# Genetic Epidemiology and Pancreatic Cancer

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**Abstract** Gene mutations that are associated with cancer syndromes explain a small portion of pancreatic cancer cases. The majority of the sporadic pancreatic cancer cases are perhaps the consequence of a joint effect of genetic factors and environmental or lifestyle risk factors. Studies on common genetic variants via the candidate gene approach have observed risk modifications by genes involved in various biological process and signaling pathways. However, most of these findings were made in studies that lacked adequate statistical power or replication effort. Recent genome-wide association studies (GWAS) have identified several genes and loci associated with the risk of pancreatic cancer: *ABO*, *NR5A2*, and *TERT1* in individuals with European ancestry, *FOXQ1*, *BICD1*, and *DPP6* in the Japanese population, and *BACH1*, *DAB2*, *PRLHR*, *TFF1*, and *FAM19A5* in the Chinese population. Future completion of larger scale GWAS in pancreatic cancer, mining of GWAS data using novel statistical approaches, and functional studies on the mechanistic links between identified genes and the disease will provide new insights into genetic susceptibility to and the molecular mechanisms of pancreatic cancer.

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## Introduction

Familial pancreatic cancer accounts for approximately 10 % of pancreatic cancer cases in the general population. Mutations in genes that are associated with cancer syndromes also explain a small portion of pancreatic cancer cases. The majority of the sporadic cases are perhaps the consequence of a joint effect of genetic factors and environmental or lifestyle risk factors. Cigarette smoking, high body mass index (BMI), long-term type 2 diabetes, and possibly higher intake of red meats or fat are major nongenetic modifiable risk factors for this disease. Because only a portion of individuals with these modifiable risk factors ever develop pancreatic cancer, genetic susceptibility factors alone or in combination with epidemiological factors may play a major role in pancreatic carcinogenesis. Research on common genetic variants via the candidate gene approach and via genome-wide association studies (GWAS) has generated a large amount of information on potential genetic susceptibility genes for this disease. In this chapter, we summarize recent information and discuss future directions in this research field.

## The Candidate Gene Approach

Since 1994, several large, retrospective case–control studies in the USA (Duell et al. 2002a; Gross et al. 1999; Li 2001; McWilliams et al. 2008; Prizment et al. 2012; Asomaning et al. 2008), China (Li et al. 2011; Zhao et al. 2009), the Czech Republic (Vrana et al. 2009), and Japan (Suzuki et al. 2008a) have achieved adequate sample size to address the main effect of common single-nucleotide polymorphisms (SNPs) on the risk of sporadic pancreatic cancer. The genes and SNPs selected in those studies included those involved in carcinogen or nutrient metabolism (Vrana et al. 2009; Suzuki et al. 2008a; Ayaz et al. 2008; Bartsch et al. 1998; Duell et al. 2002b; 2010; Jiao et al. 2007a, b; Kanda et al. 2009; Li et al. 2005, 2006; Liu et al. 2000; Miyasaka et al. 2005, 2010; Mohelnikova-Duchonova et al. 2010; Ockenga et al. 2003; Ohnami et al. 2008; Piepoli et al. 2006; Suzuki et al. 2008b; Verlaan et al. 2005; Wang et al. 2005; Vrana et al. 2010), DNA repair (Duell et al. 2002a; McWilliams et al. 2008; Dong et al. 2011a; Gargiulo et al. 2009; Jiao et al. 2006, 2007c, 2008; Li et al. 2009; McWilliams et al. 2009a; Zhang et al. 2011a), cell cycle regulation and apoptosis (Asomaning et al. 2008; Li et al. 2011; Chen et al. 2007, 2008, 2010; Couch et al. 2009, 2010; Grochola et al. 2010; Naccarati et al. 2010; Reid-Lombardo et al. 2011; Sonoyama et al. 2011; Theodoropoulos et al. 2010a; Wang et al. 2007; Yang et al. 2008), antioxidant defense (Lyn-Cook et al. 2006; Mohelnikova-Duchonova et al. 2011; Tang et al. 2010), inflammation and the immune system (Zhao et al. 2009; Reid-Lombardo et al. 2011; Duell et al. 2006; Hamacher et al. 2009; Lang et al. 2012; Olson et al. 2007; Ozhan et al. 2011;

Sun et al. 2008; Talar-Wojnarowska et al. 2011; Yang et al. 2012), and mitochondrial function (Wang et al. 2007; Lynch et al. 2011). Other genes and SNPs include those related to familial pancreatic cancer (McWilliams et al. 2009b), other cancers (Couch et al. 2009; Lang et al. 2012; Chen et al. 2011), or medical conditions such as insulin resistance (Suzuki et al. 2008c; Dong et al. 2011b) or obesity, and diabetes (Prizment et al. 2012; Wang et al. 2007; Tang et al. 2010, 2011 Fong et al. 2010; Pierce et al. 2011). Researcher's selection of candidate genes is largely based on existing knowledge of risk factors for pancreatic cancer and hallmarks of cancer. With the evolution of genotyping technology, PCR-RFLP, Taqman, mass spectrometry, Sequenom, Illumina GoldenGate, and other methods have been used in different studies. In most of these studies, weak main effects of the genes were observed occasionally; interactions with known nongenetic risk factors were reported more frequently. In this section, we briefly summarize the major findings from the existing research. Findings on genes involved in xenobiotic metabolism, oxidative stress, and cell cycle control published after 2009 are summarized in Table 1. Prior studies were summarized in a recent review (Lin et al. 2011) and a meta-analysis (Mazaki et al. 2011). Studies that included fewer than 100 cases (Ayaz et al. 2008; Bartsch et al. 1998; Piepoli et al. 2006; Hamacher et al. 2009; Fong et al. 2010; Krechler et al. 2009; Lukic et al. 2011; Scola et al. 2009; Theodoropoulos et al. 2010b) are not reviewed in this section.

## *Xenobiotic Metabolizing Genes*

Because cigarette smoking is a major risk factor for pancreatic cancer, carcinogen metabolic genes and DNA repair genes were among the first genes studied in a wave of research on genetic variants in pancreatic cancer. Studies conducted at the University of Texas MD Anderson Cancer Center reported positive associations between the *CYP1A2*, *NAT1*, and *NAT2* genotypes and risk of pancreatic cancer independently or jointly with exposure to tobacco carcinogens (Jiao et al. 2007a; Li et al. 2006; Suzuki et al. 2008b). None of four studies on glutathione S-transferase (*GST*) genes found a significant main effect on risk of pancreatic cancer (Vrana et al. 2009; Duell et al. 2002b; Jiao et al. 2007b; Liu et al. 2000). Of those four studies, one observed a possible interaction between *GSTT1* gene deletion and heavy smoking among Caucasians, in particular among women (Duell et al. 2002b), and two reported an age-related effect of the *GSTP1*-codon 105 SNP on risk of pancreatic cancer (Vrana et al. 2009; Jiao et al. 2007b). The rs743572 SNP of *CYP17A1*, a gene encoding an enzyme involved in estrogen and testosterone biosynthesis, was associated with risk of pancreatic cancer in Caucasians (Duell et al. 2010). One SNP of *CYP1B1* (rs1056836) was associated with pancreatic cancer in a Czech Republic population. However, the confounding factors were not evaluated in this study (Vrana et al. 2010) (Table 1).

**Table 1** Selected candidate gene studies on pancreatic cancer (published mostly since 2009)

| Reference | Study location (ethnicity) | No. of cases/ controls | Genes and SNPs assessed | OR (95 % CI) with $P<0.05$ | Covariates | Joint effect of risk factors and SNP | Test for joint effect |
|---|---|---|---|---|---|---|---|
| Duell et al. (2010) | USA-San Francisco (77 % Caucasian) | 308/964 | *CYP17A1*: rs743572 34 T/C(A1/A2) | A1/A2 vs. A1A1: 0.77 (0.58–1.00) A2/A2 vs. A1/A1: 0.63 (0.42–0.93) | Age, sex, race, smoking | Not detected | NA |
| Vrana et al. (2010) | Czech Republic (100 % Caucasian) | 156/337 | *CYP1B1*: rs1056836 Leu432Val rs1800400 Asn453Ser | rs1056836: Val/Val vs. Leu/Leu: 0.59 (0.36–0.96) | No | Not examined | NA |
| Wheatley-Price et al. (2008) | USA-Massachusetts General Hospital (100 % Caucasian) | 122/331 | *SOD2*: rs4880 Ala16Val *MPO*: –G463A | rs4880: Val/Val vs. any Ala: 2.05 (1.2–3.6) –G463A: any A vs. GG: 0.57 (0.4–0.9) | Age, sex smoking, alcohol use | Not examined | NA |
| Tang et al. (2010) | USA-MDACC (91 % Caucasian) | 575/648 | *SOD2*: rs4880, rs2758346 *GSTA4*: rs1802061, rs182623, rs316141 *CAT*: rs1001179 *GPX1*: rs1050450 | No | Age, sex, race, smoking, alcohol, diabetes and family history of cancer | SOD2 rs4880 stronger for any Ala and diabetes | $P=0.05$ |
| Mohelnikova-Duchonova et al. (2011) | Czech Republic (100 % Caucasian) | 235/265 | *SOD2*: rs4880 *SOD3*: rs1799895 *NQO1*: rs1800566 *NQO2*: rs1143684 | No | Age, sex, weight, diabetes, pancreatitis, smoking, alcohol, coffee, and tea consumption | Not detected | NA |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Zhang et al. (2011a) | USA-Minnesota (93.5 % Caucasian) | 189/486 | *SOD2*: rs4880<br>*CAT*: rs1001179<br>*hOGG1*: rs1052133<br>*XRCC1*: rs25487 | rs4880: any Val vs. Ala/Ala: 0.57 (0.37–0.89) | Age, sex, race, education, smoking, alcohol use, physical activity, and energy intake | Stronger for Val allele and lower intake of antioxidants | NR |
| Sonoyama et al. (2011) | Japan (Japanese) | 226/448 | *TP53*: rs1042522 Arg72/Pro | Pro/Pro vs. Arg/Arg: 1.70 (1.01–2.88) | Age, sex, smoking and alcohol use | Stronger for male heavy smoking, or heavy drinking | NR |
| Naccarati et al. (2010) | Czech Republic (100 % Caucasian) | 240/743 | *TP53*: rs1042522 G>C Arg72Pro, rs17878362 A(1)>A(2), rs12947788 C>T, rs17884306 G>A | rs1042522: any Pro vs. Arg/Arg: 1.73 (1.26–2.39) | Age, sex, BMI, smoking | Not examined | NA |
| Grochola et al. (2010) | UK (100 % Caucasian) | 103/499 | *MDM2*: 309 T/G | G-allele vs. T-allele was associated with earlier onset of pancreatic cancer | Not examined | Stronger for male | NR |
| Asomaning et al. (2008) | USA- Massachusetts General Hospital (100 % Caucasian) | 123/372 | *MDM2*: 309 T/G | T/G vs. TT: 1.89 (1.20–2.99)<br>G/G vs. T/T: 2.07 (1.03–4.16) | Age, sex, smoking status, pack-years of smoking | Not examined | NA |

*BMI* body mass index, *MDACC* The University of Texas MD Anderson Cancer Center, *NA* not applicable, *NR* not reported, *OR* (95 % CI) odds ratio (95 % confidence interval) of pancreatic cancer, *SNPs* single-nucleotide polymorphisms

## *DNA Repair Genes*

Studies on various DNA repair pathways—such as base excision repair, nucleotide excision repair, homologous recombination repair and non-homologous end joining, and mismatch repair—have observed some weak main effects of variants of DNA repair genes on the risk of pancreatic cancer, such as *LIG3* and *ATM* (Li et al. 2009), *MGMT* and *PMS2* (Dong et al. 2011a). Some joint effects of *XRCC1*, *APE1*, *MGMT*, *XRCC2*, and *XPD* variants with smoking (Jiao et al. 2006, 2007c; 2008) and *ATM* and *LIG4* variants with diabetes (Li et al. 2009) were also reported. However, two studies on the interaction between the *XPD* D312N SNP (rs1799793) and heavy smoking showed opposite directions: the minor allele was associated with increased risk in one study (McWilliams et al. 2008) and decreased risk in the other (Jiao et al. 2007c). Three studies in the USA consistently found a null association of the *XRCC1* rs25487 with risk of pancreatic cancer (Duell et al. 2002a; McWilliams et al. 2008; Jiao et al. 2006). Using a tagging SNP approach, a Mayo Clinic study examined 236 tag-SNPs of 26 DNA repair genes and identified that the genotype and haplotype of the *MMS19L* gene, which is involved in nucleotide excision repair, were associated with risk of pancreatic cancer (McWilliams et al. 2009a). Three studies have investigated *hOGG1* SNPs (McWilliams et al. 2008; Zhang et al. 2011a; Li et al. 2002), but only one found an association between the variant allele of rs1052133, and the risk of pancreatic cancer (OR: 1.57, 95 % CI: 1.04–2.39, any 326Cys compared with Ser326Ser) (Zhang et al. 2011a).

## *Oxidative Stress-Associated Genes*

Oxidative stress is one of the mechanisms whereby cigarette smoking can contribute to pancreatic cancer development. A number of studies have investigated the association between SNP rs4880 of *SOD2* and the risk of pancreatic cancer (Zhang et al. 2011a; Mohelnikova-Duchonova et al. 2011; Tang et al. 2010; Wheatley-Price et al. 2008). A study with a Czech population showed neither main effects nor interactions with smoking and alcohol, coffee, or tea consumption (Mohelnikova-Duchonova et al. 2011). A U.S. study showed that the valine allele of *SOD2* rs4880 interacted with diabetes and antioxidant use in modifying the risk of pancreatic cancer (Zhang et al. 2011a; Tang et al. 2010). No association was reported for other genes involved in oxidative stress, including *SOD3*, *CAT*, *NQO1*, and *NQO2*, in pancreatic cancer (Table 1). Mitochondria play a key role in the production of reactive oxygen species. Oxidative stress could cause mitochondrial damage and affect mitochondrial DNA copy numbers. A Mayo Clinic study found no association between 24 mitochondrial SNPs or haplogroup and risk of pancreatic cancer (Wang et al. 2007). In a nested case–control study within a Finnish male smoker cohort, a significantly higher copy number of mitochondrial DNA was detected (Lynch et al. 2011).

## *Inflammation and Immunity Genes*

Accumulating evidence suggests that chronic inflammation may be one of the underlying mechanisms that contribute to pancreatic cancer development (Farrow et al. 2004). Several studies have evaluated the polymorphisms of selected inflammatory genes in association with pancreatic cancer. A Mayo Clinic study examined 1,538 SNPs of 102 genes involved in nuclear factor κB–mediated inflammatory pathways and found significant associations between the *CD101* rs10923193 or four SNPs of *NOS1* (rs3782203, rs9658350, rs532967, and rs547954) and the risk of pancreatic cancer. However, the significant associations could not be validated in a PanScan cohort and case–control consortium study (Reid-Lombardo et al. 2011). Two other studies found possible interactions of *TNF*α −308 G/A and *RANTES* −403 G/A with pancreatitis, *CCR5* −Δ32 with smoking (Duell et al. 2006), and *IL-4R* G3017T with allergic response (Olson et al. 2007) in modifying risk of pancreatic cancer.

Cytotoxic T-lymphocyte antigen-4 (CTLA-4) plays important roles in down-regulating T-cell activation, thereby attenuating antitumor responses and increasing cancer susceptibility. The *CTLA-4* 49 G>A SNP (rs231775) weakens the binding affinity of CTLA-4 to B7.1, leading to attenuated CTLA-4-triggered inhibition of T-cell activation and proliferation (Sun et al. 2008). Two independent studies in China showed that the *CTLA-4* 49A allele was significantly associated with a higher risk of pancreatic cancer (Yang et al. 2008; Lang et al. 2012).

Cyclooxygenase-2 (COX-2) is a key enzyme in the arachidonic acid pathway. A Chinese study and a Polish study both showed a positive association of the −1195AA *COX-2* genotype with risk of pancreatic cancer (Zhao et al. 2009; Talar-Wojnarowska et al. 2011). The Chinese study also revealed that the −765GC genotype increased the risk of pancreatic cancer both independently and jointly with cigarette smoking (Zhao et al. 2009). However, the Polish study did not find such an association (Talar-Wojnarowska et al. 2011). A small hospital-based study in Turkey found that two haplotypes of *COX2* were more frequent in patients than in control subjects (Ozhan et al. 2011).

## *Folate- and Alcohol-Metabolizing Genes*

Observations have been inconsistent on the 5,10-methylenetetrahydrofolate reductase (*MTHFR*) C677T SNP (rs1801133) in pancreatic cancer (Suzuki et al. 2008a; Li et al. 2005; Ohnami et al. 2008; Wang et al. 2005; Matsubayashi et al. 2005) and null for the *MTHFR* A1298C SNP (Li et al. 2005; Wang et al. 2005; Matsubayashi et al. 2005). Those studies were summarized in two previous review articles (Lin et al. 2011; Mazaki et al. 2011). The latter article, a meta-analysis, concluded that the *MTHFR* 677TT genotype in Caucasian smokers conferred a 1.66- and 2.52-fold higher risk of pancreatic cancer compared with the CC and CT genotypes, respectively (Mazaki et al. 2011). In a step-wise genotyping study, a Japanese study investigated 227 SNPs of 46 selected genes that are involved in folate metabolism.

The variant alleles of the methionine synthase reductase (*MTRR*) gene SNPs rs162049 and rs10380 were associated with increased risk of pancreatic cancer (Ohnami et al. 2008), but the results from other previously reported SNPs of *MTHFR* and *NAT1* were not replicated in this study. Another Japanese study did not find any main effect of the folate metabolic genes, but a potential interaction of some SNPs of *MTHFR* and *MTRR* with heavy alcohol consumption was suggested (Suzuki et al. 2008a).

One of two studies on the thymidylate synthase (*TS*) variable number of tandem repeat variants found no association with pancreatic cancer in a Japanese population (Suzuki et al. 2008a). The second study found an increased risk of pancreatic cancer for the *TS* 5'-untranslated region 3Rc/3Rc genotype in a Chinese population (Dong et al. 2011a).

Heavy alcohol consumption (>4 drinks per day) has been associated with an increased risk of pancreatic cancer (Jiao et al. 2009). However, a case–control study in the Czech Republic did not find an association between the alcohol dehydrogenase *ADH1B* and *ADH1C* variants and pancreatic cancer risk (Mohelnikova-Duchonova et al. 2010). A meta-analysis of studies on the aldehyde dehydrogenase (*ALDH)2* gene found a marginally significant effect of alcohol intake on the risk of pancreatic cancer among the heterozygous *1*2 genotype carriers but not among the *2*2 homozygous genotype carriers (Mazaki et al. 2011).

## *Cell Cycle Regulation- and Apoptosis-Related Genes*

Two studies found that the *P53* Arg72Pro minor allele conferred a higher risk of pancreatic cancer (Naccarati et al. 2010; Sonoyama et al. 2011). Mouse double minute 2 homologue (MDM2) is an E3 ubiquitin ligase that blocks the transcriptional activation of p53 and is overexpressed in human pancreatic cancer (Dong et al. 2005). Two small studies provided evidence that a common *MDM2* T309G SNP was associated with a higher risk of pancreatic cancer (Asomaning et al. 2008; Grochola et al. 2010). A U.S. study of 509 cases and 462 controls reported a main effect of *P21* SNP rs1801270 but not *P27* SNP rs2066827 in pancreatic cancer (Chen et al. 2010).

The FAS/FASL system plays a crucial role in modulating apoptosis and maintaining homeostasis. A study of Chinese Han subjects found that the functional SNPs of *FasL* (−844 T-C) and caspase-8 (*CASP8*) (−652 6N ins→del) were both independently and jointly associated with risk of pancreatic cancer. Furthermore, these two genetic variants interacted with smoking and diabetes to modify this risk (Yang et al. 2008).

## *Other Cancer-Related Genes*

Hypothesis-driven analyses of existing GWAS data can be a cost-efficient approach to investigating genetic susceptibility to pancreatic cancer. A series of studies

investigated SNPs that predispose individuals to other forms of cancers. SNPs of *CASP8* (rs1045485) and *MAP3K1* (rs889312), *APC* (rs2431238) and *NIN* (rs10145182), which have been implicated in breast cancer, were shown to be associated with pancreatic cancer in the same Caucasian population (Couch et al. 2009, 2010). However, in an MD Anderson Cancer Center study, two SNPs that have been implicated in lung cancer, rs8034191 and rs1051730, which are located in the 15q24-25.1 region, were not associated with risk of pancreatic cancer (Chen et al. 2011). Genetic variations that contribute to hereditary pancreatic cancer do not seem to contribute to sporadic pancreatic cancer: polymorphisms of *PRSS1*, *PRSS2*, *CDKN2A* and 28 genes directly and indirectly involved in the Fanconi/BRCA pathway had no effect on pancreatic cancer risk (McWilliams et al. 2009b).

## *Diabetes and Obesity-Related Genes*

Type 2 diabetes and obesity have been consistently associated with increased risk of pancreatic cancer. Therefore, an association between diabetes or obesity-associated SNPs and pancreatic cancer is biologically plausible. SNPs of the genes for *GCKR*, *FTO*, *PPARγ*, *MTNR1B*, *MADD*, and *BCL11A* have all been associated with risk of pancreatic cancer (Prizment et al. 2012; Pierce et al. 2011). An interaction of the *FTO* and *ADIPOQ* SNPs and BMI was detected (Tang et al. 2011).

Strong experimental evidence supports the role of insulin-like growth factor (IGF) in pancreatic carcinogenesis. Thus far, three studies have investigated the IGF axis genes in association with pancreatic cancer (Suzuki et al. 2008c; Dong et al. 2010; Nakao et al. 2011a). An MD Anderson study observed that genotypes of the *IGF1*, *IGF1R*, and *IGFBP1* genes and haplotypes of the *IGF2R* and *IGFBP3* genes were significantly associated with pancreatic cancer risk (Dong et al. 2010). These studies also showed that genetic variants of IGF axis genes act jointly with diabetes, BMI, and alcohol consumption to affect susceptibility to pancreatic cancer. Notably, a 3′-untranslated region variant of the *IGF1* gene (rs5742714) was implicated in two independent studies (Suzuki et al. 2008c; Nakao et al. 2011a). The other study also found genetic variations of somatostatin receptor (*SSTR5*) and glucose metabolizing enzyme that modified, independently or jointly with smoking or diabetes, the risk of pancreatic cancer (Li et al. 2011; Dong et al. 2010).

## *Copy Number Variation*

Structural variations of the human genome, including copy number variation (CNV), have been recognized as a common type of genetic variation that predisposes individuals to sporadic cancer (Ionita-Laza et al. 2009; Kuiper et al. 2010). Loss of chromosome 6q13 is a frequent event in pancreatic cancer (Harada et al. 2007). CNVR2966.1 is a common CNV in a gene desert region on 6q13. A Chinese study

revealed that individuals carrying one copy of CNVR2966.1 had a significantly higher risk of pancreatic cancer compared with those carrying two copies (adjusted OR: 1.31, 95 % CI: 1.08–1.60) (Huang et al. 2012). Moreover, this study found that CNVR2966.1 functions as a potential *trans*-acting regulator of the *CDKN2B* gene that is a cell growth regulator controlling cell cycle G1 progression.

### *Summary*

In summary, efforts using the candidate gene approach to identify low-penetrating and common gene traits (minor allele frequency >5 %) that modify the risk of sporadic pancreatic cancer have been largely unsuccessful. Some weak main effects of *NAT*, *SOD2*, *TP53*, *COX2*, *IGF1* and *MTHFR* variants were reported while findings on other genes have not been independently validated in different study populations. Therefore, additional genetic epidemiologic studies of pancreatic cancer are needed to establish the relevance of the intriguing findings on genes involved in DNA repair, inflammatory response, IGF signaling, as well as obesity and diabetes. Further examination of possible gene–environment interactions are required in adequately powered studies to resolve the problem of imprecise risk estimates. Such studies will rely on accurate assessment of the major risk factors such as smoking, alcohol use, diet, BMI, and diabetes. Findings from such studies need to be replicated in racial and ethnic groups other than non-Hispanic Caucasians. Despite limited success in the past, retrospective case–control studies will likely continue to contribute to the genetic association study of pancreatic cancer in the format of consortium studies. To date, a number of consortia of preexisting studies exist, and they may facilitate the identification of additional low-penetrating variants, gene–environment and gene–gene interactions using the high throughput technology. Large consortium studies are needed to have the requisite power to examine genetic variants in minority populations, CNV, and common and rare SNPs in various pathways. However, the consortium studies should not prevent the generation of additional well-designed, sufficiently powered studies that apply uniform criteria for case selection, acquisition of environmental exposure information, and biological sample collection.

## Genome-Wide Association Studies

GWAS have identified numerous gene traits that predispose individuals to cancer. The comprehensive coverage of a large number of gene variants in this approach has uncovered novel gene variants that had previously not been considered in relation to cancer. Stringent criteria are applied in the statistical analysis of GWAS data to minimize the false-positive discoveries associated with multiple testing.

## *GWAS Publications*

To date, four GWAS have been conducted in association with risk of pancreatic cancer (Table 2). Two of those studies were conducted with people mostly with European ancestry (Amundadottir et al. 2009; Petersen et al. 2010), one study with a Japanese population (Low et al. 2010), and one with a Chinese population (Wu et al. 2012).

### PanScan I and PanScan II

The first GWAS for pancreatic cancer (PanScan I) was conducted by the National Cancer Institute using 1,896 cases and 1,939 controls pooled from 12 cohort studies and one case–control study by the Pancreatic Cancer Cohort Consortium (Amundadottir et al. 2009). Approximately 550,000 SNPs were genotyped, and the most significant ones (top 100 hits with small P values) were tested in the replication stage using 2,457 cases and 2,654 controls from eight case–control studies of the Pancreatic Cancer Case–Control Consortium (Petersen and Boffetta 2012). The initial scan identified a significant association of an *ABO* gene variant (rs505922) with risk of pancreatic cancer, and this observation was confirmed in the replication study. A significant association was also detected for some *sonic hedgehog* (*SHH*) gene variants (rs167020 and rs172310) in the initial scan, but that finding was not replicated.

The second GWAS for pancreatic cancer (PanScan II) was performed with 1,955 cases and 1,995 controls drawn from the same eight case–control studies used in the replication stage of PanScan I (Petersen et al. 2010). Approximately 620,000 SNPs were genotyped, and the combined dataset of PanScans I and II revealed three additional loci in association with the risk of pancreatic cancer. Two SNPs (rs9543325 and rs9564966) identified on the chromosome 13q22.1 region map to a non-genic region between *KLF5* and *KLF12* genes, which code for the kruppel-like transcription factors that regulate cell growth and transformation. This chromosome segment is frequently deleted in many cancers, including pancreatic cancer, and thus an unidentified tumor suppressor gene may be harbored in this region. Five SNPs on the chromosome 1q32.1 region map to the nuclear receptor subfamily 5, group A, member 2 (*NR5A2*) gene (also known as *liver receptor homologue 1*, *LRH1*); the strongest signal was rs3790844. A single SNP (rs401681) resides on the chromosome 5p15.33 region, which contains the cleft lip and palate transmembrane 1-like gene (*CLPTM1L*) and the telomerase reverse transcriptase gene (*TERT*), has been associated with multiple cancers.

### GWAS with a Japanese Population

The third GWAS was conducted with a Japanese population involving 991 cases and 5,209 controls without a replication step (Low et al. 2010). Three genes were

**Table 2** Genome-wide association studies of pancreatic cancer

| Study cohort (reference) | No. of cases/controls | Chromosome region | Top hits | Gene | *P* value | OR (95 % CI) |
|---|---|---|---|---|---|---|
| PanScan I (Huang et al. 2012) | 1,896/1,939 Replication in 2,457/2,654 | 9q34 | rs505922 | *ABO* | $5.37\times10^{-8}$ | 1.20 (1.12–1.28)[a] |
| PanScans I and II (Amundadottir et al. 2009) | 3,851/3,934 | 13q22.1 | rs9543325 | NA | $3.27\times10^{-11}$ | 1.26 (1.18–1.35)[b] |
| | | 13q22.1 | rs9564966 | NA | $5.86\times10^{-8}$ | 1.21 (1.13–1.30) |
| | | 1q32.1 | rs3790844 | *NR5A2* | $2.45\times10^{-10}$ | 0.77 (0.71–0.84) |
| | | 5p15.33 | rs401681 | *CLPTM1L-TERT* | $3.66\times10^{-7}$ | 1.19 (1.11–1.27) |
| Japanese (Petersen et al. 2010) | 991/5,209 | 6p25.3 | rs9502893 | *FOXQ1* | $3.30\times10^{-7}$ | 1.29 (1.17–1.43)[b] |
| | | 12p11.21 | rs708224 | *BICD1* | $3.30\times10^{-7}$ | 1.32 (1.19–1.47)[b] |
| | | 7q36.2 | rs6464375 | *DPP6* | $4.41\times10^{-7}$ | 3.73 (2.24–6.21)[c] |
| Han Chinese (Low et al. 2010) | 981/1,191 replication in 2,603/2,877 | 21q21.3 | rs372883 | *BACH1* | $2.24\times10^{-13}$ | 0.79 (0.75–0.84)[b] |
| | | 5p13.1 | rs2255280 | *DAB2* | $4.18\times10^{-10}$ | 0.81 (0.76–0.87) |
| | | 10q26.11 | rs12413624 | *PRLHR* | $5.12\times10^{-11}$ | 1.23 (1.16–1.31) |
| | | 21q22.3 | rs1547374 | *TFF1* | $3.71\times10^{-13}$ | 0.79 (0.74–0.84) |
| | | 13q22.1 | rs4885093 | NA | $1.57\times10^{-12}$ | 1.25 (1.18–1.33) |
| | | 13q22.1 | rs9573163 | NA | $5.14\times10^{-13}$ | 1.26 (1.18–1.34) |
| | | 22q13.32 | rs5768709 | *FAM19A5* | $1.41\times10^{-10}$ | 1.25 (1.17–1.34) |

*NA* non-genic region, *OR* (95 % CI) odds ratio (95 % confidence interval)

[a]Heterozygous OR

[b]Allelic OR

[c]Homozygous OR

significantly associated with the risk of pancreatic cancer: *FOXQ1* SNP rs9502893, located on chromosome 6p25.3, *BICD1* SNP rs708224 on chromosome 12p11.21, and *DPP6* SNP rs6464374 on chromosome 7q36.2. None of the GWAS top hits reported in PanScan I or PanScan II were confirmed in this Japanese study.

### GWAS with a Han Chinese Population

The most recent GWAS on pancreatic cancer was conducted with a Han Chinese population. This two-stage study involved 981 cases and 1,191 controls in the initial scan and 2,603 cases and 2,877 controls in the replication phase (Wu et al. 2012). Five genes were found to be highly significantly associated with pancreatic cancer: *BACH1*, *DAB2*, *PRLHR*, *TFF1*, and *FAM19A5*, which are located on chromosomes 21q21.3, 5p13.1, 10q26.11, 21q22.3, and 22q13.32, respectively. Furthermore, two of the top hits of PanScans I and II, one located on the non-genic region of chromosome 13q22.1 and one on chromosome 5p15.33, were replicated in this population.

## *Validation and Functional Characterization of Genes Identified in GWAS*

Understanding the biological mechanisms that link the GWAS top hits with the phenotype is crucial to the application of these findings in disease intervention. Among the genes/SNPs identified in pancreatic cancer GWAS, few have been validated in different populations or functionally characterized in experimental models (Table 3).

### *ABO* Genotype

The association between *ABO* genotypes and risk of pancreatic cancer has been validated in several studies. In two large prospective cohort studies (the Nurses' Health Study and the Health Professionals Follow-up Study), individuals with non-O serotypes had a 1.32- to 1.72-fold higher risk of pancreatic cancer than those with the O blood type; as much as 17 % of the cases could be explained by the non-O blood types (Wolpin et al. 2009). Similar findings were reported when the *ABO* genotype was imputed using SNPs examined in the PanScan I GWAS: the non-O genotypes contributed to 19.5 % of the pancreatic cancer cases (Wolpin et al. 2010a). Furthermore, the *ABO* A1 allele, which is associated with higher glycosyltransferase activity, was responsible for the increased risk of pancreatic cancer (Wolpin et al. 2010b). Although the GWAS conducted in the Japanese and Han Chinese populations did not confirm the association between *ABO* genotype and risk of pancreatic cancer (Low et al. 2010; Wu et al. 2012), this association was reported by another Japanese study of 185 pancreatic cancer cases and 1,465 controls (Nakao et al. 2011b). The mechanisms underlying the association between *ABO* and pancreatic

**Table 3** GWAS top hits and possible links with pancreatic cancer

| Gene symbol | Full gene name | Known protein function | Potential mechanism |
|---|---|---|---|
| *ABO* | ABO blood group (transferase A, α-1-3-*N*-acetylgalactosaminyl-transferase; transferase B, α-1-3-galactosyltransferase) | Glycosyltransferase | Inflammation, cell adhesion |
| *BACH1* | BTB and CNC homology 1 (basic leucine zipper transcription factor 1) | Transcription factor | Antioxidant-response-element-mediated gene regulation? |
| *BICD1* | Bicaudal D homolog 1 | Mediator of dynein function | Telomere length, G protein signaling |
| *CLPTM1L-TERT1* | Cleft lip and palate transmembrane 1-like–telomerase reverse transcriptase | Telomerase reverse transcriptase | Genomic stability |
| *DAB2* | Disabled homolog 2 | Mitogen-responsive phosphoprotein | Growth factor or Ras pathway modulation |
| *DPP6* | Dipeptidyl-peptidase 6 | Bind specific voltage-gated potassium channels | Electrophysiological properties? |
| *FAM19A5* | Family with sequence similarity 19 (chemokine [C-C motif]-like), member A5 | Secreted protein | Immune and nervous cell regulation |
| *FOXQ1* | Forkhead box Q1 | Transcription factor | Embryonic development, cell cycle, epithelial–mesenchymal transition |
| *NR5A2* | Nuclear receptor subfamily 5, group A member 2 | Nuclear receptor | Pancreas development and differentiation, steroidogenesis, cholesterol and bile acid homeostasis, cell proliferation |
| *PRLHR* | Prolactin-releasing hormone receptor | G protein–coupled receptor | ? |
| *TFF1* | Trefoil factor 1 | Secretory protein | Activation of NF-κB-mediated inflammation |

cancer risk are not understood. Several studies have shown a significant association between *ABO* genotype and the plasma level of proteins involved in inflammatory response, cell adhesion, and vascular functions, such as tumor necrosis factor α, intercellular adhesion molecule 1, E-selectin, and P-selectin (Melzer et al. 2008; Barbalic et al. 2010; Paterson et al. 2009). Whether ABO plays a regulatory role in inflammatory response, which in turn contributes to pancreatic carcinogenesis, requires further investigation (Lennon et al. 2010).

### *NR5A2* Gene

Among the genes identified in the PanScans I and II GWAS, some have known functional significance in regulating biological processes, such as organ development and cell differentiation, cell cycle, and genomic stability, all of which have important roles in tumorigenesis. For example, NR5A2 plays a role in controlling pancreas differentiation during embryonic development and in regulating cholesterol and bile acid homeostasis, steroidogenesis, and cell proliferation (Fayard et al. 2004). A recent study reported a critical role for *NR5A2* in the phosphatidylcholine signaling pathway regulating fatty acid and glucose homeostasis (Lee et al. 2011). *NR5A2* was overexpressed in pancreatic cancer, and its knockdown by small interfering RNA significantly inhibited pancreatic cancer cell proliferation in vitro (Benod et al. 2011), suggesting an oncogenic property of this gene in pancreatic cancer.

### *BACH1* Gene

*BACH1* (BTB and CNC homology 1) is a basic leucine zipper transcription factor and an *Nrf2* target gene. Induction of *BACH1* by *Nrf2* serves as a feedback-inhibitory mechanism for antioxidant-response-element–mediated gene regulation (Jyrkkanen et al. 2011). BACH1 effects DNA helicase activities and physically interacts with BRCA1 and MLH1 (mutL homologue 1), which differentially control DNA double-stranded break repair processes. Because *BRCA1* and *BACH1* mutations targeting the BRCA1-BACH1 interaction have been associated with breast cancer susceptibility, *BACH1* has been suggested as a tumor suppresser gene (Dohrn et al. 2012).

### *DAB2* Gene

*DAB2* encodes a mitogen-responsive phosphoprotein. This protein binds to the SH3 domains of GRB2, an adaptor protein that couples tyrosine kinase receptors to SOS (a guanine nucleotide exchange factor for Ras). Thus, this protein may modulate growth factor/Ras signaling pathways by competing with SOS for binding to GRB2 (Wang et al. 2002). Knockdown of *DAB2* in human mammary epithelial cells leads to increased Ras/MAPK signaling and promotes epithelial-to-mesenchymal transition (Martin et al. 2010).

### *TTF1* Gene

TFF1 (trefoil factor 1) is a stable secretory protein expressed in gastrointestinal mucosa. The function of this gene is ill defined, but it may protect the mucosa from

insults, stabilize the mucus layer, and affect healing of the epithelium. Overexpression of *TFF1* has been reported in many types of human cancers and preneoplastic lesions. In one study, recombinant *TFF1* stimulated the motility of both human pancreatic cancer cells and human pancreas stellate cells in vitro, and overexpression of *TFF1* in pancreatic cancer cells greatly increased metastasis in vivo (Arumugam et al. 2011). Loss of TFF1 is associated with activation of nuclear factor κB–mediated inflammation and gastric neoplasia in mice and humans (Soutto et al. 2011).

### *DPP6* and *PRLHR* Genes

The functional significance of *DPP6* (dipeptidyl-peptidase 6) and *PRLHR* (prolactin-releasing hormone receptor and their potential roles in the development of pancreatic cancer are intriguing. *DPP6* encodes a single-pass type II membrane protein that is a member of the S9B family in clan SC of the serine proteases. This protein has no detectable protease activity but binds specific voltage-gated potassium channels and alters their expression and biophysical properties. Genetic variation in *DPP6* has been associated with susceptibility to amyotrophic lateral sclerosis (van Es et al. 2008). PRLHR is a seven-transmembrane domain receptor for prolactin-releasing hormone and is a G protein-coupled receptor. Physical activity and a genetic variant of PRLHR have been associated with hypertension (Franks et al. 2004; Bhattacharyya et al. 2003).

### Other Genes

Still other genes have been identified by GWAS for pancreatic cancer. *FOXQ1* is a member of the *FOX* gene family, which are involved in embryonic development, cell cycle regulation, tissue-specific gene expression, cell signaling, and tumorigenesis (Bieller et al. 2001). Recent studies showed that FOXQ1 regulates epithelial cell differentiation and epithelial–mesenchymal transition in human cancers (Qiao et al. 2011; Zhang et al. 2011b; Feuerborn et al. 2011). TERT1 plays an essential role in maintaining telomere length and preventing fusion of chromosome ends. In addition to its role in regulating G protein signaling and internalization (Swift et al. 2010), BICD1 has been associated with telomere length (Mangino et al. 2008). *BICD1* gene variants have been associated with risk of aggressive but not indolent prostate cancer (Xu et al. 2010). The *FAM19A5* gene codes for a small secreted protein. These proteins contain conserved cysteine residues at fixed positions and are distantly related to MIP-1α, a member of the CC-chemokine family (Tom Tang et al. 2004). TAFA proteins are predominantly expressed in specific regions of the brain and are postulated to function as brain-specific chemokines or neurokines that regulate immune and nervous cells.

### Summary

Overall, genes identified by GWAS seem to have diverse functions that might contribute to cancer development. Fine mapping to identify the responsible variants and mechanistic studies on the biological and functional significance of these genes in relation to pancreatic cancer are required before the value of these GWAS findings can be appreciated.

## *Post-GWAS Data Analysis*

### Candidate Pathway Analysis

Single-locus analysis of GWAS data may miss some markers and genes that are related to a phenotype but do not pass the stringent statistical threshold. Furthermore, most genes work as a network or via a signaling transduction pathway; thus, moderate changes in the expression or function of genes involved in the same biological pathways may alter phenotypic outcomes. To further explore other genetic susceptibility factors in pancreatic cancer, a pathway-based analysis was conducted using PanScan data (Li et al. 2012). A total of 577 genes belong to 23 pathways or groups of genes known or hypothesized to be important in pancreatic carcinogenesis were analyzed using the adaptive rank truncated product method and the logic regression method.

Among the pathways, the pancreatic development pathway showed the most statistically significant association with risk of pancreatic cancer ($P = 2.0 \times 10^{-6}$) (Li et al. 2012). The major contributing genes to this pathway included *NR5A2*, *HNF1A*, *HNF4G*, *PDX1*, and *HNF1B*. These genes are important components of the transcriptional networks that govern embryonic pancreatic development and differentiation and maintain pancreatic homeostasis in adults (Maestro et al. 2007; Martin et al. 2007). Mutations in *HNF1A*, *PDX1*, and *HNF1B* are responsible for maturity-onset diabetes of young (MODY) types 3, 4, and 5, respectively (Glucksmann et al. 1997; Carette et al. 2007). Mutations in and common variants of *HNF1A* and *HNF1B* have also been associated with risk of type 2 diabetes (Voight et al. 2010; Furuta et al. 2002; Holmkvist et al. 2006). Notably, *HNF1A* was the top hit for pancreatic cancer in a separate analysis of PanScan data as identified by assessing markers previously identified in a GWAS of phenotypes other than pancreatic cancer (Pierce and Ahsan 2011). *HNF1A* gene mutations have been reported for several types of human cancer, suggesting a role for them in tumor suppression (Laurent-Puig et al. 2003; Rebouissou et al. 2004; Bluteau et al. 2002).

### Agnostic Pathway Analysis

The association between the pancreas development pathway and the risk of pancreatic cancer was confirmed in an agnostic pathway analysis of PanScan data (Wei et al. 2012). In this study, a total of 197 biological pathways identified from the Kyoto

Encyclopedia of Genes and Genomes (KEGG) database were analyzed using the gene set ridge regression in association studies algorithm and the logistic kernel machine test. Two pathways were significantly associated with risk of pancreatic cancer after adjusting for multiple comparisons ($P<0.00025$) and in replication testing: neuroactive ligand-receptor interaction, ($Ps<0.00002$), and the olfactory transduction pathway ($P=0.0001$). Functional enrichment analysis using the Database for Annotation, Visualization, and Integrated Discovery (DAVID) consistently found the G protein–coupled receptor signaling pathway to be the most significant pathway for pancreatic cancer in this study population. These findings need to be confirmed in separate datasets from future GWAS of pancreatic cancer. If confirmed, these novel findings will provide new perspectives on genetic susceptibility to and molecular mechanisms of pancreatic cancer.

### Candidate Gene Analysis

Because obesity and diabetes are known modifiable risk factors for pancreatic cancer, there is great interest in identifying genetic factors that modify these associations. One study examined 47 genetic variants that have previously been related to type 2 diabetes, fasting glucose, or β-cell function in PanScan I data. None of the genes showed association with pancreatic cancer at the genome-wide significance level. Four genes, *FTO*, *MTNB1R*, *BCL11A* and *MADD*, were nominally associated with pancreatic cancer risk (Pierce et al. 2011).

### Gene–Environment Interaction

Most human cancers are likely the consequence of joint actions of genetic and environmental factors. Identification of the interplay of gene and environment will help in understanding the biological networks underlying the complex disease risks. Yet, few studies have incorporated the known environmental or host risk factors in the analyses of GWAS data. A case–control study of 1,070 patients with pancreatic adenocarcinoma and 1,175 controls confirmed the association between *NR5A2* and risk of pancreatic cancer as observed in a GWAS (Tang et al. 2011). However, no significant interaction of *NR5A2* with BMI, diabetes, or smoking was detected. Two *FTO* gene variants were non-significantly associated with a decreased risk of pancreatic cancer in participants with a BMI $<25$ kg/m$^2$ ($P_{\text{interaction}}=0.0001$) but significantly associated with an increased risk of pancreatic cancer in participants with a BMI $\geq 25$ kg/m$^2$ ($P_{\text{interaction}}=0.0015$) (Tang et al. 2011).

### Survival Analysis

Although many previous candidate gene studies have reported associations of gene variants with patient survival, no significant findings on SNPs and survival have yet been discovered from existing GWAS data. A study of 690 cases of pancreatic

ductal adenocarcinoma and 1,277 healthy control subjects of German and British extraction replicated the associations of GWAS top hits with pancreatic cancer risk reported in PanScan. The *NR5A2* rs12029406_T allele and a SNP located at gene desert region of chromosome 15q14 were weakly associated with overall survival in the German population (Rizzato et al. 2011). Nevertheless, an exploratory GWAS of 550,000 SNPs conducted with 351 patients with pancreatic cancer (294 genetically European patients) identified a nonsynonymous SNP in interleukin (IL)-17F (rs763780, H161R) and an intronic SNP in strong linkage disequilibrium (rs7771466) in association with overall survival at the genome-wide significance level ($P \leq 1 \times 10^{-7}$) (Innocenti et al. 2012). The variant 161R form of IL-17F is a natural antagonist of the antiangiogenic effects of wild-type 161H IL-17F, and patients with the variant allele had significantly shorter median survival (3.1 months; 95 % CI, 2.3–4.3) than patients without this variant (6.8 months; 95 % CI, 5.8–7.3) ($P = 2.61 \times 10^{-8}$).

**Summary**

As observed for many complex human diseases, the identified gene variants from GWAS explain only a small proportion of the heritability of pancreatic cancer. The unexplained heritability could be due partly to gene–environment interactions or to more complex pathways involving multiple genes and exposures. Using novel statistical strategies to further mine GWAS data for gene–gene and gene–environment interactions may reveal additional gene traits that are missed in single-locus analyses (Wolpin et al. 2010b; Weinberg et al. 2011). In addition, GWAS coverage focused on SNPs with minor alleles of frequency >5 % and tagging SNPs without known functional significance may contribute to the low discovery rate. As technology advances, more coverage of rare SNPs and special selection of exome SNPs may generate more helpful information in defining the genetic susceptibility factors for pancreatic cancer. The ultimate success of using these genetic markers in risk assessment and in clinical management of the disease will also heavily depend on the understanding of the mechanistic links between the genes and the disease.

## Conclusion

The field of genetic epidemiology of pancreatic cancer has made notable progress in the past 20 years. Accumulating evidence support a polygenic feature of the disease and a contributing role of common low penetrance gene variants in the development of pancreatic cancer. However, many challenges and inconsistent findings remain. Upon the establishment of consortia and completion of additional large scale GWA studies in the near future, more genetic traits are expected to be identified. The large amount of GWAS data and exposure information will be valuable in examining gene–gene and gene–environment interactions. Findings from these studies will be utilized in establishing and improving the risk prediction models for pancreatic cancer.

Functional characterization of the implicated genes should help to better define the molecular mechanisms underlie the complex etiology of this deadly disease and offer new opportunities in developing novel preventive and treatment strategies.

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