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ORIGINAL ARTICLE

Association between polymorphisms in *SLC30A8*, *HHEX*, *CDKN2A/B*, *IGF2BP2*, *FTO*, *WFS1*, *CDKAL1*, *KCNQ1* and type 2 diabetes in the Korean population

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Abstract According to recent genome-wide association studies, a number of single nucleotide polymorphisms (SNPs) are reported to be associated with type 2 diabetes mellitus (T2DM). The aim of the present study was to investigate the association among the polymorphisms of *SLC30A8, HHEX*, *CDKN2A/B, IGF2BP2, FTO*, *WFS1*, *CDKAL1* and *KCNQ1* and the risk of T2DM in the Korean population. This study was based on a multicenter case-control study, including 908 patients with T2DM and 502 non-diabetic controls. We genotyped rs13266634, rs1111875, rs10811661, rs4402960, rs8050136, rs734312, rs7754840 and rs2237892 and measured the body weight, body mass index and fasting plasma glucose in all patients and controls. The strongest association was found in a variant of *CDKAL1* [rs7754840, odds ratio (OR) = 1.77, 95% CI = 1.50–2.10, $p = 5.0 \times 10^{-11}$]. The G allele of rs1111875 (OR = 1.43, 95% CI = 1.18–1.72, $p = 1.8 \times 10^{-4}$) in *HHEX*), the T allele of rs10811661 (OR = 1.47, 95% CI = 1.23–1.75, $p = 2.1 \times 10^{-5}$) in *CDKN2A/B*) and the C allele of rs2237892 (OR = 1.31, 95% CI = 1.10–1.56, $p = 0.003$) in *KCNQ1* showed significant associations with T2DM. Rs13266634 (OR = 1.19, 95% CI = 1.00–1.42, $p = 0.045$) in *SLC30A8* showed a nominal association with the risk of T2DM, whereas SNPs in *IGF2BP2, FTO* and *WFS1* were not associated. In conclusion, we have shown that SNPs in *HHEX*, *CDKN2A/B*, *CDKAL1*, *KCNQ1* and *SLC30A8* confer a risk of T2DM in the Korean population.

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Abbreviations

SNP	Single nucleotide polymorphisms
T2DM	Type 2 diabetes mellitus
OR	Odds ratio
CI	Confidence interval
BMI	Body mass index
FPG	Fasting plasma glucose

Introduction

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterized by hyperglycemia, variable degrees of insulin resistance, impaired insulin secretion and increased hepatic glucose production. The total global number of people with diabetes was estimated to be over 189 million in the year 2003 (Zimmet et al. 2003) and is expected to rise more rapidly in the future as obesity increases, the population becomes older and the physical activity levels of most people decrease.

In addition to the environmental factors mentioned above, genetic components are obviously associated with the development of T2DM. One of the earliest T2DM susceptibility genes published was Calpain 10 (*CAPN10*) (Hanis et al. 1996), followed by peroxisome proliferator-activated receptor gamma (*PPARG*) (Altshuler et al. 2000), potassium inwardly rectifying channel, subfamily J, member 11 (*KCNJ11*) (Gloyn et al. 2003) and transcription factor 7-like 2 (*TCF7L2*) (Grant et al. 2006), polymorphisms of which were discovered to be strongly associated with T2DM in 2006. Since 2007, new genetic loci have been identified as T2DM susceptibility genes by genome-wide association scanning, including: loci near hematopoietically expressed homeobox (*HHEX*)-insulin-degrading enzyme (*IDE*), cyclin-dependent kinase 5 (CDK5) regulatory subunit-associated protein 1-like 1 (*CDKAL1*), fat mass and obesity associated (*FTO*), cyclin-dependent kinase inhibitor 2A/B (*CDKN2A/B*), zinc transporter-8 (ZnT-8) solute carrier family 30 member 8 gene (*SLC30A8*), insulin-like growth factor 2 mRNA-binding protein 2 (*IGF2BP2*) and *KCNQ1* (Saxena et al. 2007; Scott et al. 2007; Sladek et al. 2007; Steinthorsdottir et al. 2007; Zeggini et al. 2007; Yasuda et al. 2008).

However, it has recently been reported that there are significant differences in the contribution of known single nucleotide polymorphisms (SNPs) in susceptibility genes among various ethnic populations. Therefore, replication studies in other populations are important. We investigated the association between known SNPs in several T2DM candidate genes and the prevalence of T2DM in the Korean population.

Research design and methods

Subjects and measurements

The studied population included 502 non-diabetic control subjects and 908 unrelated Korean type 2 diabetic patients recruited from the outpatient clinics of Yonsei Medical University Hospital and Inha Medical University Hospital. Diabetes was diagnosed according to the criteria of the American Diabetes Association. Patients were excluded if they were positive for the glutamic acid decarboxylase antibody. The non-diabetic control subjects comprised the normoglycemic population from health check-up subjects with no history of severe metabolic or infectious disease and from regular follow-up patients from the outpatient clinics of the Diabetes Center of Yonsei University Severance Hospital and the Inha Medical University Hospital. Blood samples were collected after an overnight fast, and the FPG level was determined by an enzymatic colorimetric assay. The HbA1c values were determined by high-performance liquid chromatography (Variant II, GREEN-CROSS, Seoul, Korea). The protocol of this study was approved by the ethics committee of the Yonsei University College of Medicine. All patients and controls received adequate information about this study and gave written informed consent.

DNA extraction and genotyping

Genomic DNA was isolated from peripheral blood lymphocytes. We selected *SLC30A8* rs13266634, *HHEX* rs1111875, *CDKN2A/B* rs10811661, *IGF2BP2* rs4402960, *FTO* rs8050136, *WFS1* rs734312, *CDKAL1* rs7754840 and *KCNQ1* rs2237892 because their minor allele frequencies (MAF) are relatively high (>10%) and are reported to be associated with T2DM in Asian populations (Kang et al. 2008a, b). Because rs7754840 and rs10946398 in *CDKAL1* were in complete linkage ($D' = 1$, $r^2 = 1$) in our 200 samples and in the study by Palmer et al. (2008), we only genotyped rs7754840. As regarding *WFS1*, we genotyped rs734312 among four SNPs (rs734312, rs752854, rs6446482 and rs10010131) according to our pilot data of 88 samples that MAF of rs752854, rs6446482 and rs10010131 were 0, 1.1 and 0%, respectively. Genotyping was performed according to the processes as previously described (Kang et al. 2008a, b). TaqMan PCR Assay ID was C2684958_10 for rs13266634 in *SLC30A8*, C11214581_10 for rs1111875 in *HHEX*, C31288917_10

for rs10811661 in *CDKN2A/B*, C2165199_10 for rs4402960 in *IGF2BP2,* C2031259_10 for rs8050136 in *FTO*, C2401729_1 for rs734312 in *WFS1* and C29246232_10 for rs7754840 in *CDKAL1*. *KCNQ1* rs2237892 genotype was assayed by single base primer extension assay using an ABI PRISM SNaPShot Multiplex kit (ABI, Foster City, CA), according to manufacturer's instructions.

Forty-eight (3.4%) duplicate samples and negative controls were included to ensure the accuracy of genotyping, and 100% of the duplicates replicated the original genotype. The rates of successful genotyping were 100% (rs13266634), 96.2% (rs1111875 and rs10811661), 96.6% (rs4402960), 99.2% (rs8050136), 99.7% (rs734312), 99.1% (rs7754840) and 98.8% (rs2237892), respectively.

Statistical analyses

The genotype frequencies were tested for Hardy–Weinberg equilibrium using the χ^2 test. All continuous variables were expressed as the mean ± standard deviation (SD). Student's *t* test was used to compare the continuous variables between the T2DM and non-diabetic control groups. Pearson's χ^2 test was used to evaluate the difference in the prevalence of T2DM among genotypes. One-way ANOVA was used to compare continuous variables among the three genotypes. For these calculations, patients with the non-risk allele were denoted as 0, heterozygotes were denoted as 1, and patients homozygous for the risk allele were denoted as 2. In order to control for age, sex and BMI effects, multivariable logistic regression tests were used, and odds ratio (OR) and 95% confidence intervals (CI) were calculated. We analyzed the data using two-sided *p* values, and a *p* value less than 0.05 was considered statistically significant. Statistical analyses were performed using SPSS for Windows software (version 12.0; SPSS, Chicago, IL). Power calculations were performed using PASS software version 2005 (NCSS statistical Software, Kaysville, UT).

Results

Genotyping of eight representative SNPs from T2DM susceptibility genes were replicated in 502 non-diabetic control subjects and 908 unrelated type 2 diabetic patients from the Korean population. The baseline clinical and biochemical characteristics of the subjects are shown in Table 1. The mean age, body mass index (BMI), weight and fasting plasma glucose (FPG) level were 55.0 ± 9.4 years, 22.1 ± 3.0 kg/m^2, 58.7 ± 9.4 kg and 5.1 ± 1.0 mmol/l, respectively. A slightly higher proportion of females (51.6%) was observed in the case group than in the control groups (46.4%), which may be due to a participation bias. Diabetic patients were older than non-diabetic control subjects (58.2 ± 11.1 vs. 55.0 ± 9.4, $p < 0.001$). The mean body weight and BMI between the two groups were significantly different (63.6 ± 10.8 vs. 58.7 ± 9.4 kg, $p < 0.001$; 24.3 ± 3.2 vs. 22.1 ± 3.0 kg/m^2, $p < 0.001$, respectively). The FPG level was also significantly higher in the diabetic group subjects compared to normal control subjects (7.5 ± 2.2 vs. 5.1 ± 1.0, $p < 0.001$).

Table 1 Clinical characteristics of the study population

	Control	T2DM	*p* value
N (% female)	502 (46.4%)	908 (51.6%)	0.063*
Age at diagnosis (years)	NA	47.8 ± 10.8	
Age at examination (years)	55.0 ± 9.4	58.2 ± 11.1	<0.001
BMI (kg/m^2)	22.1 ± 3.0	24.3 ± 3.2	<0.001
Weight (kg)	58.7 ± 9.4	63.6 ± 10.8	<0.001
FPG (mmol/l)	5.1 ± 1.0	7.5 ± 2.2	<0.001

Data presented as means ± SD or *N* (%) unless otherwise indicated. *p* values were calculated from *t* tests

NA not available, *BMI* body mass index

**p* values assessed by Pearson's χ^2 test

The genotype and allele frequencies of T2DM susceptibility gene SNPs in type 2 diabetic patients and control subjects are shown in Table 2. Genotype distributions were in agreement with Hardy-Weinberg equilibrium. Among eight SNPs, rs1111875 in *HHEX*, rs10811661 in *CDKN2A/B*, rs7754840 in *CDKAL1* and rs2237892 in *KCNQ1* locus were significantly associated with T2DM. The observed associations between T2DM and two SNPs — rs1111875 and rs7754840 — were strengthened after adjusting for age, sex and BMI using multivariable logistic regression analysis. The strongest association was found in the variant in *CDKAL1* rs7754840 (OR = 1.77, adjusted $p = 4.6 \times 10^{-10}$). However, rs13266634 in the *SLC30A8* gene locus showed nominal association with T2DM (OR = 1.19, adjusted $p = 0.045$), and no significant associations with T2DM were observed in *IGF2BP2* rs4402960, *FTO* rs8050136 and *WFS1* rs734312 from our study population (adjusted $p = 0.123$, 0.347 and 0.362, respectively). The rs13266634, rs10811661 and rs2237892 risk alleles were major alleles, while the other risk alleles were minor alleles in our population, consistent with previous reports in European populations (Scott et al. 2007; Saxena et al. 2007; Zeggini et al. 2007). Interestingly, the G allele of rs1111875, which was reported to be a major allele in Caucasian ethnic groups, was revealed as a minor allele in our study; this is supported by similar results from Japanese populations (Furukawa et al. 2008; Horikoshi et al. 2007; Omori et al. 2008).

For each SNP proven to be a possible T2DM-susceptible variant according to our study, we further analyzed the

Table 2 Association analysis of candidate SNPs for T2DM in the Korean population

SNP	A/a	Control		T2DM		Genotype-specific p value[b]	Allele-specific		Allele-specific (adjusted)[c]		p for HWET
		AA/Aa/aa	MAF	AA/Aa/aa	MAF		p value	OR (95% CI)	p value	OR (95% CI)	
rs13266634	C[a]/T	156/248/98	0.442	324/459/125	0.390	0.006	0.007	1.24 (1.06–1.45)	0.045	1.19 (1.00–1.42)	0.975
SLC30A8											
rs1111875	A/G[a]	239/223/39	0.300	341/414/101	0.360	0.001	0.002	1.31 (1.11–1.55)	1.8×10^{-4}	1.43 (1.18–1.72)	0.187
HHEX											
rs10811661	T[a]/C	144/260/97	0.442	341/410/104	0.361	1.6×10^{-6}	2.4×10^{-6}	1.46 (1.25–1.72)	2.1×10^{-5}	1.47 (1.23–1.75)	0.291
CDKN2A/B											
rs4402960	G/T[a]	240/218/41	0.301	385/384/84	0.324	0.210	0.210	1.11 (0.94–1.32)	0.123	1.16 (0.96–1.39)	0.384
IGF2BP2											
rs8050136	C/A[a]	373/116/12	0.140	672/200/14	0.129	0.412	0.410	0.91 (0.73–1.14)	0.347	0.89 (0.70–1.14)	0.409
FTO											
rs734312	A/G[a]	358/136/8	0.151	667/212/13	0.133	0.181	0.189	0.86 (0.69–1.08)	0.362	0.89 (0.70–1.14)	0.223
WFS1											
rs7754840 *CDKAL1*	G/C[a]	170/260/70	0.400	221/402/262	0.523	1.0×10^{-9}	4.6×10^{-10}	1.65 (1.41–1.93)	5.0×10^{-11}	1.77 (1.50–2.10)	0.062
rs2237892	C[a]/T	182/239/75	0.392	389/377/99	0.332	0.002	0.002	1.30 (1.10–1.52)	0.003	1.31 (1.10–1.56)	0.560
KCNQ1											

Data are shown as *N* (%)

A/a major allele/minor allele, *HWET* Hardy–Weinberg equilibrium test of control subjects

[a] Risk allele

[b] *P* values were calculated by comparing three genotype groups using Pearson's χ^2 test for linear-by-linear association

[c] Adjusted for age, sex and BMI

effect of genotypes under three different genetic models (Table 3). The C/C and C/T genotypes of *SLC30A8* conferred a significantly increased risk for T2DM compared to the T/T genotype in the additive or dominant model. The G allele of *HHEX* rs1111875, the T allele of *CDKN2A/B* rs10811661 and the C allele of *CDKAL1* rs7754840 all were associated with an increased prevalence of T2DM in all three genetic models. Only individuals with the CC genotype of rs2237892 in the recessive model had a higher risk of T2DM. No association was observed in any genetic models for rs4402960, rs8050136 and rs734312. There was no significant association between the genotypes of eight SNPs and clinical characteristics (age, sex and BMI) in the type 2 diabetic patients (data not shown).

Discussion

The identification of a new gene for polygenic T2DM was recently achieved by genome-wide SNP assays. Among several SNPs associated with susceptibility to T2DM, polymorphisms in *SLC30A8, HHEX, CDKN2A/B*, *IGF2BP2*, *FTO*, *WFS1*, *CDKAL1* and *KCNQ1* were first reported by several studies performed in European and Asian populations (Scott et al. 2007; Sladek et al. 2007; Saxena et al. 2007; Zeggini et al. 2007; Sandhu et al. 2007; Yasuda et al. 2008). These genetic variants have been repetitively confirmed by multiple studies in various populations (Horikoshi et al. 2007; Steinthorsdottir et al. 2007; Omori et al. 2008; Ng et al. 2008). Nevertheless, the effects of genetic variants on the risk of T2DM are somewhat inconsistent among different ethnic groups. For example, Furukawa et al. (2008) reported a nominal association between rs13266634, a nonsynonymous SNP in *SLC30A8*, and T2DM in a Japanese population, while Horikoshi et al. (2007) reported that there was no significant association in another Japanese population.

In this case-control study, we demonstrated the association between the polymorphisms of the *SLC30A8, HHEX*, *CDKN2A/B*, *CDKAL1* and *KCNQ1* genes and the prevalence of T2DM in Korean subjects. According to our results, the overall risk allele frequencies of those SNPs were significantly different between the Korean and other non-Asian ethnic groups. The frequency of risk allele C in

Table 3 Effects of susceptible gene genotypes on the risk of T2DM under different genetic models

		Additive model		Dominant model		Recessive model	
		OR (95% CI)	*p* value	OR (95% CI)	*p* value	OR (95% CI)	*p* value
rs13266634	T/T						
SLC30A8	C/T	1.45 (1.07–1.97)	0.017	1.52 (1.14–2.03)	0.005	1.23 (0.98–1.55)	0.080
	C/C	1.63 (1.18–2.26)	0.003				
rs1111875	A/A						
HHEX	A/G	1.30 (1.03–1.64)	0.026	1.38 (1.10–1.72)	0.005	1.59 (1.08–2.33)	0.019
	G/G	1.82 (1.21–2.72)	0.004				
rs10811661	C/C						
CDKN2A/B	C/T	1.47 (1.07–2.02)	0.017	1.73 (1.28–2.35)	3.2×10^{-4}	1.65 (1.30–2.09)	3.6×10^{-5}
	T/T	2.21 (1.58–3.10)	3.5×10^{-6}				
rs4402960	G/G						
IGF2BP2	G/T	1.10 (0.87–1.38)	0.443	1.13 (0.90–1.41)	0.309	1.22 (0.83–1.80)	0.332
	T/T	1.28 (0.85–1.92)	0.266				
rs8050136	C/C						
FTO	C/A	0.957 (0.74–1.24)	0.742	0.928 (0.72–1.20)	0.562	0.654 (0.30–1.43)	0.282
	A/A	0.648 (0.30–1.42)	0.272				
rs734312	A/A						
WFS1	A/G	0.837 (0.65–1.08)	0.163	0.839 (0.66–1.07)	0.160	0.913 (0.38–2.22)	0.841
	G/G	0.872 (0.36–2.12)	0.763				
rs7754840 *CDKAL1*	G/G						
	G/C	1.19 (0.92–1.53)	0.180	1.55 (1.22–1.97)	3.3×10^{-4}	2.58 (1.93–3.46)	6.4×10^{-11}
	C/C	2.88 (2.07–4.01)	1.9×10^{-10}				
rs2237892	T/T						
KCNQ1	T/C	1.20 (0.85–1.68)	0.306	1.38 (0.998–1.90)	0.051	1.41 (1.12–1.77)	0.003
	C/C	1.62 (1.14–2.29)	0.006				

rs13266634 from our study (55.8%) was lower than those reported in European or African populations (69.9–97.1%) (Sladek et al. 2007; Steinthorsdottir et al. 2007). There were also differences in the frequencies of risk alleles in rs1111875, rs10811661, rs8050136 and rs734312. For rs1111875, the risk allele G was a minor allele in Asian subjects, including our group, while the allele G was revealed as a major allele in European populations (Saxena et al. 2007; Scott et al. 2007; Sladek et al. 2007; Palmer et al. 2008); for rs10811661, rs8050136 and rs734312, the Korean population showed much lower MAF compared to the non-Asian groups. These significant differences in risk allele frequencies across ethnic groups indicate that the genetic variations of T2DM susceptibility genes are diversely distributed among different populations.

In our study, each SNP in the *HHEX*, *CDKN2A/B*, *CDKAL1* and *KCNQ1* genes showed a significant association with T2DM. The adjusted allele-specific OR value of rs1111875 (1.43) was similar to that of Japanese groups (1.30–1.42) (Furukawa et al. 2008; Horikoshi et al. 2007; Omori et al. 2008), but higher than that reported from white populations (1.10–1.15) (Saxena et al. 2007; Scott et al. 2007; Sladek et al. 2007). The *HHEX* gene product is known to act as both a transcription activator and repressor required for the development of the pancreas, liver and blood vessels and is also a target of the Wnt/β-catenin signaling pathway (McLin et al. 2007; Foley and Mercola 2005). Since SNP rs1111875 is located near the outside of an *HHEX* exon, it does not change the amino acid sequence, indicating that further study of the biological function of this SNP is necessary.

Furthermore, we observed considerably higher ORs of rs10811661 in *CDKN2A/B* locus (1.47) and rs7754840 in *CDKAL1* locus (1.77) than those found in other Asian or European populations (1.16–1.37) (Sladek et al. 2007; Saxena et al. 2007; Scott et al. 2007; Horikoshi et al. 2007; Ng et al. 2008). *CDKN2A/B* is a tumor suppressor gene that plays an important role in tumorigenesis and aging (Kim and Sharpless 2006). In addition to its function in cell proliferation and apoptosis, *CDKN2A/B* has recently been reported to be expressed in islets as well as vascular endothelial cells and is affected by hyperglycemia and oxidative stress (Chen et al. 2007; Scott et al. 2007). The function of *CDKAL1* protein is elusive; however, there is a similarity between *CDKAL1* and CDK5 regulatory subunit-associated protein 1 (CDK5RAP1), which inhibits CDK5 activity. Considering the findings that inhibition of CDK5 prevented the decrease of insulin gene expression by restoring PDX-1, CDKAL1 may play an important role in CDK5-mediated regulation of beta cell function (Wei et al. 2005; Ubeda et al. 2006).

As regarding *KCNQ1*, which was recently discovered by the Japanese group (Yasuda et al. 2008), we showed a lower value of OR of 1.31 (95% CI = 1.10–1.56) for rs2237892 than those reported in East Asian populations. KCNQ1 protein is a subunit of the voltage-gated K+ channel (KvLQT1) that is expressed in the pancreas as well as cardiac muscles. Modulation of membrane potentials in beta cells by KvLQT1 might be a possible mechanism to affect insulin-secretory functions.

We confirmed that rs13266634 in *SLC30A8* has nominal association with the risk of T2DM (adjusted $p = 0.045$), while there were no significant relationships among rs4402960 (*IGF2BP2*), rs8050136 (*FTO*), rs734312 (*WFS1*) and a predisposition for T2DM (adjusted $p = 0.123$, 0.347 and 0.362, respectively). Several reports have demonstrated that not only the rs1111875 (Pascoe et al. 2007) and rs10811661 (Horikoshi et al. 2007) SNPs, but also the risk allele of *SLC30A8*, rs13266634 are associated with reduced insulin-secretory function (Staiger et al. 2007; Steinthorsdottir et al. 2007; Boesgaard et al. 2008; Cauchi et al. 2008; Kang et al. 2008b). Since early beta cell secretory defects are more important predisposing factors to T2DM than insulin resistance in various Asian populations (Fukushima et al. 2004; Yoon et al. 2003), dysfunction of genes related to insulin secretion may play an essential role in the development of T2DM in Korean adults, supported by our findings that genetic variants in the *SLC30A8* or *CDKN2A/B*, not obesity genes such as *FTO*, showed a statistical association with T2DM. The *SLC30A8* gene encodes ZnT-8, a novel member of the cation diffusion facilitator family, exclusively expressed in pancreatic beta cells (Chimienti et al. 2006). ZnT-8 is thought to be a key protein for insulin secretion by regulating the homeostasis of zinc, which is known as an essential metal ion for insulin storage and secretion into intracellular vesicles (Chausmer 1998). Because the rs13266634 SNP causes an amino acid change (R325 W) in the intracellular C-terminus of the ZnT-8 protein, this single nucleotide substitution might act as a gain-of-function mutation that increases protein translation efficiency or modifies the posttranslational structure, thereby enhancing the beta cell secretory functions.

There were some limitations in this study. First, we did not analyze the association between the candidate SNPs and indices of beta cell secretory functions or insulin resistance due to a lack of data. Second, not all proven T2DM susceptibility genes were examined because of the low frequency of risk alleles (data not shown) in our population. For example, *TCF7L2*, one of the most promising T2DM susceptibility genes in other studies, showed an MAF of only 5.4% in our previous study (Kang et al. 2008a). The estimated powers of our study were 40.2, 76.1, 60.7, 35.7, 48.5, 24.7, 35.9 and 98.6% for rs13266634 (*SLC30A8*), rs1111875 (*HHEX*), rs10811661 (*CDKN2A/B*), rs4402960 (*IGF2BP2*), rs8050136 (*FTO*), rs734312

(*WFS1*), rs7754840 (*CDKAL1*) and rs2237892 (*KCNQ1*), respectively, based on the reference ORs and allele frequencies from an Asian population (for rs1111875 and rs2237892 only) (Omori et al. 2008; Yasuda et al. 2008) and European populations (for other SNPs) (Frayling 2007). Much larger numbers of subjects are required to replicate previous studies with high power.

In conclusion, we have confirmed that there are significant associations between SNPs within the *HHEX, CDKN2A/B, CDKAL1* and *KCNQ1* genes and T2DM in the Korean population. To further confirm this association, additional studies are needed to elucidate the functional mechanism of these SNPs and to analyze the association between these polymorphisms and T2DM in other populations.

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