-dependent regulation of insulin gene expression. Heterozygous mutations in *PDX1* resulted in impaired glucose tolerance and symptoms of diabetes as seen in maturity-onset diabetes of the young type 4 (MODY4) and late-onset T2DM (149-151).

The signal on chromosome 22q2.1 (rs16986825) maps to an intron in *ZNRF3* (zinc and ring finger 3), which encodes a cell surface transmembrane E3 ubiquitin protein ligase that is a negative regulator of the WNT signaling pathway (152). Additionally, a low-penetrance breast cancer gene, *CHEK2*, is also located in proximity to the detected signal. This gene encodes a cell-cycle checkpoint kinase that cooperates with p53, BRCA1 and ATM and regulates cell division in response to DNA damage (153). Germline mutations and variants of *CHEK2* had been implicated in susceptibility to several cancer types (154-158), including FPC (41,42,159).

PanC4

PanC4 was conducted on 9,925 pancreatic cancer cases and 11,569 controls, pooling 4,164 newly genotyped cases and 3,792 controls from nine studies in the PanC4 consortium with PanSan I and II cohorts in the gene discovery stage, and analyzed an independent set of 2,497 cases and 4,611 controls from the PANDoRA consortium in the replication stage. Not only this study replicated all previously identified risk loci for pancreatic cancer in European populations, three novel associated signals were also detected on chromosome 17q25.1 (*LINC00673*), 7p13 (*SUGCT*) and 3q29 (*TP63*) (106). Significant association was also found on chromosome 2q13.3 (*ETAA1*), a region with prior suggestive evidence in the Han Chinese (160).

The top variant on 17q25.1 (rs11655237) maps to *LINC00673* (long inter-genic non-protein coding RNA 673). This association subsequently replicated in a Han Chinese population (rs11655237, OR=1.26, $P=3.95\times10^{-14}$) (161). Through its epigenetic regulation of gene expression, *LINC00673* may function as an oncogene in several types of cancers. Overexpression

of LINC00673 promotes tumor proliferation, invasion and metastasis in non-small-cell lung cancer (162-164) and tongue squamous cell carcinoma (165), and was correlated with poor prognosis in breast cancer (166). In contrast, expression of LINC00673 was significantly lower in PDAC cancer cells than in normal cells and tissues and overexpression of LINC00673 in the PDAC cell line substantially reduced the rate of cell proliferation. It was found that the single-nucleotide change at rs11655237 creates a miR-1231 binding site, which diminishes the effect of LINC00673 in an allele-specific manner and thus confer susceptibility to pancreatic tumorigenesis (161).

PanC4 reported a significant association on 7p13 with an intronic variant (rs17688601) of the succinyl-CoA:glutarate-CoA transferase *(SUGCT*) gene. Mutations of this gene cause a benign form of glutaric aciduria (glutaric aciduria type III), a rare metabolic abnormality characterized by persistent isolated accumulation or excretion of glutaric acid (167). The role of this gene in pancreatic cancer risk is unclear.

Two strongly correlated intronic variants of *TP63* (tumor protein p63) were found to be associated with pancreatic cancer in PanC4 (top variants rs9864771). Protein encoded by *TP63* (p51/p63) is a p53 homologue with pleiotropic functions including cell proliferation, survival, apoptosis, differentiation, senescence, and aging. Frequent overexpression of p63 was observed in resected PDAC tissues (168). It was suggested that different isoforms of p63 have opposite effects. While TAp63 induces cell death and cell cycle arrest with tumor suppressor features (169), DNp63 as the predominant isoform in pancreatic cancer cell lines, promotes pancreatic cancer growth, motility and invasion (170,171). As a tumor suppressor, p63 had reduced anti-oncogenetic effects compared with p53 in human cancer cells (172). However, loss of p63 can cooperate with loss of p53, leading to higher tumor burden and metastasis as seen in genetic mice models (168,171). It is hypothesized that it is the ratio of TAp63 and DNp63 that determines the biological outcome and chemo-sensitivity.

Imputation analysis of PanScan I–III

Recently, an imputation analysis of the GWAS data in 5,107 cases and 8,845 controls from PanScan I–III had uncovered three new pancreatic cancer signals on chromosome 1q32.1 (*NR5A2*), 8q24.21 (*MYC*), and 5p15.33 (*CLPTM1L-TERT*), all of which are independent from previously reported susceptibility variants (107).

The detected variants on 8q24.21 (rs10094872) is a novel risk loci for pancreatic cancer, independent from the previously reported loci with suggestive evidence in PanScan III (rs1561927). These two variants are both located in the 2 Mb region known to contain multiple susceptibility loci that influence risk of bladder, breast, prostate, colorectal, lung, ovarian, pancreatic, and renal cancer (173-177). *MYC* (MYC proto-oncogene, bHLH transcription factor) is the gene located in the closest proximity to the detected variant. Oncogene MYC is a transcription factor that has been implicated in the pathogenesis of one-third of all human malignancies, and may play an important role in KRAS-driven neoplastic transformation in the pancreas (178). MYC overexpression occurs in up to 42% of advanced PDAC (179,180). Activation of MYC in adult mice has led to the development of ductal adenocarcinomas with metastasis to the liver (181). Although evidence have suggested regulatory roles of the 8q24.21 risk loci in the expression of MYC, functional analyses are warranted to allow a deeper understanding of the underlying mechanism (178).

GWAS in Asian populations

Two GWAS have been conducted in populations of Asian descent (*Table 3*). The Japanese pancreatic cancer study of 991 cases and 5,209 controls found suggestive associations on chromosome 6q25.3 (*FOXQ1*), 12p11.21 (*BICD1*) and 7q36.2 (*DPP6*) (182). The second GWAS in a Chinese population of 3,584 pancreatic cancer cases and 4,868 controls (ChinaPC) identified five susceptibility loci on chromosome 21q21.3 (*BACH1*), 21q22.3 (*TFF1*), 10q26.11 (*PRLHR*), 22q13.32 (*FAM19A5*), and 5p13.1 (*DAB2*) (160). The most significant association identified in ChinaPC was for rs372883, a variant located in the 3' untranslated region (3'UTR) of *BACH1* (BTB domain and CNC homolog 1) gene on chromosome 21q21.3. BACH1 is a transcription factor that belongs to the cap 'n' collar type of basic region leucine zipper factor family (CNC-bZip). Recent studies have demonstrated a critical role of BACH1 in cell migration and metastasis through its regulation of metastasis-related gene expression in breast, colon and prostate cancer (183-185). The second significant association was detected on chromosome 21q22.3 (rs1547374). This region harbors the trefoil family protein 1 (*TFF1*) gene that encodes secretory proteins expression in gastrointestinal mucosa. Upregulated expression of TFF1 in precursor lesions of PDAC, including pancreatic

Table 3 Genetic susceptibility loci for pancreatic cancer identified in Asian populations

Chr†	Nearest gene(s)	Top SNP	Minor/major alleles	Consequence type	Allelic OR (95% CI)	P
5p13.1	*DAB2*	rs2255280	C/A	Intron	0.81 (0.76–0.87)	4.18×10^{-10}
10q26.11	*RPLHR*	rs12413624	T/A	Regulatory region	1.23 (1.16–1.31)	5.12×10^{-11}
21q21.3	*BACH1*	rs372883	C/T	3' UTR	0.79 (0.75–0.84)	2.24×10^{-13}
21q22.3	*TFF1*	rs1547374	G/A	Downstream	0.79 (0.74–0.84)	3.71×10^{-13}
22q13.32	*FAM19A5*	rs5768709	G/A	Intron	1.25 (1.17–1.34)	1.41×10^{-10}

†, Chromosomal location in NCBI genome build 37. SNP, single nucleotide polymorphisms; OR, odds ratio; CI, confidence interval; 3' UTR, 3' untranslated region.

intraepithelial neoplasia (PanIN), intraductal papillary-mucinous neoplasms (IPMNs) and mucinous cystic neoplasms (MSNs), suggests its potential involvement at the early stage of pancreatic carcinogenesis (186-188). Recent studies found that reduced expression of TFF1 in the invasion front of human PDAC was associated with lymph node metastasis and poor survival in patients with PDAC (189). In pancreatic cancers, expression of TFF1 promotes tumorigenesis by suppressing oncogene-induced senescence (190) and is correlated with increase metastasis (191). An intronic variant (rs2255280) in *DAB2* (clathrin adaptor protein) gene region on 5p13.1 was among the identified susceptibility loci in ChinaPC. Frequent loss expression of DAB2 in human malignant cancer cells suggests its potential role as a tumor suppressor (192). Overexpression of DAB2 inhibits cell growth, migration and invasion, and was correlated with poor survival in cancer patients (193-196). Significant association on 10q26.11 was observed for a regulatory variant of *PRLHR* (prolactin releasing hormone receptor) gene (rs12413624). Polymorphisms of this gene was associated with colorectal cancer (197). A intronic variant of *FAM19A5* (family with sequence similarity 19 member A5) gene on 22q13.32 was also associated with an increased risk of pancreatic cancer (rs5768709). This gene encodes a TAFA protein expressed predominately in brain and may function as brain-specific chemokines or neurokines (198). Prior to the ChinaPC study, there is no implication of *PRLHR* or *FAM19A5* in the risk of pancreatic cancer and thus their susceptibility role is currently unknown.

Current status of screening high-risk populations

Screening and early detection of pancreatic cancer offer the best chance of reducing the high mortality rates of this disease. The goal of screening asymptomatic individuals is to identify pancreatic cancer at early stage or, ideally to identify high-grade precancerous lesions that can be resected to prevent the development of cancer. Because of the low incidence of pancreatic cancer in the general population, population level screening will demand a highly specific screening assay. Selective screening of individuals at increased risk for pancreatic cancer is considered worthwhile. The International Cancer of the Pancreas Screening (CAPS) Consortium recommends screening on FDRs of FPC patients, patients with PJS, and carriers of *CDKN2A/p16*, *BRCA2*, and carriers of MMR gene mutations with ≥1 affected FDR (199). FDRs of FPC patients represent a group of high-risk individuals that are relatively easy to identify in clinical settings. Of all identified risk factors for pancreatic cancer, PJS confers the greatest risk for the disease, making PJS patients good candidates for pancreatic cancer screening. Among the established pancreatic cancer genes, germline *BRCA2* mutations followed by *ATM* account for the highest percentage of inherited pancreatic cancer (34,36,40,42,58). It is recommended that *BRCA2* mutation carriers with ≥1 affected FDR and those with two or more affected family members should be considered for screening, particularly Ashkenazi Jewish individuals. In addition, given the substantially higher risk of pancreatic cancer in patients with *CDKN2A/p16* and MMR gene mutations, screening is also recommended to those mutation carriers with >1 affected FDRs (199).

Endoscopic ultrasonography (EUS) and/or MRI/magnetic resonance cholangiopancreatography (MRCP) are recommended by CAPS as initial screening tools. However, the CAPS Consortium could not reach consensus on ages to initiate or stop surveillance, the interval for follow-up imaging, nor on the long-term management of initial

abnormal results (199). Screening and early detection strategies should be accompanied by effective treatment or preventive strategies if they are to produce a significant survival benefit. Given morbidity and mortality associated with pancreatic surgery, there is little consensus about when surgery is required for pancreatic lesion in asymptomatic high-risk individuals (199). Multidisciplinary assessment is however recommended to make individualized decision of the necessity of surgical intervention. The lack of consensus on many aspects of pancreatic cancer screening underscores the need for more research to fill the knowledge gap and to make evidence-based decisions.

Summary and future directions

Pancreatic cancer is rare and deadly disease with the highest case-fatality rate of any major cancer. Due to the lack of effective means for prevention, diagnosis and treatment, pancreatic cancer remains a major public health challenge. Family history, cigarette smoking, chronic pancreatitis, and diabetes are well-established risk factors for pancreatic cancer. Pancreatic cancer is fundamentally a genetic disease caused by both inherited and acquired genetic mutations. Family-based heritability analysis reported 36% of pancreatic cancer was due to genetics. FPC kindreds and patients affected by certain genetic syndromes, for example HP, PJS, HBOC, FAMMM, and HNPCC, are at particularly high risk of pancreatic cancer. About 15–20% of FPC are caused by germline mutations in one of the established pancreatic cancer gene (*BRCA2*, *ATM*, *PALB2*, *PRSS1*, *STK11*, *BRCA1*, *CDKN2A*, *MLH1*, *MSH2*, *MSH6*, and *PMS2*). The genetic basis of susceptibility underlying the majority of FPC cases, however, remains unexplained. To date, GWAS of pancreatic cancer have discovered 16 low-risk susceptibility loci in European populations and 5 in Asian populations, many of which had strong biological plausibility. Together, these GWAS loci explained <5% of pancreatic cancer. Screening, surveillance and management guidelines for genetically high-risk individuals are currently evolving. DNA-damaging related agents are promising in treating pancreatic cancer caused by mutations in *BRCA1*, *BRCA2*, *PALB2 or ATM* genes. Identification of disease-causing genes can aid in the characterization of individuals at highest genetically defined risk in which effective prevention approach can be developed.

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Footnote

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