**Name of journal: World Journal of Gastroenterology**

**ESPS Manuscript NO: 9927**

**Columns:** **case control study**

**case-control study of diabetes-related genetic variants and pancreatic cancer risk in Japan**

Kuruma S***et al.***Genetic variants and pancreatic cancer

Sawako Kuruma, Naoto Egawa, Masanao Kurata, Goro Honda, Terumi Kamisawa, Junko Ueda, Hiroshi Ishii, Makoto Ueno, Haruhisa Nakao, Mitsuru Mori, Keitaro Matsuo, Satoyo Hosono, Shinichi Ohkawa, Kenji Wakai, Kozue Nakamura, Akiko Tamakoshi, Masanori Nojima, Mami Takahashi, Kazuaki Shimada, Takeshi Nishiyama, Shogo Kikuchi,Yingsong Lin

**Sawako Kuruma, Naoto Egawa, Terumi Kamisawa,** Department of Internal Medicine, Tokyo Metropolitan Komagome Hospital, Tokyo 113-8677, Japan

**Naoto Egawa**, Department of Internal Medicine, Tokyo Metropolitan Matsuzawa Hospital, Tokyo 156-0057, Japan

**Masanao Kurata, Goro Honda,** Department of Surgery, Tokyo Metropolitan Komagome Hospital, Tokyo 113-8677, Japan

**Junko Ueda, Shogo Kikuchi, Yingsong Lin,** Department of Public Health, Aichi Medical University School of Medicine, Nagakute 480-1195, Japan

**Hiroshi Ishii,** Hepatobiliary and Pancreatic Section, Gastroenterological Division, Cancer Institute Hospital, Tokyo 135-8550, Japan

**Makoto Ueno**, Hepatobiliary and Pancreatic Medical Oncology Division, Kanagawa Cancer Center Hospital, Kanagawa 241-8515, Japan

**Haruhisa Nakao**, Division of Gastroenterology, Department of Internal Medicine, Aichi Medical University School of Medicine, Nagakute 480-1195, Japan

**Mitsuru Mori, Masanori Nojima**, Department of Public Health, Sapporo Medical University School of Medicine, Sapporo 060-8556, Japan

**Keitaro Matsuo**, Department of Preventive Medicine, Kyushu University Faculty of Medical Science, Fukuoka 812-8582, Japan

**Satoyo Hosono**, Division of Epidemiology and Prevention, Aichi Cancer Center Research Institute, Nagoya 464-8681, Japan

**Kenji Wakai,** Department of Preventive Medicine, Nagoya University Graduate School of Medicine, Nagoya 466-8550, Japan

**Kozue Nakamura**, Department of Food and Nutrition, Gifu City Women’s College, Gifu 501-2592, Japan

**Akiko Tamakoshi,** Department of Public Health, Hokkaido University Graduate School of Medicine, Sapporo 060-8638, Japan

**Mami Takahashi**, Central Animal Division, National Cancer Center Research Institute, Tokyo 104-0045, Japan

**Kazuaki Shimada**, Department of Hepatobiliary and Pancreatic Surgery, National Cancer Center Hospital, Tokyo 104-0045, Japan

**Author contributions:** Kikuchi S supervised the study; Kikuchi S, Lin Y, Kuruma S, Egawa N, Wakai K, Nakamura K, Tamakoshi A, Takahashi M and Shimada k designed the research; Kurama S, Egawa N, Lin Y and Nishiyama T drafted the manuscript and conducted the statistical analysis; Ueda J, Hosono S and Matsuo K performed genotyping and SNP data analysis; Kuruma S, Egawa N, Kurata M, Honda G, Kamisawa T, Ishii H, Ueno M, Nakao H, Mori M, Ohkawa S and Nojima M participated in data collection; all authors read and approved the final manuscript.

**Supported by** Grants-in-Aid for Cancer Research from the Ministry of Health, Labour and Welfare, Japan

**Correspondence to**: **Dr. Yingsong Lin,** Department of Public Health, Aichi Medical University School of Medicine, 1-1 Yazakokarimata, Nagakute, Aichi 480-1195, Japan. linys@aichi-med-u.ac.jp

**Telephone:** +81-561-623311 **Fax:** +81-561-625270

**Received:** March 4, 2014 **Revised:** April 18, 2014

**Accepted:** July 24, 2014

**Published online:**

**Abstract**

**Aim:** To examine whether diabetes-related genetic variants are associated with pancreatic cancer risk.

**Methods:** We genotyped 7 single-nucleotide polymorphisms (SNPs) in *PPARG2* (rs1801282), *ADIPOQ* (rs1501299), *ADRB3* (rs4994), *KCNQ*1 (rs2237895), *KCNJ11* (rs5219), *TCF7L2* (rs7903146), and *CDKAL1* (rs2206734), and examined their associations with pancreatic cancer risk in a multi-institute case-control study including 360 cases and 400 controls in Japan.A self-administered questionnaire was used to collect detailed information on lifestyle factors. Genotyping was performed using Fluidigm SNPtype assays. Unconditional logistic regression methods were used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for the association between these diabetes-associated variants and pancreatic cancer risk.

**Results:** With the exception of rs1501299 in the *ADIPOQ* gene (*p =* 0.09), no apparent differences in genotype frequencies were observed between cases and controls.Rs1501299 in the *ADPIOQ* gene was positively associated with pancreatic cancer risk; compared with individuals with the AA genotype, the age- and sex-adjusted OR was 1.79 (95%CI: 0.98–3.25) among those with the AC genotype and 1.86 (95%CI: 1.03–3.38) among those with the CC genotype. The ORs remained similar after additional adjustment for body mass index and cigarette smoking. In contrast, rs2237895 in the *KCNQ1* gene was inversely related to pancreatic cancer risk, with a multivariable-adjusted OR of 0.62 (0.37–1.04) among individuals with the CC genotype compared with the AA genotype. No significant associations were noted for other 5 SNPs.

**Conclusion:** Our case-control study indicates that rs1501299 in the ADIPOQ gene may be associated with pancreatic cancer risk. These findings should be replicated in additional studies.

© 2014 Baishideng Publishing Group Inc. All rights reserved.

**Key words:** Single-nucleotide polymorphisms; Pancreatic cancer; Risk; Case-control study; Odds ratio

**Core tip:** Although it is likely that a common genetic background predisposes individuals to developing both diabetes and pancreatic cancer, very few molecular epidemiologic studies have addressed this issue. We therefore genotyped 7 diabetes-related genetic variants and found that rs1501299 in the *ADIPOQ* gene may be associated with pancreatic cancer risk. The role of adiponectin variants needs further study.

Kuruma S, Egawa N, Kurata M, Honda G, Kamisawa T, Ueda J, Ishii H, Ueno M, Nakao H, Mori M, Matsuo K, Hosono S, Ohkawa S, Wakai K, Nakamura K, Tamakoshi A, Nojima M, Takahashi M, Shimada K, Nishiyama T, Kikuchi S,Lin Y. Case-control study of diabetes-related genetic variants and pancreatic cancer risk in Japan. *World J Gastroenterol* 2014; In press

**Introduction**

The etiology of sporadic pancreatic cancer remains largely unknown. Epidemiologic studies have consistently shown that pancreatic cancer is positively associated with cigarette smoking and long-standing diabetes[1,2]. A 2005 meta-analysis reported that the risk for pancreatic cancer is 82% higher among diabetics compared with those without diabetes[3], though it is unclear which factors underlying diabetes are associated with pancreatic cancer. Most epidemiological studies have been limited by self-reporting of diabetes and by the lack of objective biomarkers, such as fasting plasma glucose or insulin levels, to address the temporal relationship between diabetes and pancreatic cancer. There is increasing evidence from clinical studies that pancreatic cancer induces new-onset diabetes[4,5]. The evidence available thus far strongly suggests that the relationship between diabetes and pancreatic cancer is bi-directional.

Given the well-recognized, positive association between type 2 diabetes and pancreatic cancer risk in epidemiological studies, it may be interesting to examine whether diabetes-related genetic variants may also be associated with pancreatic cancer risk. Genome-wide association studies (GWAS) have reported that at least 30 loci are associated with susceptibility to diabetes in various populations, with the majority originating from individuals of European descent[6]. Because of the potential differences in fat distribution and genetic background between Asian and Western populations[7,8], we focused on diabetes-related genetic variants reported in studies of Japanese populations, and variants that were first reported in GWAS of other populations and then replicated in Japanese populations. Among the 7 diabetes susceptibility genes we chose for the present study, *PPARG2*, *ADIPOQ*, and *ADRB3* have been shown to be closely associated with diabetes risk in Japanese subjects[9]; *KCNQ1* was reported as a diabetes susceptibility gene simultaneously by 2 independent Japanese research groups in 2008[10,11]; *KCN11*, *TCF7L2*, and *CDKAL1* were also reported to be associated with diabetes susceptibility in GWAS of Japanese subjects[12,13].

Although it is likely that a common genetic background predisposes individuals to developing both diabetes and pancreatic cancer, very few molecular epidemiologic studies have addressed this issue. We hypothesized that diabetes susceptibility genetic variants may be associated with an increased risk of pancreatic cancer in Japanese subjects. We therefore genotyped 7 single-nucleotide polymorphisms (SNPs) in *PPARG2* (rs1801282), *ADIPOQ* (rs1501299), *ADRB3* (rs4994), *KCNQ1* (rs2237895), *KCNJ11* (rs5219), *TCF7L2* (rs7903146), and *CDKAL1* (rs2206734) and examined their associations with pancreatic cancer risk in a multi-institute, case-control study in Japan.

**Materials and Methods**

***Study subjects***

The purpose of our case-control study was to evaluate the role of genetic polymorphisms and gene-environment interactions in the development of pancreatic cancer in Japanese subjects. The details of the study design have been described elsewhere[14]. Briefly, cases were defined as patients who were newly diagnosed with pancreatic ductal adenocarcinoma at five participating hospitals from April 1, 2010, through May 15, 2012. A diagnosis was made according to imaging modalities and further confirmed by pathology reports. Pathologically confirmed cases represented approximately 90% of all cases in this study. During the same time period, we recruited the majority of control subjects from inpatients and outpatients as well as from individuals who underwent medical checkups at one of the participating hospitals. None of the control subjects had a history of cancer. The diagnoses for hospital control subjects included a variety of diseases, such as anemia, gastric ulcers, and irritable bowel syndrome. The response rate was 85% (441/516) for cases and 98% (525/534) for control subjects as of July 1, 2012. The control subjects were frequency matched to the case patients on sex and age (within 10-year categories). As a result, 360 case patients and 400 control subjects were included in the present analysis.

All the study subjects provided written informed consent. Our study was approved by the Ethics Board of Aichi Medical University and by all the participating hospitals.

***Data collection***

Using a self-administered questionnaire, we collected detailed information on demographic characteristics, medical history, and lifestyle factors. In addition to the questionnaire survey, we obtained a 7-mL venous blood sample from all consenting participants. Genomic DNA was extracted from peripheral lymphocytes and subsequently stored at -30 °C until analysis.

***Genotyping assays***

Genotyping was performed using Fluidigm 192.24 Dynamic Array with BioMark HD Systems and EP1 (Fluidigm Corp., CA). We applied SNPtype assay (Fluidigm Corp., CA) which employs allele-specifically designed fluorescences (FAM or VIC) primers and a common reverse primer. We analyzed the data by the BioMark SNP Genotyping Analysis software to obtain genotype calls. The software defined genotype of each sample based on the relative intensities of fluorescences. The laboratory staff members were blinded to case or control status. Four quality control samples were included in each assay, and the successful genotyping rate was 100%.

***Statistical analysis***

A *χ2* test was used to test genotype frequencies in control subjects for Hardy-Weinberg equilibrium (HWE) by comparing the observed genotype frequencies with those expected under HWE. The differences in genotype frequencies between cases and controls were also tested using a *χ2* test. Because the biological function of most SNPs has not been clearly defined, a co-dominant genomic model was assumed for SNP effects. We used unconditional logistic regression methods to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for the association between diabetes-associated variants and pancreatic cancer risk. All analyses were adjusted for age (continuous), sex (male or female), BMI (< 20, 20-22.4, 22.5-24.9, or ≥ 25.0), and cigarette smoking (current, former, or never smokers). ORs were also estimated for the risk allele on the basis of a log-additive model.

All P values were two-sided, with *P* < 0.05 indicating statistical significance. All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University), which is a graphical user interface for the R program (The R Foundation for Statistical Computing). More precisely, EZR is a modified version of R commander designed to add statistical functions frequently used in biostatistics.

**Results**

The distribution of genotypes for all SNPs among control subjects did not deviate from HWE. Table 1 shows the selected characteristics of cases and controls. The mean BMI was similar between cases and controls. The number of individuals who had a history of diabetes was 87 (24.1%) in cases and 35 (8.7%) in controls. The OR was 2.95 (95%CI: 1.90–4.57) for those who had a history of diabetes. Individuals who had a BMI of 30 or greater had a 1.21-fold increased risk; however, the association was not statistically significant. The number of ever smokers (including current and former smokers) was 215 (59.7%) in cases and 198 (49.5%) in controls. The SNP profile is summarized in Table 2.

Table 3 shows the associations of pancreatic cancer with individual SNPs in the following genes: *PPARG2* (rs1801282), *ADIPOQ* (rs1501299), *ADRB3* (rs4994), *KCNQ1* (rs2237895), *KCNJ11* (rs5219), *TCF7L2* (rs7903146), and *CDKAL1* (rs2206734). With the exception of rs1501299 in the *ADIPOQ* gene (*p =* 0.09), no apparent differences in genotype frequencies were observed between cases and controls. Rs1501299 in the *ADPOQ* gene was positively associated with pancreatic cancer risk; the age- and sex-adjusted OR was 1.79 (95%CI: 0.98–3.25) among those with the AC genotype and 1.86 (95%CI: 1.03–3.38) among those with the CC genotype when compared with individuals with the AA genotype. The ORs remained similar after additional adjustment for cigarette smoking and BMI. Under the log-additive model, each additional copy of risk allele C was associated with a 1.2-fold increased risk of pancreatic cancer (OR = 1.22, 95%CI: 0.96–1.55). In contrast, rs2237895 in the *KCNQ1* gene was inversely related to pancreatic cancer risk, with a multivariable-adjusted OR of 0.62 (0.37-1.04) among individuals with the CC genotype compared with those with the AA genotype. No significant associations were noted for the other 5 SNPs.

**Discussion**

In this case-control study, we genotyped 7 diabetes-associated genetic polymorphisms, and found that 2 variants in the *ADIPOQ* and *KCNQ1* genes were associated with pancreatic cancer risk in Japanese subjects. The risk variant in the *ADIPOQ* gene had a 1.9-fold increased risk, whereas the risk variant in the *KCNQ1* gene was inversely associated with risk.

Studies examining the association between diabetes-related genetic variants and pancreatic cancer risk were very limited, and the results were inconsistent. In a case-control study examining 15 SNPs in several obesity- and diabetes-related genes, two *FTO* gene variants (rs8050136 and rs9939609) and one *ADIPOQ* gene variant (rs17366743) were positively associated with pancreatic cancer risk; however, these associations were observed only in individuals who were overweight[15].

Of the 37 diabetes risk alleles examined by Pierce *et al*[16], only two SNPs (rs8050136 in *FTO* and rs1387153 in *MTNR1B*) showed significant positive associations with pancreatic cancer risk. However, *ADIPOQ* gene variants were not included in their analyses. We found that rs1501299 in the *ADIPOQ* gene had a positive association with pancreatic cancer risk, with the risk variant CC genotype conferring an approximate 1.9-fold increased risk compared with the AA genotype. The precise mechanism linking this SNP to pancreatic cancer risk is not clear. Adiponectin, which is secreted by adipose tissue, acts as an endogenous insulin-sensitizing hormone[17] and activates intracellular signaling pathways, including AMPK, PPARα, and NF-kB, by binding to two receptors, AdipoR1 and AdipoR2[17]. AdipoR1 has been reported to be upregulated in pancreatic cancer[18]. The adiponectin gene is located on chromosome 3q26, a region associated with susceptibility to the development of type 2 diabetes[19]. Rs1501299 in the *ADIPOQ* gene has been shown to be correlated with adiponectin levels, with the CC genotype exhibiting decreased levels of adiponectin compared with the AA genotype[9,20], Low adiponectin concentrations contribute to insulin resistance, type 2 diabetes, and atherosclerosis[21] as well as obesity-related cancers, including breast and colorectal cancers[22,23]. A prospective study showed that low plasma adiponectin levels are associated with an increased risk of pancreatic cancer, independent of other markers of insulin resistance[24]. Given the essential role of adiponectin in insulin resistance and the strong evidence supporting the positive association of pancreatic cancer with obesity, insulin resistance, and hyperinsulinemia in both epidemiological and mechanistic studies, it is likely that genetic variations in the adiponectin pathway may affect pancreatic cancer risk through their effects on circulating adiponectin.

*KCNQ1* (potassium voltage-gated channel KQT-like subfamily, member 1) encodes the pore-forming subunit of a voltage-gated K+ channel (KvLQT1) and plays a key role in the repolarization of cardiac action potential as a water and salt transporter in epithelial tissues[25]. *KCNQ1* is also expressed in pancreatic islets[26], and a blockade of the channel with the *KCNQ1* inhibitor 293B stimulated insulin secretion[27]. To date, variants in the *KCNQ1* gene exert the greatest effects on the risk of type 2 diabetes in Asians[28]. Of the several SNPs in the *KCNQ1* gene that are associated with increased type 2 diabetes risk in Asians[10,11], we selected rs2237895 because this SNP was reported to be significantly associated with diabetes risk in both GWAS of Japanese people. Furthermore, in a previous study examining the effects of 4 SNPs in the *KCNQ1* gene (rs2237892, rs2283228, rs2237895, and rs2237897) on serum insulin levels following an oral glucose tolerance test in approximately 6000 Scandinavian individuals, only the C risk allele of rs2237895 was associated with reduced insulin release[29]. A 2012 meta-analysis confirmed that the C risk allele of rs2237895 in the *KCNQ1* gene increases the risk of diabetes by 32%[30]. However, we found that the C risk allele of rs2237895 was associated with a decreased risk of pancreatic cancer, which is unexpected and contrary to our hypothesis. This finding may be due to chance, but the mechanisms underlying this inverse association should be explored in further studies.

Diabetes is a complex disease, and susceptibility is determined by both genetic and environmental factors. Additionally, pancreatic cancer develops only in a subset of diabetics. Thus, these factors led us to postulate that certain diabetes-predisposing variants may be associated with a decreased risk of pancreatic cancer. A nested case-control study offered supporting evidence that circulating markers of peripheral insulin resistance, rather than pancreatic β-cell dysfunction, were independently associated with pancreatic cancer risk[31]. This finding, together with our observation of the positive association between rs1501299 in the *ADIPOQ* gene and pancreatic cancer risk, indicates that genetic variations influencing insulin resistance and their impact on circulating biomarkers are closely associated with pancreatic cancer risk.

No significant differences were observed in the genotype distributions between cases and controls in this study, with the exception of rs1501299 in the *ADIPOQ* gene. Other than SNPs in the *ADIPOQ* and *KCNQ1* genes, none of the 5 SNPs we genotyped were associated with pancreatic cancer risk. Among the genes examined in this study, *TCF7L2*, the most significant diabetes-related gene in Western populations, did not show any significant associations in this study. One possible reason for this result is the difference in the minor allele frequency. The very low frequency of *TCF7L2* risk genotypes in this study might make the detection of significant associations difficult. The null association for these SNPs suggests that other causal SNPs in these genes may be involved in pancreatic cancer susceptibility, and further studies are warranted to identify novel risk variants.

Our findings should be interpreted cautiously due to several limitations of this study. First, the results obtained may be due to chance because of the inadequate statistical power or bias inherent in case-control studies. Second, pathology reports were not available for all cases. However, we performed an analysis excluding those cases without pathology reports, and found that the positive association between rs1501299 in the *ADIPOQ* gene and pancreatic cancer remained unchanged. Third, we did not genotype SNPs that have been shown to be related to diabetes-related quantitative traits, including fasting plasma glucose, insulin, and homeostasis model assessment of β-cell function (HOMA-β). These biomarkers have been shown to be associated with pancreatic cancer risk in previous prospective studies[32,33]. Fourth, we did not examine serum levels of adiponectin in this study. Additional studies are necessary to clarify the effects of genetic polymorphisms on serum levels of adiponectin and evaluate their roles in the development of pancreatic cancer. Finally, we cannot exclude the possibility that the observed SNPs are in linkage disequilibrium with causal variants in the same gene or other genes. Further comprehensive analyses of SNPs in the two genes are required to identify the causal variants that confer susceptibility to diabetes or pancreatic cancer.

In summary, the results of our case-control study indicate that rs1501299 in the *ADIPOQ* gene may be associated with pancreatic cancer risk. These findings should be replicated in additional studies.

**Acknowledgments**

We thank Kiyoko Yagyu for the contribution to the study design and data collection. We thank Mayuko Masuda, Kikuko Kaji, Kazue Ando, Etsuko Ohara, and Sumiyo Asakura for assisting us with data collection. We also thank Miki Watanabe, Tomoko Ito, Sanae Inui, and Sachiko Mano for technical assistance with genotyping

**COMMENTS**

***Background***

Given the well-recognized, positive association between type 2 diabetes and pancreatic cancer risk in epidemiological studies, it may be interesting to examine whether diabetes-related genetic variants may also be associated with pancreatic cancer risk.

***Research frontiers***

Although it is likely that a common genetic background predisposes individuals to developing both diabetes and pancreatic cancer, very few molecular epidemiologic studies have addressed this issue.

***Innovations and breakthroughs***
This case-control study indicates that rs1501299 in the *ADIPOQ* gene may be associated with pancreatic cancer risk in Japanese subjects.

***Applications***
Genetic variations in the adiponectin pathway may affect pancreatic cancer risk through their effects on circulating adiponectin. Further comprehensive analyses of SNPs in this gene are required to identify the causal variants that confer susceptibility to diabetes or pancreatic cancer.

***Terminology***
Single-nucleotide polymorphisms (SNP) are the most common type of genetic variation among individuals. Some SNPs have been linked to increased susceptibility to disease.

***Peer review***Very few molecular epidemiologic studies have addressed the issue about the common genetic background which predisposes individuals to developing both diabetes and pancreatic cancer. This a good case-control study, try to examine whether diabetes-related genetic variants are associated with pancreatic cancer risk in Japan. 7 diabetes-related genetic variants were therefore genotyped and it was found that rs1501299 in the *ADIPOQ* gene may be associated with pancreatic cancer risk, although the role of adiponectin variants has not been clarified yet.

**References**

1 **Duell EJ**. Epidemiology and potential mechanisms of tobacco smoking and heavy alcohol consumption in pancreatic cancer. *Mol Carcinog* 2012; **51**: 40-52 [PMID: 22162230 DOI: 10.1002/mc.20786]

2 **Ben Q**, Xu M, Ning X, Liu J, Hong S, Huang W, Zhang H, Li Z. Diabetes mellitus and risk of pancreatic cancer: A meta-analysis of cohort studies. *Eur J Cancer* 2011; **47**: 1928-1937 [PMID: 21458985 DOI: 10.1016/j.ejca.2011.03.003.]

3 **Huxley R**, Ansary-Moghaddam A, Berrington de González A, Barzi F, Woodward M. Type-II diabetes and pancreatic cancer: a meta-analysis of 36 studies. *Br J Cancer* 2005; **92**: 2076-2083 [PMID: 15886696 DOI: 10.1038/sj.bjc.6602619]

4 **Chari ST**, Leibson CL, Rabe KG, Timmons LJ, Ransom J, de Andrade M, Petersen GM. Pancreatic cancer-associated diabetes mellitus: prevalence and temporal association with diagnosis of cancer. *Gastroenterology* 2008; **134**: 95-101 [PMID: 18061176 DOI: 10.1053/j.gastro.2007.10.040]

5 **Pannala R**, Leibson CL, Rabe KG, Timmons LJ, Ransom J, de Andrade M, Petersen GM, Chari ST. Temporal association of changes in fasting blood glucose and body mass index with diagnosis of pancreatic cancer. *Am J Gastroenterol* 2009; **104**: 2318-2325 [PMID: 19513024 DOI: 10.1038/ajg.2009.253]

6 **McCarthy MI**. Genomics, type 2 diabetes, and obesity. *N Engl J Med* 2010; **363**: 2339-2350 [PMID: 21142536 DOI: 10.1056/NEJMra0906948]

7 **Chan JC**, Malik V, Jia W, Kadowaki T, Yajnik CS, Yoon KH, Hu FB. Diabetes in Asia: epidemiology, risk factors, and pathophysiology. *JAMA* 2009; **301**: 2129-2140 [PMID: 19470990 DOI: 10.1001/jama.2009.726]

8 **McCarthy MI**. Casting a wider net for diabetes susceptibility genes. *Nat Genet* 2008; **40**: 1039-1040 [PMID: 19165915 DOI: 10.1038/ng0908-1039]

9 **Kadowaki T**, Yamauchi T. Adiponectin and adiponectin receptors. *Endocr Rev* 2005; **26**: 439-451 [PMID: 15897298 DOI: 10.1210/er.2005-0005]

10 **Yasuda K**, Miyake K, Horikawa Y, Hara K, Osawa H, Furuta H, Hirota Y, Mori H, Jonsson A, Sato Y, Yamagata K, Hinokio Y, Wang HY, Tanahashi T, Nakamura N, Oka Y, Iwasaki N, Iwamoto Y, Yamada Y, Seino Y, Maegawa H, Kashiwagi A, Takeda J, Maeda E, Shin HD, Cho YM, Park KS, Lee HK, Ng MC, Ma RC, So WY, Chan JC, Lyssenko V, Tuomi T, Nilsson P, Groop L, Kamatani N, Sekine A, Nakamura Y, Yamamoto K, Yoshida T, Tokunaga K, Itakura M, Makino H, Nanjo K, Kadowaki T, Kasuga M. Variants in KCNQ1 are associated with susceptibility to type 2 diabetes mellitus. *Nat Genet* 2008; **40**: 1092-1097 [PMID: 18711367]

11 **Unoki H**, Takahashi A, Kawaguchi T, Hara K, Horikoshi M, Andersen G, Ng DP, Holmkvist J, Borch-Johnsen K, Jørgensen T, Sandbaek A, Lauritzen T, Hansen T, Nurbaya S, Tsunoda T, Kubo M, Babazono T, Hirose H, Hayashi M, Iwamoto Y, Kashiwagi A, Kaku K, Kawamori R, Tai ES, Pedersen O, Kamatani N, Kadowaki T, Kikkawa R, Nakamura Y, Maeda S. SNPs in KCNQ1 are associated with susceptibility to type 2 diabetes in East Asian and European populations. *Nat Genet* 2008; **40**: 1098-1102 [PMID: 18711366 DOI: 10.1038/ng.208]

12 **Takeuchi F**, Katsuya T, Chakrewarthy S, Yamamoto K, Fujioka A, Serizawa M, Fujisawa T, Nakashima E, Ohnaka K, Ikegami H, Sugiyama T, Nabika T, Kasturiratne A, Yamaguchi S, Kono S, Takayanagi R, Yamori Y, Kobayashi S, Ogihara T, de Silva A, Wickremasinghe R, Kato N. Common variants at the GCK, GCKR, G6PC2-ABCB11 and MTNR1B loci are associated with fasting glucose in two Asian populations. *Diabetologia* 2010; **53**: 299-308 [PMID: 19937311 DOI: 10.1007/s00125-009-1595-1]

13 **Okada Y**, Kubo M, Ohmiya H, Takahashi A, Kumasaka N, Hosono N, Maeda S, Wen W, Dorajoo R, Go MJ, Zheng W, Kato N, Wu JY, Lu Q, Tsunoda T, Yamamoto K, Nakamura Y, Kamatani N, Tanaka T. Common variants at CDKAL1 and KLF9 are associated with body mass index in east Asian populations. *Nat Genet* 2012; **44**: 302-306 [PMID: 22344221]

14 **Lin Y**, Ueda J, Yagyu K, Ishii H, Ueno M, Egawa N, Nakao H, Mori M, Matsuo K, Kikuchi S. Association between variations in the fat mass and obesity-associated gene and pancreatic cancer risk: a case-control study in Japan. *BMC Cancer* 2013; **13**: 337 [PMID: 23835106 DOI: 10.1186/1471-2407-13-337]

15 **Tang H**, Dong X, Hassan M, Abbruzzese JL, Li D. Body mass index and obesity- and diabetes-associated genotypes and risk for pancreatic cancer. *Cancer Epidemiol Biomarkers Prev* 2011; **20**: 779-792 [PMID: 21357378 DOI: 10.1158/1055-9965]

16 **Pierce BL**, Austin MA, Ahsan H. Association study of type 2 diabetes genetic susceptibility variants and risk of pancreatic cancer: an analysis of PanScan-I data. *Cancer Causes Control* 2011; **22**: 877-883 [PMID: 21445555 DOI: 10.1007/s10552-011-9760-5]

17 **Kadowaki T**, Yamauchi T, Kubota N, Hara K, Ueki K, Tobe K. Adiponectin and adiponectin receptors in insulin resistance, diabetes, and the metabolic syndrome. *J Clin Invest* 2006; **116**: 1784-1792 [PMID: 16823476 DOI: 10.1172/JCI29126]

18 **Dalamaga M**, Migdalis I, Fargnoli JL, Papadavid E, Bloom E, Mitsiades N, Karmaniolas K, Pelecanos N, Tseleni-Balafouta S, Dionyssiou-Asteriou A, Mantzoros CS. Pancreatic cancer expresses adiponectin receptors and is associated with hypoleptinemia and hyperadiponectinemia: a case-control study. *Cancer Causes Control* 2009; **20**: 625-633 [PMID: 19051043 DOI: 10.1007/s10552-008-9273-z]

19 **Mori Y**, Otabe S, Dina C, Yasuda K, Populaire C, Lecoeur C, Vatin V, Durand E, Hara K, Okada T, Tobe K, Boutin P, Kadowaki T, Froguel P. Genome-wide search for type 2 diabetes in Japanese affected sib-pairs confirms susceptibility genes on 3q, 15q, and 20q and identifies two new candidate Loci on 7p and 11p. *Diabetes* 2002; **51**: 1247-1255 [PMID: 11916952 DOI: 10.2337/diabetes.51.4.1247]

20 **AlSaleh A**, O'Dell SD, Frost GS, Griffin BA, Lovegrove JA, Jebb SA, Sanders TA. Single nucleotide polymorphisms at the ADIPOQ gene locus interact with age and dietary intake of fat to determine serum adiponectin in subjects at risk of the metabolic syndrome. *Am J Clin Nutr* 2011; **94**: 262-269 [PMID: 21562092 DOI: 10.3945/ajcn.111.014209]

21 **Li S**, Shin HJ, Ding EL, van Dam RM. Adiponectin levels and risk of type 2 diabetes: a systematic review and meta-analysis. *JAMA* 2009; **302**: 179-188 [PMID: 19584347 DOI: 10.1001/jama.2009.976]

22 **Kaklamani VG**, Sadim M, Hsi A, Offit K, Oddoux C, Ostrer H, Ahsan H, Pasche B, Mantzoros C. Variants of the adiponectin and adiponectin receptor 1 genes and breast cancer risk. *Cancer Res* 2008; **68**: 3178-3184 [PMID: 18451143 DOI: 10.1158/0008-5472.CAN-08-0533]

23 **Kaklamani VG**, Wisinski KB, Sadim M, Gulden C, Do A, Offit K, Baron JA, Ahsan H, Mantzoros C, Pasche B. Variants of the adiponectin (ADIPOQ) and adiponectin receptor 1 (ADIPOR1) genes and colorectal cancer risk. *JAMA* 2008; **300**: 1523-1531 [PMID: 18827209 DOI: 10.1001/jama.300.13.1523]

24 **Bao Y**, Giovannucci EL, Kraft P, Stampfer MJ, Ogino S, Ma J, Buring JE, Sesso HD, Lee IM, Gaziano JM, Rifai N, Pollak MN, Cochrane BB, Kaklamani V, Lin JH, Manson JE, Fuchs CS, Wolpin BM. A prospective study of plasma adiponectin and pancreatic cancer risk in five US cohorts. *J Natl Cancer Inst* 2013; **105**: 95-103 [PMID: 23243202 DOI: 10.1093/jnci/djs474]

25 **Wang Q**, Curran ME, Splawski I, Burn TC, Millholland JM, VanRaay TJ, Shen J, Timothy KW, Vincent GM, de Jager T, Schwartz PJ, Toubin JA, Moss AJ, Atkinson DL, Landes GM, Connors TD, Keating MT. Positional cloning of a novel potassium channel gene: KVLQT1 mutations cause cardiac arrhythmias. *Nat Genet* 1996; **12**: 17-23 [PMID: 8528244 DOI: 10.1038/ng0196-17]

26 **Demolombe S**, Franco D, de Boer P, Kuperschmidt S, Roden D, Pereon Y, Jarry A, Moorman AF, Escande D. Differential expression of KvLQT1 and its regulator IsK in mouse epithelia. *Am J Physiol Cell Physiol* 2001; **280**: C359-C372 [PMID: 11208532]

27 **Ullrich S**, Su J, Ranta F, Wittekindt OH, Ris F, Rösler M, Gerlach U, Heitzmann D, Warth R, Lang F. Effects of I(Ks) channel inhibitors in insulin-secreting INS-1 cells. *Pflugers Arch* 2005; **451**: 428-436 [PMID: 16133261 DOI: 10.1007/s00424-005-1479-2]

28 **Wang H**, Miao K, Zhao J, Liu L, Cui G, Chen C, Wang DW, Ding H. Common variants in KCNQ1 confer increased risk of type 2 diabetes and contribute to the diabetic epidemic in East Asians: a replication and meta-analysis. *Ann Hum Genet* 2013; **77**: 380-391 [PMID: 23786590 DOI: 10.1111/ahg.12029]

29 **Holmkvist J**, Banasik K, Andersen G, Unoki H, Jensen TS, Pisinger C, Borch-Johnsen K, Sandbaek A, Lauritzen T, Brunak S, Maeda S, Hansen T, Pedersen O. The type 2 diabetes associated minor allele of rs2237895 KCNQ1 associates with reduced insulin release following an oral glucose load. *PLoS One* 2009; **4**: e5872 [PMID: 19516902 DOI: 10.1371/journal.pone.0005872]

30 **Sun Q**, Song K, Shen X, Cai Y. The association between KCNQ1 gene polymorphism and type 2 diabetes risk: a meta-analysis. *PLoS One* 2012; **7**: e48578 [PMID: 23133642 DOI: 10.1371/journal.pone.0048578]

31 **Wolpin BM**, Bao Y, Qian ZR, Wu C, Kraft P, Ogino S, Stampfer MJ, Sato K, Ma J, Buring JE, Sesso HD, Lee IM, Gaziano JM, McTiernan A, Phillips LS, Cochrane BB, Pollak MN, Manson JE, Giovannucci EL, Fuchs CS. Hyperglycemia, insulin resistance, impaired pancreatic β-cell function, and risk of pancreatic cancer. *J Natl Cancer Inst* 2013; **105**: 1027-1035 [PMID: 23847240 DOI: 10.1093/jnci/djt123]

32 **Stolzenberg-Solomon RZ**, Graubard BI, Chari S, Limburg P, Taylor PR, Virtamo J, Albanes D. Insulin, glucose, insulin resistance, and pancreatic cancer in male smokers. *JAMA* 2005, **294**: 2872-2878 [PMID:16352795 doi: 10.1001/jama.294.22.2872]

33 **Jee SH**, Ohrr H, Sull JW, Yun JE, Ji M, Samet JM. Fasting serum glucose level and cancer risk in Korean men and women. *JAMA* 2005; **293**: 194-202 [PMID: 15644546 DOI: 10.1001/jama.293.2.194]

**P-Reviewer:** Fu DL, Li CY **S-Editor:** Ma N **L-Editor:** **E-Editor:**

**Table 1 Selected characteristics of cases and controls *n* (%)**

|  |  |  |
| --- | --- | --- |
|  | **Cases** | **Controls** |
|  | ***n =* 360** | ***n =* 400** |
| **age, mean ± SD** | 67.8 ± 8.8 | 64.8 ± 9.5 |
| **Sex** |  |  |
| **Male** | 215 (59.7) | 226 (56.5) |
| **Female** | 145 (40.３) | 174 (43.5) |
| **BMI, mean ± SD** | 22.9 ± 3.3 | 22.8 ± 3.2 |
| **History of diabetes,**  |  |  |
| **Yes** | 87 (24.1) | 35 (8.7) |
| **No** | 269 (74.7) | 362 (90.5) |
| **Cigarette smoking** |  |  |
|  **Ever** | 215 (59.7) | 198 (49.5) |
|  **Never** | 145 (40.2) | 202 (50.5) |
| **Age upon starting smoking (mean ± SD)** | 21.8 ± 4.8 | 20.5 ± 4.5 |
| **Number of cigarettes smoked per day (mean ± SD)** | 20.3 ± 9.0 | 16.2 ± 9.2 |

BMI: body mass index.

**Table 2 single-nucleotide polymorphisms profile**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Rs number** | **Gene** | **Chromosome location** | **Risk allele1** | **Alternative allele** |
| rs1801282 | *PPARG2* | 3p25 | C | G |
| rs1501299 | *ADIPOQ* | 3q27 | C  | A  |
| rs4994 | *ADRB3* | 8p12 | C | T |
| rs2237895 | *KCNQ1* | 11p15 | C | A |
| rs5219 | *KCNJ11* | 11q23 | T | C |
| rs7903146 | *TCF7L2* | 10q25 | T | C |
| rs2206734 | *CDKAL1* | 6p22 | A | G |

1Based on the odds ratios reported for the association between T2D risk allele and T2D risk in previous studies.

**Table 3 Associations between diabetes-associated single-nucleotide polymorphisms and pancreatic cancer risk**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Gene** | **SNP** | **Genotype** | **Case, n** | **Control, n** | **Age- and sex-adjusted OR (95%CI)** | **1Multivariable-adjusted OR (95%CI)** |
| *PPARG2* | rs1801282 | GG + CG | 26 | 27 | 1.00  | 1.00  |
|  |  | CC | 334 | 373 | 0.83 (0.47-1.46) | 0.77 (0.43-1.38) |
| *ADIPOQ* | rs1501299 | AA | 19 | 38 | 1.00  | 1.00  |
|  |  | AC | 155 | 167 | 1.79 (0.98-3.25) | 1.71 (0.93-3.15) |
|  |  | CC | 186 | 195 | 1.86 (1.03-3.38) | 1.85 (1.01-3.39) |
| *CDKAL1* | rs2206734 | GG | 114 | 138 | 1.00  | 1.00  |
|  |  | AG | 184 | 195 | 1.15 (0.83-1.59) | 1.18 (0.85-1.64) |
|  |  | AA | 62 | 67 | 1.16 (0.75-1.79) | 1.21 (0.78-1.89) |
| *ADRB3* | rs4994 | TT | 228 | 255 | 1.00  | 1.00  |
|  |  | CT | 114 | 131 | 0.92 (0.67-1.25) | 0.88 (0.64-1.21) |
|  |  | CC | 18 | 14 | 1.37 (0.66-2.83) | 1.36 (0.65-2.87) |
| *KCNQ1* | rs2237895 | AA | 153 | 156 | 1.00  | 1.00  |
|  |  | AC | 175 | 193 | 0.95 (0.70-1.29) | 0.92 (0.67-1.26) |
|  |  | CC | 32 | 51 | 0.62 (0.37-1.02) | 0.62 (0.37-1.04) |
| *KCNJ11* | rs5219 | CC | 150 | 159 | 1.00  | 1.00  |
|  |  | CT | 157 | 192 | 0.87(0.64-1.18) | 0.90 (0.66-1.24) |
|  |  | TT | 53 | 49 | 1.14 (0.72-1.79) | 1.19 (0.75-1.90) |
| *TCF7L2* | rs7903146 | CC | 354 | 394 | 1.00  | 1.00  |
|  |  | CT + TT | 6 | 6 | 1.20 (0.38-3.83) | 1.16 (0.36-3.72) |
| 1Adjusted for age, sex, body mass index, and cigarette smoking.  |  |