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Association of the PIK3C2G gene polymorphisms with type 2 DM in a Japanese population

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Abstract

The associations of five SNPs (SNPs1-5: A-5468G, A-3333G, C-1794T, C437T and T9148C) of the class II phosphoinositide 3-kinase γ-subunit (PIK3C2G) gene with type 2 diabetes were examined using a population of the Takahata Study (*n* (M/W): 2930 (1328/1602); age: 63.3 ± 10.2 years), a Japanese community-based study. Quantitative association study of the SNPs with HbA1c levels showed significant association for SNPs 2 and 4 ($p = 0.018$ and 0.004, respectively). A case-control association study of SNP 4 with diabetes by multiple logistic regression analysis showed a significant association of the genotype TT of the SNP with an odds ratio of 2.21 ($p = 0.001$) independently of age, gender and BMI. In the NGT subjects, serum fasting insulin levels in the at-risk genotype group of SNP 4 were significantly lower than those in the others (TT, TC, and CC, 4.9 ± 2.6, 5.4 ± 3.0, and 5.6 ± 3.4 μU/ml, respectively; $p = 0.029$).

Keywords: PI3 kinase; PIK3C2G; Quantitative association study; Serum insulin levels; Community-based study; Haplotype and diplotype analysis

Phosphoinositide 3-kinases (PI3Ks), which are members of a unique and conserved family of intracellular lipid kinases phosphorylating the D-3 position of the inositol ring of phosphoinositides, are known to be involved in a large variety of cellular functions, such as cell metabolism, survival and polarity and vesicular trafficking [1–5]. PI3Ks are grouped into three classes (I–III) on the basis of their structure and substrate preference (Phosphoinositide (PI) for all classes; PI and PI-4-P for classes I and II; PI-4,5-P_2 for class I only) [1–5]. Class I PI3Ks are further divided into two types, class IA and class IB, depending on the receptors to which they couple; class IA PI3Ks are activated by growth factor tyrosine kinases, while class IB PI3Ks are activated by G-protein-coupled receptors [1–5]. Among the various isoforms of PI3Ks, class IA PI3K has been the most closely studied [1–5]. The class IA PI3K-AKT (v-akt murine thymoma viral oncogene homologue) signaling pathway has been determined to have a central role in the regulation downstream of the insulin receptor and IRS adaptor molecules [1–5]. Moreover, the

Abbreviations: PIK3C2G, class II phosphoinositide 3-kinase γ-subunit; DM, diabetes.

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association of several polymorphisms of the class IA PI3K regulatory subunit p85α subunit (PIK3R1) gene with an increased risk of type 2 diabetes (diabetes) has been reported [6,7]. However, the relationship of the other isoforms of PI3Ks with pathophysiologies leading to diabetes has not been thoroughly studied.

Class II PI3Ks, which are characterized by the presence of a C2 domain and a Phox homology domain (PX) at the extreme C terminus and phosphorylate PI and PI-4-P to generate PI-3-P and PI-3,4-P_2, consist of three isoforms, PI3K-C2α, PI3K-C2β, and PI3K-C2γ [1–5]. Although the function of class II PI3Ks has not been thoroughly examined yet, the activations of PI3K-C2α and PI3K-C2β by insulin in cells expressing a large number of insulin receptors and/or in rat skeletal muscle have been reported [8–10]. Therefore, class II PI3Ks, or at least these two isoforms, seemed to play a role in insulin-signaling pathway as class IA PI3K. The function of PI3K-C2γ has not been thoroughly examined. Although PI3K-C2α and PI3K-C2β are ubiquitously expressed, the expression of PI3K-C2γ is restricted to several tissues, such as liver and prostate, and, to a lesser extent, the small intestine, kidney, and pancreas [11–13]. Therefore, PI3K-C2γ may have a different role from that of the other two isoforms.

As a first step to evaluate whether PI3K-C2γ has functions related to the pathophysiology leading to diabetes, we here conducted an association study of the PI3K-C2γ (PIK3C2G) gene polymorphisms with diabetes in a population-based study of the Japanese.

Materials and methods

Subjects. The Takahata Study is a population-based cross-sectional study of Japanese over 35 years old to clarify risk factors, including genetic variances for life-style-related conditions, such as diabetes [14]. In Takahata, an agricultural and suburban area about 300 km north of Tokyo, the population over 35 years of age was 15,819 in 2005. From 2004 to 2005, 3165 residents attended the study. Of them, 2930 subjects (mean age: 63.3 ± 10.2 years; sex ratio (men/women): 1328/1602) were enrolled in this study.

This study was approved by the Ethics Committee of Yamagata University School of Medicine, and informed consent to participate was obtained from all the participants. Along with the genetic analysis, the following traits were analyzed: height, body weight, body mass index (BMI), fasting plasma glucose levels, HbA1c, fasting serum insulin levels, an insulin resistance index assessed by homeostasis model assessment (HOMA-IR) and secretion (HOMA-β), systolic blood pressure, diastolic blood pressure, and serum levels of uric acid, urea nitrogen, creatinin, adiponectin, triglyceride, and total, HDL, LDL, and RLP cholesterol. Glucose tolerance was classified according to the 1998 WHO criteria [15]. Those on medication for DM were diagnosed as diabetic. The clinical characteristics of the study population are shown in Table 1. The number of subjects with normal glucose tolerance (NGT), impaired fasting glucose (IFG) and diabetes was 2549, 153 and 228, respectively. Hypertension was defined as present if the subject had a systolic blood pressure of ⩾140 mmHg, a diastolic pressure of ⩾90 mmHg, or was undergoing medical treatment for hypertension. Hyperlipidemia was defined as present if the subject had a serum total cholesterol level of ⩾240 mg/dl, a

Table 1
Base characteristics and PIK3C2G genotype differences in clinical characteristics

Trait	Total	Genotype (C437T)			
		CC	CT	TT	*p*-Value
Number (gender: M/F)	2930 (1328/1602)	1641 (727/914)	1111 (516/595)	178 (85/93)	0.432
Age (year)	63.3 ± 10.2	63.0 ± 10.3	63.0 ± 10.2	62.8 ± 10.0	0.974
Height (cm)	156.6 ± 9.0	156.5 ± 8.9	156.8 ± 9.1	156.9 ± 9.0	0.542
Body weight (kg)	57.8 ± 10.2	57.7 ± 10.1	58.0 ± 10.3	57.9 ± 11.1	0.649
Body mass index (kg/m^2)	23.5 ± 3.2	23.5 ± 3.2	23.5 ± 3.2	23.4 ± 3.3	0.947
Fasting plasma glucose (mg/dl)[#]	94.3 ± 16.7	94.2 ± 16.5	94.2 ± 16.3	96.7 ± 20.6	0.186
HbA1c (%)	5.25 ± 0.68	5.24 ± 0.67	5.23 ± 0.63	5.41 ± 1.01	0.004**
Fasting serum insulin (μU/ml)[#]	5.9 ± 7.2	5.9 ± 4.3	5.9 ± 5.9	6.8 ± 22.2	0.258
HOMA-IR[##]	1.34 ± 1.02	1.37 ± 1.01	1.33 ± 1.06	1.19 ± 0.77	0.106
HOMA-β[##]	76.9 ± 138.7	80.3 ± 180.8	73.4 ± 43.7	66.3 ± 42.5	0.295
Systolic blood pressure (mmHg)	134.1 ± 15.9	134.4 ± 16.0	133.6 ± 15.7	134.1 ± 15.8	0.424
Diastolic blood pressure (mmHg)	79.2 ± 10.1	79.3 ± 10.1	79.3 ± 10.2	78.5 ± 9.7	0.611
Total cholesterol (mg/dl)	200.7 ± 31.7	201.1 ± 31.9	200.5 ± 31.9	199.2 ± 28.5	0.719
Triglyceride (mg/dl)	106.5 ± 63.5	106.2 ± 64.8	106.2 ± 60.0	111.5 ± 72.0	0.556
HDL cholesterol (mg/dl)	59.0 ± 14.5	59.2 ± 14.6	58.8 ± 14.2	58.8 ± 15.1	0.830
LDL cholesterol (mg/dl)	124.2 ± 29.6	124.5 ± 30.0	124.4 ± 29.4	120.4 ± 30.0	0.208
RLP cholesterol (mg/dl)	6.74 ± 3.91	6.74 ± 3.89	6.65 ± 3.51	7.28 ± 5.89	0.138
Serum uric acid (mg/dl)	5.07 ± 1.35	5.06 ± 1.36	5.07 ± 1.34	5.08 ± 1.36	0.961
Serum urea nitrogen (mg/dl)	16.3 ± 4.6	16.4 ± 4.5	16.2 ± 4.7	16.4 ± 4.4	0.639
Serum creatinin (mg/dl)	0.68 ± 0.22	0.68 ± 0.23	0.68 ± 0.22	0.66 ± 0.17	0.303
Adiponectin (μg/dl)	10.1 ± 5.6	10.2 ± 5.7	10.0 ± 5.5	10.2 ± 5.7	0.750
Hypertension: *n* (%)	1619 (55.3)	903 (55.0)	619 (55.7)	97(54.5)	0.918
Hyperlipidemia: *n* (%)	942 (32.2)	506 (30.8)	370 (33.3)	66 (37.1)	0.138
Diabetes/IFG: *n* (%)	228 (7.8)/153 (5.2)	118 (7.2)/89 (5.4)	85 (7.7)/53 (4.8)	25 (14.0)/11 (6.2)	0.019*
Drinking alcohol: *n* (%)	1215 (41.5)	669 (40.8)	463 (41.7)	83 (46.6)	0.316
Smoking (never/past/current)	1983/407/540	1133/227/281	732/156/223	118/24/36	0.339

$p < 0.05$ and 0.01 are indicated by * and **, respectively. [#]Data were not obtained from some of the subjects (*n* (CC/CT/TT): 1545/1048/161). [##]The subjects whose fasting plasma glucose levels were more than 140 mg/dl were excluded (*n* (CC/CT/TT)):1518/1025/155).