ABO blood group and other genetic variants associated with pancreatic cancer

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Abstract
Pancreatic adenocarcinoma is the fourth leading cause of cancer death in the United States. Recent reports, including genome-wide association studies and self-reported blood serotype studies, have shown that individuals of European ancestry who carry non-O blood group are at an increased risk of developing pancreatic cancer. Two recent genome-wide association studies of pancreatic cancer have identified associations between pancreatic cancer risk and genetic variants in the ABO blood group gene, the locus containing the telomerase reverse transcriptase (hTERT) gene, the nuclear receptor family gene NR5A2 and a non-genic region on chromosome 13q22.1.

Pancreatic adenocarcinoma is the fourth leading cause of cancer death in men and women in the United States and has the lowest survival rate for any solid cancer. Over 42,000 individuals are diagnosed with pancreatic cancer in the United States each year and over 35,000 will die of the disease [1]. Similar mortality figures are reported in Europe, with 1- and 5-year survival rates of only 15% and 4%, respectively [2]. One important reason for this poor survival is that about 85% of patients present with advanced disease, limiting our ability to treat the disease at an early, curable stage [3]. For this reason, there is considerable interest in identifying the disease in its earliest stages, such as by screening high-risk individuals [4], identifying better diagnostic markers of early-stage disease [5], identifying familial and genetic risk factors that contribute to the disease [6], and ultimately developing risk prediction models to identify at-risk individuals [7].

Risk factors for pancreatic cancer include family history, inheriting deleterious mutations in pancreatic cancer susceptibility genes (BRCA2, p16, STK11, PALB2 and PRSS1), cigarette smoking, chronic pancreatitis, long-standing diabetes, obesity, Helicobacter pylori infection and occupational exposures [8]. However, these factors do not fully account for the prevalence of pancreatic cancer. Furthermore, it is unclear how some of these risk factors mediate pancreatic cancer risk. An association between non-O blood group and pancreatic cancer was first identified in the 1960s, but it has been underappreciated as a risk factor despite the fact that other studies found similar associations with gastric and other cancers [9-11]. Recently, several studies have reported a significant association between the ABO blood group and pancreatic cancer risk [12-15].

ABO blood group and pancreatic cancer
The Panscan consortium (which consists of the Pancreatic Cancer Cohort Consortiums and the Pancreatic Cancer Case-Control Consortiums (Panc4)) performed a genome-wide association study (GWAS) with approximately 550,000 single nucleotide polymorphisms (SNPs) comparing 1,896 individuals with pancreatic cancer and 1,939 controls ascertained from 12 cohort studies and the Mayo clinic case-control study (PanScanI) [14]. The SNP variants that provided the strongest evidence of association were then validated in an independent set of 2,457 cases and 2,654 controls from eight case-control studies. In this work, several common variants at the ABO blood group locus showed significant evidence of association with pancreatic cancer in the combined data [14]. Among individuals of European ancestry, the SNP rs505992, located within the first intron of the ABO gene, was strongly associated with pancreatic cancer (multiplicative per-allele odds ratio (OR) 1.20, 95% confidence interval (CI) 1.12 to 1.28, \( P = 5.37 \times 10^{-8} \)). This SNP is in complete linkage disequilibrium with, and is thereby perfectly correlated with, the O/non-O blood group variant.

The ABO system was first described by Karl Landsteiner in 1900, and the ABO gene was cloned in 1990 [16]. The ABO gene encodes glycosyltransferase enzymes that transfer specific sugar residues to the H antigen. There are three variant alleles (A, B and O), which encode
three different glycosyltransferases. The A allele encodes the enzyme α1R3 N-acetylgalactosaminyltransferase, which attaches N-acetylgalactosamine to the H antigen to form the A antigen. The B allele encodes α1R3 galactosyltransferase, which attaches D-galactose, and the O allele encodes a non-functional glycosyltransferase and thus the H antigen remains unmodified.

The association between ABO genotypes and pancreatic cancer reported by PanScan [14] was supported by Wolpin et al. [12], who identified an association between ABO serotypes and pancreatic cancer risk. They used two large prospective cohort studies (the Nurses’ Health Study and Health Professionals Follow-up Study) with 107,503 participants [12]. Cox proportional hazards model, adjusted for age, tobacco use, body mass index, physical activity and history of diabetes mellitus, was used to calculate hazard ratios for pancreatic cancer by ABO blood type. Compared with individuals of O serotype, individuals with blood group A, AB or B had a significantly increased rate of pancreatic cancer (Table 1).

To examine this association further, Wolpin et al. [12] then used the SNP data generated from the 12 cohort studies included in full PanScan GWAS to derive ABO genotypes (OO, AO, AA, AB, BO and BB) and ABO serotypes (A, B, AB and O) and then examined the association of these two measures with pancreatic cancer risk [13]. Patients with pancreatic cancer were compared with controls without pancreatic cancer and matched for year of birth, gender, race/ethnicity and source of DNA, and four of the cohorts were matched for smoking status and baseline age. This analysis further supported their earlier findings: compared with individuals of blood group O, the odds of developing pancreatic cancer were significantly higher for individuals with blood group A, AB or B. The analyses also provided important information on the influence of genotype: individuals with AA, BB or AB genotype were at higher risk of pancreatic cancer than individuals with AO or BO genotype (Table 2). The authors estimated that inheritance of non-O blood group accounted for 19.5% of all pancreatic cancer in individuals of European ancestry.

The mechanism(s) by which ABO status influences pancreatic cancer risk remains unclear. ABO antigens are found not only on the surface of red blood cells but also on the surface of epithelial cells of the gastrointestinal, bronchopulmonary and urogenital tracts [17]. ABO blood group is associated with differences in several circulating inflammatory, infectious and vascular mediators, and therefore chronic inflammation has been suggested as a potential mechanism for the association between ABO blood group and cancer risk. On the other hand, loss of expression of ABO blood group has been described in some pancreatic cancers and a systemic mechanism by which ABO blood groups predispose to pancreatic cancer would not be expected to require loss of expression of ABO in pancreatic cancers [9,18]. Also, if an inflammatory modifier role of ABO is causal in cancer development, then ABO should be important in the development of numerous inflammation-mediated cancers, such as esophageal or gall-bladder cancer or colitis-associated colorectal cancer, but no such association has been found yet [19]. The association between ABO and a limited number of cancers and evidence for loss of expression during tumor development implicate a tumor suppressor role for blood groups A and B in cancer development. Further studies to better elucidate the mechanism by which ABO mediates cancer susceptibility are needed to fully understand this association.

### Table 1. Hazard ratios for risk of pancreatic cancer by blood group

| Serotype | Hazard ratio relative to O serotype | 95% confidence interval |
|----------|-----------------------------------|------------------------|
| A        | 1.32                              | 1.02-1.72              |
| AB       | 1.51                              | 1.02-2.23              |
| B        | 1.72                              | 1.25-2.38              |

Values were calculated using the Cox proportional hazard model by Wolpin et al. [13] using data from the Nurses’ Health Study and the Health Professionals Follow-up Study.

### Table 2. Odds ratios for risk of pancreatic cancer by blood group and ABO genotype

| Serotype to O serotype | Odds ratio relative to O serotype or OO genotype | 95% confidence interval |
|------------------------|--------------------------------------------------|------------------------|
| A                      | 1.38                                              | 1.18-1.62              |
| AB                     | 1.47                                              | 1.07-2.02              |
| B                      | 1.53                                              | 1.21-1.92              |
| Genotype               |                                                  |                        |
| AA                     | 1.61                                              | 1.22-2.18              |
| BB                     | 2.42                                              | 1.28-4.57              |
| AB                     | 1.47                                              | 1.07-2.02              |
| AA                     | 1.33                                              | 1.13-1.58              |
| BO                     | 1.45                                              | 1.14-1.85              |

Reproduced from Wolpin et al. [13].

### Other genomic associations with pancreatic cancer

Recently, the PanScan consortium conducted a second GWAS (PanScanII) in which they genotyped approximately 620,000 SNPs in an additional 1,955 cases and 1,955 controls [15] from the same eight case-control studies used for replication of top loci in the original GWAS [14]. SNPs from the two studies were combined, resulting in data on approximately 550,000 SNPs from 3,851 individuals with pancreatic cancer and 3,934 controls. Analysis of these combined regions identified
three new genomic regions on chromosomes 13q22.1, 1q32.1 and 5p15.33 associated with an increased risk of pancreatic cancer. The locus on 13q22.1 was associated with SNP rs9543325, in a non-genic region between the transcription factor genes KLF5 and KLF12, which regulate cell growth and transformation. Five SNPs were closely associated with the nuclear receptor family gene NRS5A2 on 1q32.1, whose product is known to interact with β-catenin. The strongest SNP was rs3790844 ($P = 2.45 \times 10^{-16}$, per-allele OR 0.77, 95% CI 0.71 to 0.84). A third locus marked by rs401681 ($P = 3.66 \times 10^{-7}$, per-allele OR 1.19, 95% CI 1.11 to 1.27) was identified on chromosome 1p15.33, within intron 13 of CLPTM1L and close to the telomerase reverse transcriptase gene, hTERT.

Although not much is known yet about the potential role of NRS5A2, KLF5 and KLF12 in pancreatic cancer susceptibility, the $hTERT$-CLPTM1L locus has been previously implicated as a cancer susceptibility gene [20-24]. Another SNP in this locus, rs4635969, ranked 12th most significant in the PanScan GWAS, with $P = 1.05 \times 10^{-5}$, just short of genome-wide significance. Although CLPTM1L is upregulated in cisplatin-resistant cell lines and may have a role in apoptosis, because of the importance of telomeres in cancer susceptibility it is suspected that these variants are more likely to be important for their influence on $hTERT$ and telomere length and function rather than on CLPTM1L.

$hTERT$ is expressed in approximately 90% of human cancers and is essential for maintaining telomeres ends. Germline mutations in $hTERT$ can cause acute myeloid leukemia and aplastic anemia, and rare variants in $hTERT$ cause inherited bone marrow failure [25-27]. Telomere length has a strong inherited component [28]. Telomeres are made up of DNA repeat sequences (TTAGGG) and telomere binding proteins [29] that prevent fusion between ends of chromosomes. Telomeric fusions occur at critically shortened telomeres and lead to ring and dicentric chromosomes that form anaphase bridges. Breakage of anaphase bridges generates highly recombinogenic free DNA ends, fusion of broken ends and chromosomal rearrangements that can be self-perpetuating and are typical of many cancers [30]. Telomere shortening will cause senescence unless pathways such as p53 are overcome [31], and neoplastic clones later express $hTERT$ and telomerase for cellular immortalization [32-38]. Pancreatic adenocarcinomas have very short telomeres [35], complex karyotypes, numerous chromosomal abnormalities and high fractional allelic losses [36,37]. The T allele of rs401681 is associated with increased risk of pancreatic cancer and melanoma [23], but the C allele is associated with an increased risk of lung, prostate, basal cell and bladder cancers [20-23]. Initial attempts to find a correlation between the $hTERT$ variant rs401681 with telomere length were inconclusive, perhaps because other factors such as age, sex, smoking and exercise influence telomere length [38-40].

**Implications for research and therapy**

One challenge with GWAS discoveries has been determining how these findings could benefit clinical practice. Generally, GWAS discoveries have provided important clues to disease mechanisms that will hopefully eventually have an impact on clinical management of disease. The small magnitude of risk estimates attributable to an individual disease-associated SNP have not generally been large enough to provide immediate clinical benefits in areas such as risk prediction [41,42]. Studies are now underway to determine whether pancreatic cancer GWAS alleles influence pancreatic cancer prognosis and response to therapy.

In summary, the results of the first pancreatic cancer GWASs have added to our knowledge of genetic loci associated with pancreatic cancer. The PanScan GWAS was a robust study that included a large number of cases and controls, many of whom were originally enrolled in large, well-designed prospective studies. At the same time, these first GWASs [15,16] were powered to detect alleles with relatively large effects, and alleles with moderate to small effect on pancreatic cancer risk may have been overlooked. Further studies are now needed to investigate the mechanisms by which the association between ABO blood group antigens and variants in other loci, such as the $hTERT$ locus, contribute to pancreatic cancer susceptibility. Given the early success of the first pancreatic cancer GWAS, larger association studies are likely to provide additional insights into pancreatic cancer susceptibility. GWASs are very useful for identifying common low-penetrance alleles that contribute to disease susceptibility [43-45], and diseases that have gone through several rounds of GWASs and post-GWAS validation continue to yield important new findings and to refine the significance of earlier findings [46]. Understanding the genetic and biological mechanisms of pancreatic cancer will eventually improve our ability to diagnose and treat this deadly disease.

**Abbreviations**

BMI: body mass index; CI: confidence interval; GWAS: genome-wide association study; OR: odds ratio; SNP: single nucleotide polymorphism.

**Competing interests**
The authors declare that they have no competing interests.

**Authors’ contributions**

AML and MG wrote the manuscript; APK edited the manuscript.

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