

MINIREVIEW

ABO blood group and other genetic variants associated with pancreatic cancer

Anne Marie Lennon¹, Alison P Klein^{2,3,4} and Michael Goggins^{1,2,3*}

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 Consortia and the Pancreatic Cancer Case-Control Consortia (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

*Correspondence: mgoggins@jhmi.edu
Departments of Medicine¹, Pathology² and Oncology³, The Sol Goldman Pancreatic Cancer Research Center, Johns Hopkins Medical Institutions, Baltimore, MD 21205-2196, USA

three different glycosyltransferases. The A allele encodes the enzyme α 1R3 *N*-acetylgalactosaminyltransferase, which attaches *N*-acetylgalactosamine to the H antigen to form the A antigen. The B allele encodes α 1R3 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

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	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
AO	1.33	1.13-1.58
BO	1.45	1.14-1.85

Reproduced from Wolpin *et al.* [13].

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.

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 *NR5A2* on 1q32.1, whose product is known to interact with β -catenin. The strongest SNP was rs3790844 ($P = 2.45 \times 10^{-10}$, 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 5p15.33, within intron 13 of *CLPTMIL* and close to the telomerase reverse transcriptase gene, *hTERT*.

Although not much is known yet about the potential role of *NR5A2*, *KLF5* and *KLF12* in pancreatic cancer susceptibility, the *hTERT-CLPTMIL* 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 $P = 1.05 \times 10^{-6}$, just short of genome-wide significance. Although *CLPTMIL* 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 *CLPTMIL*.

hTERT is expressed in approximately 90% of human cancers and is essential for maintaining telomere 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.

Acknowledgements

This work was supported by the National Cancer Institute grants (CA120432, CA62924, CA97075), the V foundation and the Michael Rolfe Foundation.

References

- Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun M: **Cancer statistics.** *CA Cancer J Clin* 2009, **59**:225-249.
- Faire J, Forman D, Esteve J, Obradovic M, Sant M: **Survival of patients with primary liver cancer, pancreatic cancer and biliary tract cancer in Europe.** **EUROCORE Working Group.** *Eur J Cancer* 1998, **34**:2184-2190.
- Winter JM, Cameron JL, Campbell KA, Arnold MA, Chang DC, Coleman J, Hodgins MB, Sauter PK, Hruban RH, Riall TS, Schulick RD, Choti MA, Lillemoe KD, Yeo CJ: **1423 pancreaticoduodenectomies for pancreatic cancer: a single-institution experience.** *J Gastrointest Surg* 2006, **10**:1199-1210; discussion 1210-1211.
- Canto MI, Goggins M, Hruban RH, Petersen GM, Giardiello FM, Yeo C, Fishman EK, Brune K, Axilbund J, Griffin C, Ali S, Richman J, Jagannath S, Kantsevoy SV, Kalloo AN: **Screening for early pancreatic neoplasia in high-risk individuals: a prospective controlled study.** *Clin Gastroenterol Hepatol* 2006, **4**:766-781.
- Goggins M: **Identifying molecular markers for the early detection of pancreatic neoplasia.** *Semin Oncol* 2007, **34**:303-310.
- Petersen GM, de Andrade M, Goggins M, Hruban RH, Bondy M, Korczak JF, Gallinger S, Lynch HT, Syngal S, Rabe KG, Seminara D, Klein AP: **Pancreatic cancer genetic epidemiology consortium.** *Cancer Epidemiol Biomarkers Prev* 2006, **15**:704-710.
- Wang W, Chen S, Brune KA, Hruban RH, Parmigiani G, Klein AP: **PancPRO: risk assessment for individuals with a family history of pancreatic cancer.** *J Clin Oncol* 2007, **25**:1417-1422.
- Hidalgo M: **Pancreatic cancer.** *New Engl J Med* 2010, **362**:1605-1617.
- Izkowitz SH, Yuan M, Ferrell LD, Ratcliffe RM, Chung YS, Satake K, Umeyama K, Jones RT, Kim YS: **Cancer-associated alterations of blood group antigen expression in the human pancreas.** *J Natl Cancer Inst* 1987, **79**:425-434.
- Aird I, Lee DR, Roberts JA: **ABO blood groups and cancer of oesophagus, cancer of pancreas, and pituitary adenoma.** *Br Med J* 1960, **1**:1163-1166.
- Aird I, Bentall HH, Roberts JA: **A relationship between cancer of stomach and the ABO blood groups.** *Br Med J* 1953, **1**:799-801.
- Wolpin BM, Chan AT, Hartge P, Chanock SJ, Kraft P, Hunter DJ, Giovannucci EL, Fuchs CS: **ABO blood group and the risk of pancreatic cancer.** *J Natl Cancer Inst* 2009, **101**:424-431.
- Wolpin BM, Kraft P, Gross M, Helzlsouer K, Bueno-de-Mesquita HB, Stepilowski E, Stolzenberg-Solomon RZ, Arslan AA, Jacobs EJ, Lacroix A, Petersen G, Zheng W, Albanes D, Allen NE, Amundadottir L, Anderson G, Boutron-Ruault MC, Buring JE, Canzian F, Chanock SJ, Clipp S, Gaziano JM, Giovannucci EL, Hallmans G, Hankinson SE, Hoover RN, Hunter DJ, Hutchinson A, Jacobs K, Kooperberg C, Lynch SM, *et al.*: **Pancreatic cancer risk and ABO blood group alleles: results from the pancreatic cancer cohort consortium.** *Cancer Res* 2010, **70**:1015-1023.
- Amundadottir L, Kraft P, Stolzenberg-Solomon RZ, Fuchs CS, Petersen GM, Arslan AA, Bueno-de-Mesquita HB, Gross M, Helzlsouer K, Jacobs EJ, Lacroix A, Zheng W, Albanes D, Bamlet W, Berg CD, Berrino F, Bingham S, Buring JE, Bracci PM, Canzian F, Clavel-Chapelon F, Clipp S, Cotterchio M, de Andrade M, Duell EJ, Fox JW Jr, Gallinger S, Gaziano JM, Giovannucci EL, Goggins M, *et al.*: **Genome-wide association study identifies variants in the ABO locus associated with susceptibility to pancreatic cancer.** *Nat Genet* 2009, **41**:986-990.
- Petersen GM, Amundadottir L, Fuchs CS, Kraft P, Stolzenberg-Solomon RZ, Jacobs KB, Arslan AA, Bueno-de-Mesquita HB, Gallinger S, Gross M, Helzlsouer K, Holly EA, Jacobs EJ, Klein AP, Lacroix A, Li D, Mandelsson MT, Olson SH, Risch HA, Zheng W, Albanes D, Bamlet WR, Berg CD, Boutron-Ruault MC, Buring JE, Bracci PM, Canzian F, Clipp S, Cotterchio M, de Andrade M, *et al.*: **A genome-wide association study identifies pancreatic cancer susceptibility loci on chromosomes 13q22.1, 1q32.1 and 5p15.33.** *Nat Genet* 2010, **42**:224-228.
- Yamamoto F, Marken J, Tsuji T, White T, Clausen H, Hakomori S: **Cloning and characterization of DNA complementary to human UDP-GalNAc: Fuc alpha 1-2Gal alpha 1-3GalNAc transferase (histo-blood group A transferase) mRNA.** *J Biol Chem* 1990, **265**:1146-1151.
- Hakomori S: **Antigen structure and genetic basis of histo-blood groups A, B and O: their changes associated with human cancer.** *Biochim Biophys Acta* 1999, **1473**:247-266.
- Pour PM, Tempero MM TH, Uchida E, Takiyama Y, Burnett DA, Stepilowski Z: **Expression of blood group-related antigens ABH, Lewis A, Lewis B, Lewis X, Lewis Y, and CA 19-9 in pancreatic cancer cells in comparison with the patient's blood group type.** *Cancer Res* 1988, **48**:5422-5426.
- Beasley WH: **The ABO blood groups of carcinoma of the oesophagus and of benign prostatic hyperplasia.** *J Clin Pathol* 1964, **17**:42-44.
- Wang Y, Broderick P, Webb E, Wu X, Vijayakrishnan J, Matakidou A, Qureshi M, Dong Q, Gu X, Chen WW, Spitz MR, Eisen T, Amos CI, Houlston RS: **Common 5p15.33 and 6p21.33 variants influence lung cancer risk.** *Nat Genet* 2008, **40**:1407-1409.
- McKay JD, Hung RJ, Gaborieau V, Boffetta P, Chabrier A, Byrnes G, Zaridze D, Mukeria A, Szeszenia-Dabrowska N, Lissowska J, Rudnai P, Fabianova E, Mates D, Bencko V, Foretova L, Janout V, McLaughlin J, Shepherd F, Montpetit A, Narod S, Krokavcova HE, Skorpenev F, Elvestad MB, Vatten L, Njåstad I, Lubinski J, Matyjask J, Lener M, Oszutowska D, Field J, *et al.*: **Lung cancer susceptibility locus at 5p15.33.** *Nat Genet* 2008, **40**:1404-1406.
- Rafnar T, Sulem P, Stacey SN, Geller F, Gudmundsson J, Sigurdsson A, Jakobsdottir M, Helgadóttir H, Thorlacius S, Aben KK, Blöndal T, Thorgeirsson TE, Thorleifsson G, Kristjánsson K, Thorióttóttir K, Ragnarsson R, Sigurgeirsson B, Skuladottir H, Gudbjartsson T, Isaksson HJ, Einarsson GV, Benediksdóttir KR, Agnarsson BA, Olafsson K, Salvarsdóttir A, Bjarnason H, Asgeirsdóttir M, Kristinnsson KT, Matthíasdóttir S, Sveinsson SG, *et al.*: **Sequence variants at the TERT-CLPTM1L locus associate with many cancer types.** *Nat Genet* 2009, **41**:221-227.
- Stacey SN, Sulem P, Masson G, Gudjonsson SA, Thorleifsson G, Jakobsdottir M, Sigurdsson A, Gudbjartsson DF, Sigurgeirsson B, Benediksdóttir KR, Thorióttóttir K, Ragnarsson R, Scherer D, Hemminki K, Rudnai P, Gurzau E, Koppova K, Botella-Estrada R, Soriano V, Juberias P, Saez B, Gilaberte Y, Fuentelsaz V, Corredera C, Grasa M, Höiom V, Lindblom A, Bonenkamp JJ, van Rossum MM, Aben KK, *et al.*: **New common variants affecting susceptibility to basal cell carcinoma.** *Nat Genet* 2009, **41**:909-914.
- Shete S, Hosking FJ, Robertson LB, Dobbins SE, Sanson M, Malmer B, Simon M, Marie Y, Boisselier B, Delattre JY, Hoang-Xuan K, El Hallani S, Idbaih A, Zelenika D, Andersson U, Henriksson R, Bergenheim AT, Feychting M, Lönn S, Ahlborn A, Schramm J, Linnebank M, Hemminki K, Kumar R, Hepworth SJ, Price A, Armstrong G, Liu Y, Gu X, Yu R, *et al.*: **Genome-wide association study identifies five susceptibility loci for glioma.** *Nat Genet* 2009, **41**:899-904.
- Calado RT, Regal JA, Hills M, Yewdell WT, Dalmazzo LF, Zago MA, Lansdorp PM, Hogge D, Chanock SJ, Estey EH, Falcão RP, Young NS: **Constitutional polymorphic telomerase mutations in patients with acute myeloid leukemia.** *Proc Natl Acad Sci USA* 2009, **106**:1187-1192.
- Savage SA, Alter BP: **Dyskeratosis congenita.** *Hematol Oncol Clin North Am* 2009, **23**:215-231.
- Yamaguchi H, Calado RT, Ly H, Kajigaya S, Baerlocher GM, Chanock SJ, Lansdorp PM, Young NS: **Mutations in TERT, the gene for telomerase reverse transcriptase, in aplastic anemia.** *N Engl J Med* 2005, **352**:1413-1424.
- Codd V, Mangino M, van der Harst P, Braund PS, Kaiser M, Beveridge AJ, Rafelt S, Moore J, Nelson C, Soranzo N, Zhai G, Valdes AM, Blackburn H, Mateo Leach I, de Boer RA; Wellcome Trust Case Control Consortium, Goodall AH, Ouwehand W, van Veldhuisen DJ, van Gilst WH, Navis G, Burton PR, Tobin MD, Hall AS, Thompson JR, Spector T, Samani NJ: **Common variants near TERC are associated with mean telomere length.** *Nat Genet* 2010, **42**:197-199.
- Harley CB, Villeponteau B: **Telomeres and telomerase in aging and cancer.** *Curr Opin Genet Dev* 1995, **5**:249-255.
- Hackett JA, Greider CW: **Balancing instability: dual roles for telomerase and telomere dysfunction in tumorigenesis.** *Oncogene* 2002, **21**:619-626.
- Artandi SE, DePinho RA: **Telomeres and telomerase in cancer.** *Carcinogenesis* 2010, **31**:9-18.
- Bodnar AG, Ouellette M, Frolkis M, Holt SE, Chiu CP, Morin GB, Harley CB, Shay JW, Lichtsteiner S, Wright WE: **Extension of life-span by introduction of telomerase into normal human cells.** *Science* 1998, **279**:349-352.
- Hahn WC, Counter CM, Lundberg AS, Beijersbergen RL, Brooks MW, Weinberg RA: **Creation of human tumour cells with defined genetic elements.** *Nature* 1999, **400**:464-468.
- Kim NW, Piatyszek MA, Prowse KR, Harley CB, West MD, Ho PL, Coviello GM, Wright WE, Weinrich SL, Shay JW: **Specific association of human telomerase activity with immortal cells and cancer.** *Science* 1994, **266**:2011-2015.
- Gisselsson D, Jonson T, Petersen A, Strombeck B, Dal Cin P, Hoglund M, Mitelman F, Mertens F, Mandahl N: **Telomere dysfunction triggers extensive DNA fragmentation and evolution of complex chromosome abnormalities in human malignant tumors.** *Proc Natl Acad Sci USA* 2001, **98**:12683-12688.
- Abe T, Fukushima N, Brune K, Boehm C SN, Matsubayashi H, Canto M, Petersen GM, Hruban RH, Goggins M: **Genome wide allelotypes of familial pancreatic adenocarcinomas and familial and sporadic intraductal papillary mucinous neoplasms.** *Clin Cancer Res* 2007, **13**:6019-6025.
- Calhoun ES, Hucl T, Gallmeier E, West KM, Arking DE, Maitra A, Iacobuzio-Donahue CA, Chakravarti A, Hruban RH, Kern SE: **Identifying allelic loss and**

- homozygous deletions in pancreatic cancer without matched normals using high-density single-nucleotide polymorphism arrays. *Cancer Res* 2006, **66**:7920-7928.
38. Ludlow AT, Zimmerman JB, Witkowski S, Hearn JW, Hatfield BD, Roth SM: **Relationship between physical activity level, telomere length, and telomerase activity.** *Med Sci Sports Exerc* 2008, **40**:1764-1771.
 39. Cherkas LF, Hunkin JL, Kato BS, Richards JB, Gardner JP, Surdulescu GL, Kimura M, Lu X, Spector TD, Aviv A: **The association between physical activity in leisure time and leukocyte telomere length.** *Arch Intern Med* 2008, **168**:154-158.
 40. Nordfjall K, Eliasson M, Stegmayr B, Lundin S, Roos G, Nilsson PM: **Increased abdominal obesity, adverse psychosocial factors and shorter telomere length in subjects reporting early ageing; the MONICA Northern Sweden Study.** *Scand J Public Health* 2008, **36**:744-752.
 41. Kraft P, Hunter DJ: **Genetic risk prediction - are we there yet?** *N Engl J Med* 2009, **360**:1701-1703.
 42. Wacholder S, Hartge P, Prentice R, Garcia-Closas M, Feigelson HS, Diver WR, Thun MJ, Cox DG, Hankinson SE, Kraft P, Rosner B, Berg CD, Brinton LA, Lissowska J, Sherman ME, Chlebowski R, Kooperberg C, Jackson RD, Buckman DW, Hui P, Pfeiffer R, Jacobs KB, Thomas GD, Hoover RN, Gail MH, Chanock SJ, Hunter DJ: **Performance of common genetic variants in breast-cancer risk models.** *N Engl J Med* 2010, **362**:986-993.
 43. Hardy J, Singleton A: **Genomewide association studies and human disease.** *N Engl J Med* 2009, **360**:1759-1768.
 44. Goldstein DB: **Common genetic variation and human traits.** *N Engl J Med* 2009, **360**:1696-1698.
 45. Hirschhorn JN: **Genomewide association studies - illuminating biologic pathways.** *N Engl J Med* 2009, **360**:1699-1701.
 46. Ioannidis JP, Thomas G DM: **Validating, augmenting and refining genome-wide association signals.** *Nat Rev Genet* 2009, **10**:318-329.

doi:10.1186/gm160

Cite this article as: Lennon AM, *et al.*: ABO blood group and other genetic variants associated with pancreatic cancer. *Genome Medicine* 2010, **2**:39.