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Genome-Wide Association Study Identifies Two Novel Loci with Sex-Specific Effects for Type 2 Diabetes Mellitus and Glycemic Traits in a Korean Population

Min Jin Go, Joo-Yeon Hwang, Tae-Joon Park, Young Jin Kim, Ji Hee Oh, Yeon-Jung Kim, Bok-Ghee Han, Bong-Jo Kim

Division of Structural and Functional Genomics, Center for Genome Science, Korea National Institute of Health, Cheongwon, Korea

Background: Until recently, genome-wide association study (GWAS)-based findings have provided a substantial genetic contribution to type 2 diabetes mellitus (T2DM) or related glycemic traits. However, identification of allelic heterogeneity and population-specific genetic variants under consideration of potential confounding factors will be very valuable for clinical applicability. To identify novel susceptibility loci for T2DM and glycemic traits, we performed a two-stage genetic association study in a Korean population.

Methods: We performed a logistic analysis for T2DM, and the first discovery GWAS was analyzed for 1,042 cases and 2,943 controls recruited from a population-based cohort (KARE, $n=8,842$). The second stage, de novo replication analysis, was performed in 1,216 cases and 1,352 controls selected from an independent population-based cohort (Health 2, $n=8,500$). A multiple linear regression analysis for glycemic traits was further performed in a total of 14,232 nondiabetic individuals consisting of 7,696 GWAS and 6,536 replication study participants. A meta-analysis was performed on the combined results using effect size and standard errors estimated for stage 1 and 2, respectively.

Results: A combined meta-analysis for T2DM identified two new (rs11065756 and rs2074356) loci reaching genome-wide significance in CCDC63 and C12orf51 on the 12q24 region. In addition, these variants were significantly associated with fasting plasma glucose and homeostasis model assessment of β-cell function. Interestingly, two independent single nucleotide polymorphisms were associated with sex-specific stratification in this study.

Conclusion: Our study showed a strong association between T2DM and glycemic traits. We further observed that two novel loci with multiple diverse effects were highly specific to males. Taken together, these findings may provide additional insights into the clinical assessment or subclassification of disease risk in a Korean population.

Keywords: Genome-wide association study; Glycemic trait; Sex-specific; Type 2 diabetes

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a major public health problem due to its rapidly rising incidence and prevalence worldwide [1]. T2DM, which is characterized by insulin resistance and hyperglycemia, is known to be associated with a marked increase in the risk for cardiovascular and metabolic diseases, such as obesity, hypertension, and dyslipidemia [2,3]. T2DM-related quantitative traits, such as fasting plasma glucose (FPG), fasting plasma insulin (FPI), homeostasis model assessment of β-cell function (HOMA-B), and homeostasis model assessment of insulin resistance (HOMA-IR), are diagnostic/prognostic indices [4].

The etiology of T2DM is affected by a multi-factorial interplay between genetic and environmental factors. Recent studies have demonstrated that genetic factors play an important role

Corresponding author: Bong-Jo Kim
Division of Structural and Functional Genomics, Center for Genome Science, National Institute of Health, Korea Centers for Disease Control and Prevention, 187 Osongsaengmyeong2-ro, Yeonjae-ri, Osong-eup, Cheongwon 363-951, Korea
E-mail: kbj6181@cdc.go.kr
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in fasting glucose variation, β-cell function, and insulin sensitivity as well as T2DM [5-8]. Genome-wide association study (GWAS)-based findings have provided compelling evidence of T2DM loci, which show an association with glycemic traits as an independent factor [9-12].

Although over 75 loci for T2DM have been intensively identified through genome-wide meta-analyses of multi-ancestry [13-16], progress towards understanding the genetic basis for allelic heterogeneity or population-specific genetic effects has not been fully explored in East-Asian populations [17-19]. To gain insight into the genetic heterogeneity of T2DM, we identified ethnic-specific novel variants influencing T2DM and extended their association with glycemic traits in a Korean population.

METHODS

Study subjects

Stage 1 subjects for the GWA screen were recruited from the Korea Association Resource (KARE) [20]. In this study, 1,042 subjects were included as T2DM cases according to the following criteria: (1) treatment of T2DM; (2) FPG ≥7 mmol/L or plasma glucose 2-hour after ingestion of 75 g oral glucose ≥11.1 mmol/L; and (3) age of disease onset ≥40 years. The inclusion criteria of nondiabetic control subjects (n=2,943) were as follows: (1) no history of diabetes; and (2) FPG <5.6 mmol/L and plasma glucose 2-hour after ingestion of 75 g oral glucose <7.8 mmol/L at both baseline and follow-up studies. For GWA analysis of T2DM related quantitative traits (such as FPG, FPI, HOMA-B, and HOMA-IR values), 7,696 nondiabetic subjects were selected from KARE study participants.

Stage 2 subjects for the replication study were selected from another population-based cohort, Health2 cohort, which consisted of a total of 8,500 participants aged 40 to 69 years from five regional cities in Korea [20]. The stage 2 criteria for grouping T2DM cases (n=1,216) and nondiabetic controls (n=1,352) were the same as those for stage 1, except stage 2 control subjects were >60 years old and had no first-degree relatives with diabetes. For association analysis between T2DM related quantitative traits and single nucleotide polymorphisms (SNPs) that passed the stage 1 threshold, 6,536 nondiabetic subjects were selected from Health2 study participants.

All studies were approved by the ethics review committees of the respective institutes and all participants provided their written informed consent.

Genotyping

KARE study subjects were genotyped using the Affymetrix Genome-Wide Human SNP array 5.0 (Affymetrix Inc., Santa Clara, CA, USA) [20]. Only unrelated samples with a missing genotype call rate below 4% and a heterozygosity of less than 30% were included for subsequent GWA analyses for T2DM and its related traits. SNPs with a high missing gene call rate (>5%), low minor allele frequency (MAF; <0.01) and significant deviation from Hardy-Weinberg equilibrium ($P<1\times10^{-6}$) were eliminated before association analyses. Detailed criteria for sample and SNP filtering from KARE genome-wide scan are available by Cho et al. [20].

Among the 21 SNPs taken forward to the stage 2 replication study (Appendix 1), four SNPs (rs4376068, rs11086668, rs6439472, and rs2074356) were genotyped by an allelic discrimination assay using the TaqMan reaction (Applied Biosystems, Foster City, CA, USA), while 17 SNPs were genotyped by the GoldenGate assay in a set of 384 multiplexed SNPs (Illumina Inc., San Diego, CA, USA) from approximately 7,861 Health2 study subjects. For three SNPs (rs360481, rs6439472, and rs4777379), we were not able to design a functional assay on either platform. Duplicate genotyping for approximately 1% to 2.5% of samples was performed as a quality control. All 21 genotyped SNPs satisfied a concordance rate in duplicates of over 99% and a genotype success rate over 98%.

SNP imputation

In each GWAS data, imputation analysis was performed using IMPUTE against all of the HapMap Asian (Japanese in Tokyo, Japan+Han Chinese in Beijing, China) population (release 22/NCBI build 36 and dbSNP build 126 for total 4,573,409 SNPs [21]. Of these SNPs, we removed SNPs with a posterior probability score <0.90, low genotype information content (info <0.5), HWE ($P<1\times10^{-7}$), MAF<0.01, and SNP missing rate >0.1.

Association analyses

An association analysis was performed using PLINK (http://pngu.mgh.harvard.edu/~purcell/plink/) and SAS programs version 9.1 (SAS institute Inc., Cary, NC, USA). Associations between SNPs and T2DM were tested using logistic regression analysis with an additive model (1-degree of freedom) after adjusting for age, sex, BMI, and recruitment area. T2DM related quantitative traits, such as FPG, FPI, HOMA-B, and HOMA-IR, were tested for association using the linear regression analysis with an additive model (1-degree of freedom) after adjust-

ing for age, sex, BMI, and recruitment area. HOMA values were estimated by the HOMA Calculator v2.2.2 program (http://www.dtu.ox.ac.uk/index.php?maindoc=/homa/index.php) using FPG and insulin concentrations. Among the T2DM related traits, FPI, HOMA-B, and HOMA-IR showing a skewed distribution of measurements were transformed by the natural log before the association analysis. Stage 1 and 2 association results were combined using an inverse-variance meta-analysis method assuming fixed effects with Cochran's Q test, which was used to assess between-study heterogeneity [22]. To detect the significant evidence of the sex-specific association of SNPs with T2DM and its related traits, the interaction between SNPs and sex was tested by a likelihood ratio test for a linear regression model.

RESULTS

Stage 1 KARE GWA for T2DM was analyzed using the trend test while controlling for age, sex, BMI, and recruitment area as covariates. The quantile-quantile plot of the observed *P* values derived from the trend test showed a significant deviation from the null distribution only in the tail, which suggested an association of these SNPs with T2DM (Fig. 1A). The estimated genomic control inflation factor (λ) was 1.008, which indicated limited evidence of population stratification in the KARE study samples. Stage 1 association results revealed 24 independent SNPs (pair-wise linkage disequilibrium [LD] statistic $r^2 < 0.2$ within a genomic region 500-Kb window) that passed our arbitrary stage 1 threshold for replication (GWAS *P* value of $< 10^{-4}$ and MAF of ≥0.01 in T2DM cases and controls) (Fig. 1B). We were able to genotype 21 of 24 selected SNPs in our stage 2 samples of 1,216 patients and 1,352 controls recruited to the Health2 study cohort from five different regions of the country; we analyzed their association with T2DM and performed a meta-analysis of the stage 1 and stage 2 results (Appendix 1).

Nine independent SNPs were replicated from the stage 2 association analysis, four of which showed strong evidence of an association with T2DM and achieved genome-wide significance ($P < 5 \times 10^{-8}$) (Table 1). Rs7754840 on chromosome 6p22.3 localizes to CDKAL1 (odds ratio [OR], 1.30; 95% confidence interval [CI], 1.19 to 1.41; $P = 8.16 \times 10^{-10}$), and rs10811661 on chromosome 9p21.3 localizes near CDKN2A/B (OR, 1.29; 95% CI, 1.18 to 1.40; $P = 6.14 \times 10^{-9}$) (Table 1). Both SNPs have been previously reported for their association with T2DM [23-25]. Two novel T2DM-associated loci were found in the chromosome 12q24 region, one on 12q24.11 (rs11065756; OR, 1.40;

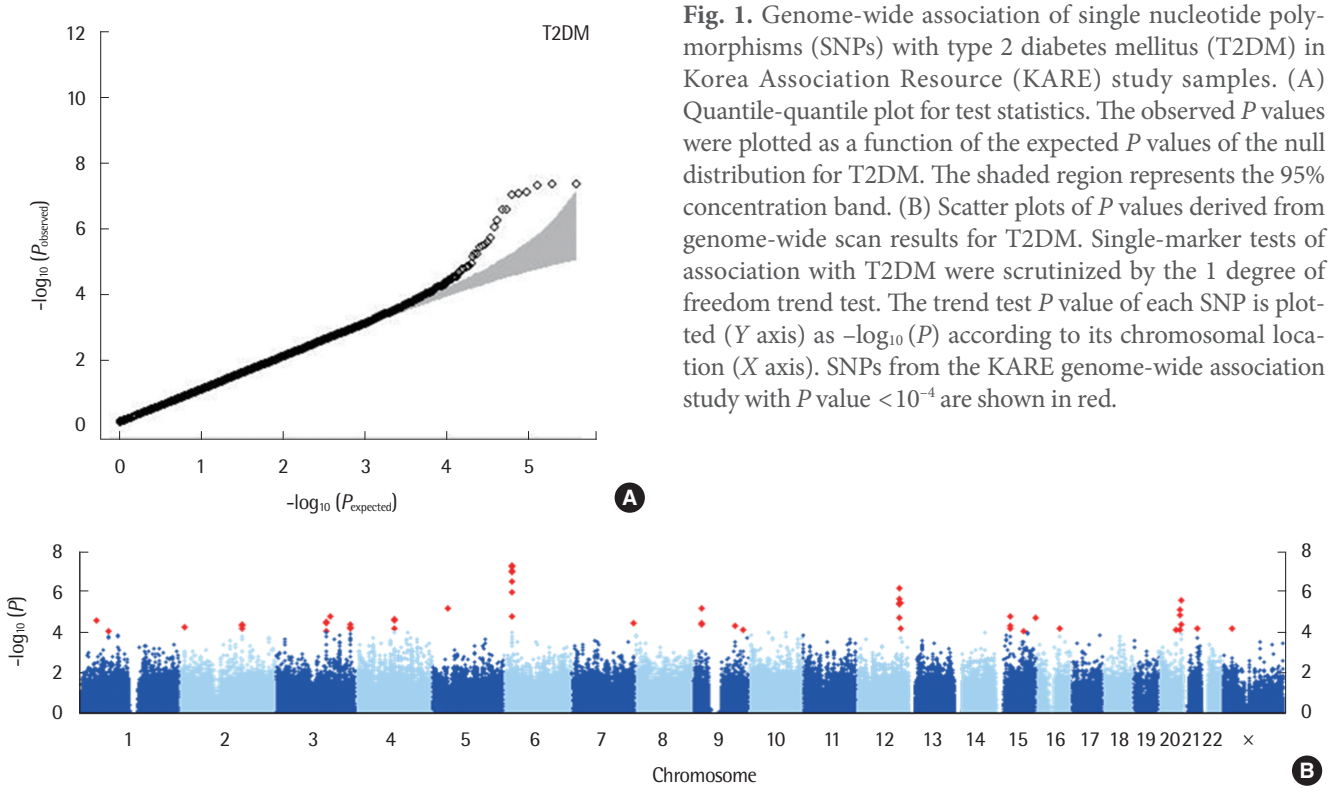

Fig. 1. Genome-wide association of single nucleotide polymorphisms (SNPs) with type 2 diabetes mellitus (T2DM) in Korea Association Resource (KARE) study samples. (A) Quantile-quantile plot for test statistics. The observed *P* values were plotted as a function of the expected *P* values of the null distribution for T2DM. The shaded region represents the 95% concentration band. (B) Scatter plots of *P* values derived from genome-wide scan results for T2DM. Single-marker tests of association with T2DM were scrutinized by the 1 degree of freedom trend test. The trend test *P* value of each SNP is plotted (*Y* axis) as $-\log_{10}(P)$ according to its chromosomal location (*X* axis). SNPs from the KARE genome-wide association study with *P* value $< 10^{-4}$ are shown in red.

Table 1. Genetic loci associated with type 2 diabetes mellitus after adjusting for age, sex, body mass index, and recruitment area

SNP	CHR	Position (bp)	Nearby gene	Risk allele	Stage 1 (KARE-GWAS) (1,042/2,943)			Stage 2 (replication) (1,216/1,352)			All Korean (stage 1+stage 2) (2,258/4,295)	
					RAF	OR	*P* value	RAF	OR (95% CI)	*P* value	OR (95% CI)	*P* value
SNPs showing strong evidence of association												
rs7754840	6	20769229	*CDKAL1*	C	0.53/0.46	1.35 (1.21–1.51)	5.09E-08	0.51/0.46	1.22 (1.08–1.39)	2.19E-03	1.30 (1.19–1.41)	8.16E-10
rs10811661	9	22124094	*CDKN2A/B*	T	0.6/0.55	1.28 (1.15–1.43)	7.26E-06	0.61/0.55	1.29 (1.13–1.48)	2.18E-04	1.29 (1.18–1.40)	6.14E-09
rs11065756	12	109823177	*CCDC63*	G	0.85/0.81	1.42 (1.22–1.65)	4.47E-06	0.84/0.81	1.36 (1.14–1.63)	5.39E-04	1.40 (1.25–1.56)	9.43E-09
rs2074356	12	111129784	*C12orf51*	C	0.88/0.84	1.46 (1.24–1.72)	3.96E-06	0.88/0.84	1.40 (1.15–1.70)	6.87E-04	1.43 (1.27–1.62)	1.12E-08
SNPs showing moderate evidence of association												
rs4376068	3	186980329	*IGF2BP2*	C	0.32/0.28	1.27 (1.13–1.43)	6.56E-05	0.3/0.26	1.24 (1.07–1.44)	4.86E-03	1.26 (1.15–1.38)	1.08E-06
rs6882351	5	40517411		T	0.67/0.61	1.31 (1.16–1.47)	7.08E-06	0.64/0.61	1.16 (1.01–1.33)	3.05E-02	1.24 (1.14–1.35)	1.50E-06
rs10258075	7	154730440	*INSIG1*	A	0.16/0.12	1.39 (1.19–1.62)	3.46E-05	0.13/0.11	1.26 (1.03–1.55)	2.72E-02	1.34 (1.18–1.51)	3.66E-06
rs3821964	4	96259727	*BMPR1B*	G	0.55/0.5	1.27 (1.14–1.41)	2.29E-05	0.53/0.51	1.14 (1.00–1.31)	4.91E-02	1.22 (1.12–1.32)	6.13E-06
rs2868088	20	42347066	*HNF4A*	G	0.59/0.54	1.25 (1.12–1.40)	7.37E-05	0.58/0.56	1.17 (1.02–1.34)	2.60E-02	1.22 (1.12–1.33)	7.52E-06

SNP, single nucleotide polymorphism; CHR, chromosome; KARE, Korea Association Resource; GWAS, genome-wide association study; RAF, risk allele frequency; OR, odds ratio; CI, confidence interval.

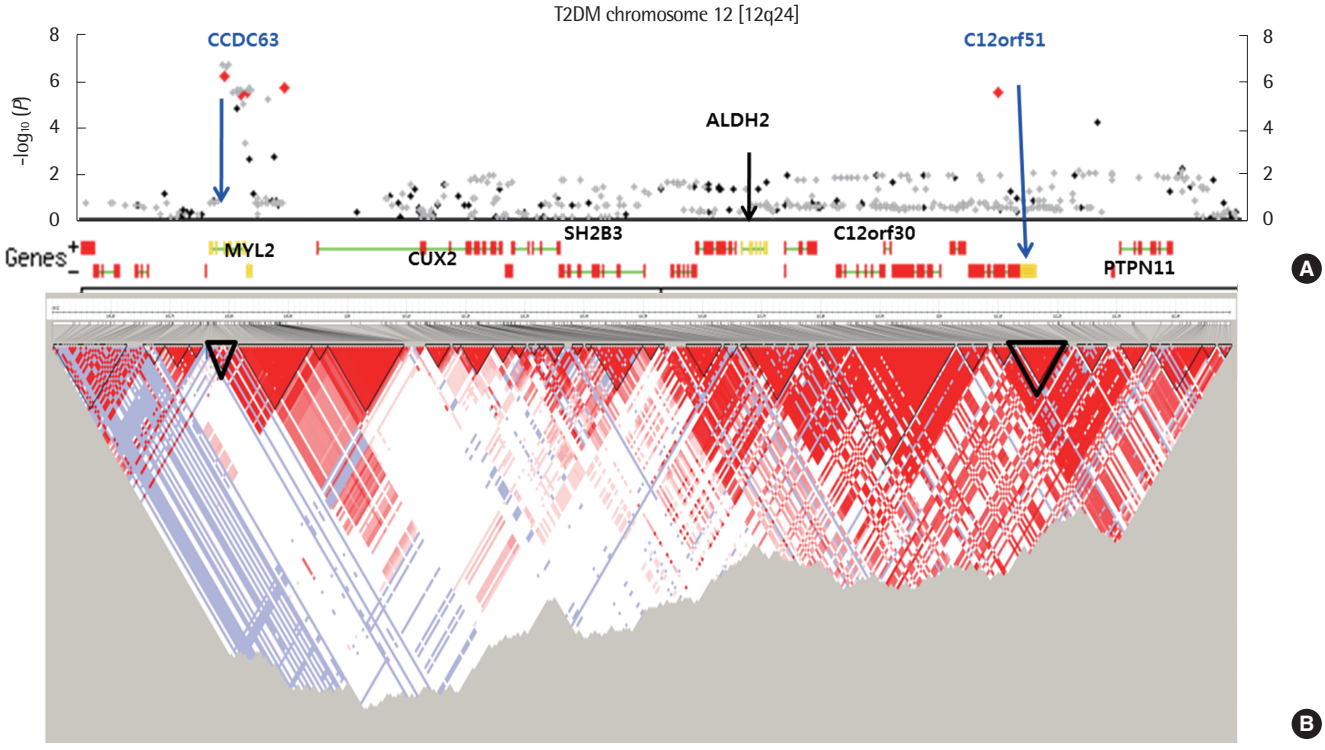

Fig. 2. Signal region on chromosome 12q24 covering type 2 diabetes mellitus (T2DM)-associated loci. (A) Signal plot of $-\log_{10}$ (*P* values) using the trend test for T2DM association in a genomic region (in Mb). Black and gray dots indicate genotyped single nucleotide polymorphisms (SNPs) in Korea Association Resource genome-wide association study and imputed SNPs, respectively. Red diamonds indicate the strongest association signals detected in the genome-wide scan. Genomic positions are based on National Center for Biotechnology Information (NCBI) genome build 36 and dbSNP build 128. In the bottom of the signal plot, the locations of known genes are indicated with red boxes and green lines, which indicate exons and introns, respectively. Genetic information was obtained from NCBI build 36. (B) Plot of linkage disequilibrium (r^2) for all SNPs across the region from Japanese in Tokyo, Japan and Han Chinese in Beijing, China founders in HapMap (release 22). This plot was generated using the Haploview 4.1 program.

95% CI, 1.25 to 1.56; $P=9.43\times10^{-9}$) in intron 9 of CCDC63 (coiled-coil domain containing 63) and the other on 12q24.13 (rs2074356; OR, 1.43; 95% CI, 1.27 to 1.62; $P=1.12\times10^{-8}$) in intron 30 ofC12orf51 (Fig. 2A) with different patterns of LD (Fig. 2B). To dissect locus heterogeneity by an interrelationship between these two loci in the 12q24 region (~1.7 Mb), we performed conditional association analyses in which each SNP (rs11065756 and rs2074356) was tested for an association with T2DM after adjusting for the genotype of the other SNP as a covariate. The strength of the association for each SNP was not significantly decreased after adjustment (data not shown), which demonstrated that the T2DM association signals detected by both loci were independent for one variant phenotype.

The T2DM-associated SNPs were further tested for their association with T2DM-related quantitative traits, such as FPG, FPI, HOMA-B, and HOMA-IR, in a total of 14,232 nondiabetic individuals consisting of 7,696 GWA and 6,536 subsequent replication study samples. Along with two SNPs previously associated with T2DM, rs7754840 in CDKAL1 ($P=1.73\times10^{-8}$, β=0.0324±0.0058 mmol/L) and rs10811661 near CDKN2A/B ($P=8.28\times10^{-7}$, β=0.0286±0.0058 mmol/L), these two new loci, rs11065756 in CCDC63 ($P=2.41\times10^{-6}$, β=0.0360±0.0076 mmol/L) and rs2074356 in C12orf51 ($P=1.21\times10^{-13}$, β=0.0606±0.0082 mmol/L) showed compelling evidence for an association with FPG (Table 2). Consistent evidence for an association with T2DM at these loci was further detected for reduced β-cell function as assessed using HOMA-B (rs7754840 in CDKAL1, $P=3.29\times10^{-4}$, β=–0.0160±0.0044; rs10811661 near CDKN2A/B, $P=1.34\times10^{-3}$, β=–0.0142±0.0044; rs11065756 in CCDC63, $P=3.56\times10^{-4}$, β=–0.0207±0.0058; rs2074356 in C12orf51, $P=1.27\times10^{-9}$, β=–0.0376±0.0062). In contrast, these variants responsible for elevated levels of FPG and reduced HOMA-B did not show an effect on FPI or insulin sensitivity as estimated using HOMA-IR (Table 2).

To gain insight into the sex-specific heritability of the loci identified in our study on T2DM and its related traits, we performed sex-specific analyses and looked for evidence of an interaction of these loci with sex by performing a likelihood ratio test within a linear regression model. Male-specific association was observed for only two 12q24 loci for T2DM, FPG and HOMA-B. This sex-specific stratification was further demonstrated by a significant SNP-sex interaction. However, previous SNPs (rs7754840 in CDKAL1 and rs10811661 in CDKN2A/B) did not generate significant evidence for sex-specificity (Table 3).

Table 2. Corroborative association of strong type 2 diabetes mellitus-associated single nucleotide polymorphisms with glycemic traits

rs_num	Gene	Stage	Risk allele	RAF	Fasting plasma glucose		Fasting plasma insulin		HOMA-B		HOMA-IR	
					Effect size (β)	*P* value	Effect size (β)	*P* value	Effect size (β)	*P* value	Effect size (β)	*P* value
rs7754840	CDKAL1	Stage 1 (7,696)	C	0.47	0.0244±0.0077	1.54E-03	–0.0063±0.01	5.28E-01	–0.0137±0.0071	5.32E-02	–0.0017±0.0023	4.68E-01
		Stage 2 (6,500)		0.48	0.042±0.0087	1.29E-06	–0.0032±0.0064	6.20E-01	–0.0186±0.0049	1.36E-04	–0.0013±0.0021	5.34E-01
		Combined (14,196)			0.0324±0.0058	1.73E-08	–0.0049±0.0062	4.29E-01	–0.016±0.0044	3.29E-04	–0.0015±0.0016	3.40E-01
rs10811661	CDKN2A/B	Stage 1 (7,696)	T	0.56	0.0245±0.0076	1.21E-03	–0.004±0.0098	6.84E-01	–0.0126±0.007	7.01E-02	–0.0013±0.0023	5.81E-01
		Stage 2 (6,500)		0.56	0.0335±0.009	1.92E-04	–0.0039±0.0066	5.53E-01	–0.0161±0.005	1.48E-03	–0.002±0.0022	3.65E-01
		Combined (14,196)			0.0286±0.0058	8.28E-07	–0.004±0.0061	5.17E-01	–0.0142±0.0044	1.34E-03	–0.0016±0.0016	3.17E-01
rs11065756	CCDC63	Stage 1 (7,696)	G	0.82	0.0324±0.0099	1.09E-03	–0.0055±0.0129	6.67E-01	–0.0174±0.0091	5.53E-02	–0.0014±0.003	6.34E-01
		Stage 2 (6,500)		0.83	0.0402±0.0118	6.78E-04	–0.0127±0.0087	1.44E-01	–0.0245±0.0067	2.30E-04	–0.0041±0.0029	1.61E-01
		Combined (14,196)			0.036±0.0076	2.41E-06	–0.0088±0.008	2.72E-01	–0.0207±0.0058	3.56E-04	–0.0026±0.0021	2.08E-01
rs2074356	C12orf51	Stage 1 (7,696)	C	0.85	0.0498±0.0106	2.56E-06	–0.025±0.0137	6.92E-02	–0.0358±0.0097	2.21E-04	–0.0027±0.0032	3.92E-01
		Stage 2 (6,500)		0.86	0.0735±0.0127	8.27E-09	–0.0169±0.0094	7.28E-02	–0.0398±0.0072	3.07E-08	–0.0053±0.0031	9.20E-02
		Combined (14,196)			0.0606±0.0082	1.21E-13	–0.0213±0.0086	1.34E-02	–0.0376±0.0062	1.27E-09	–0.0039±0.0022	8.24E-02

RAF, risk allele frequency; HOMA-B, homeostasis model assessment of β-cell function; HOMA-IR, homeostasis model assessment of insulin resistance.

Table 3. Results of a sex-specific effect for type 2 diabetes mellitus (T2DM) and T2DM-related traits

rs_num	Gene	Phenotype	Total		Male		Female		Gender test *P*
			Effect size (β)	*P* value	Effect size (β)	*P* value	Effect size (β)	*P* value	Adjusted (age, BMI, rea)
rs7754840	CDKAL1	T2DM	0.2624±0.0414	8.16E-10	0.2548±0.0600	2.19E-05	0.2563±0.0596	1.73E-05	9.86E-01
		FPG	0.0324±0.0058	1.73E-08	0.039±0.0094	3.12E-05	0.0265±0.0071	1.79E-04	1.81E-01
		HOMA-B	−0.016±0.0044	3.29E-04	−0.0224±0.0062	3.43E-04	−0.0125±0.0051	1.49E-02	1.57E-01
rs10811661	CDKN2A/B	T2DM	0.2546±0.0418	6.14E-09	0.2352±0.0618	1.40E-04	−0.2747±0.0612	7.24E-06	7.82E-01
		FPG	0.0286±0.0058	8.28E-07	0.0237±0.0094	1.15E-02	0.0333±0.0071	2.49E-06	4.56E-01
		HOMA-B	−0.0142±0.0044	1.34E-03	−0.0029±0.0062	6.42E-01	−0.0090±0.0050	7.14E-02	7.32E-01
rs11065756	CCDC63	T2DM	0.3365±0.0552	9.43E-09	0.5602±0.0840	2.55E-11	0.0069±0.086	9.36E-01	5.03E-05
		FPG	0.036±0.0076	2.41E-06	0.0841±0.012	2.38E-12	−0.0073±0.0098	4.59E-01	2.19E-10
		HOMA-B	−0.0207±0.0058	3.56E-04	0.0414±0.0084	8.13E-07	−0.0075±0.0074	3.11E-01	1.94E-03
rs2074356	C12orf51	T2DM	0.3577±0.0636	1.12E-08	0.7514±0.0956	3.92E-15	0.1022±0.0807	2.05E-01	3.97E-09
		FPG	0.0606±0.0082	1.21E-13	0.1083±0.0125	4.49E-18	0.0147±0.0105	1.64E-01	2.99E-09
		HOMA-B	−0.0376±0.0062	1.27E-09	−0.0512±0.0086	3.15E-09	−0.0280±0.0079	4.07E-04	5.67E-02

CI, confidence interval; BMI, body mass index; FPG, fasting plasma glucose; HOMA-B, homeostasis model assessment of β-cell function.

DISCUSSION

Considering the effect of common diseases of major public health, the genetic architecture of T2DM has been intensively studied using GWA analyses for many years [10,13,25-29]. Most previous T2DM-associated GWAS-findings were identified from European ancestries, but those from non-European groups were not fully understood on the basis of the genetic effects of ethnic predisposition on T2DM. We performed GWAS and follow-up replication analysis in a Korean population. Our meta-analysis newly identified two genome-wide significant associations as novel predisposing factors for T2DM and glycemic traits, such as FPG and HOMA-B.

To address population-specific genetic heterogeneity [30], we tested lookup validation for the newly identified SNPs (rs11065756 in *CCDC63* and rs2074356 in *C12orf51*) in 1,924 cases and 2,938 controls from the Wellcome Trust Case Control Consortium (WTCCC). A significant association between T2DM and rs11065756 in *CCDC63* ($P=0.37$) was not detected from WTCCC samples. Importantly, the minor A allele frequency of SNP rs11065756 in WTCCC samples was 0.07, whereas that in KARE study samples was 0.19. For rs2074356 in *C12orf51*, an association analysis could not be performed in WTCCC samples because this SNP was monomorphic in Europeans (minor T allele frequency is 0.00). In KARE study samples, the minor T allele frequency of this SNP was 0.16. Taken together, the MAF differences in these two SNPs between Asian (Korean) and European populations may reflect different association results for T2DM in the two populations. This comparison demonstrates that the difference in allele frequency is the one of the major factors indicating population-specificity of disease-causing alleles. Previous Eurocentric GWAS findings, which were not replicated in our study, showed a considerable difference in MAF between Asian and European populations [18].

A 12q24 region has been linked to T2DM and obesity related traits [31-34] in numerous studies. Recent GWAS also demonstrated genetic associations of 12q24 loci with type 1 diabetes mellitus (T1DM), which indicate *SH2B3* (SH2B adaptor protein 3), *TRAFD1* (TRAF-type zinc finger domain containing 1), and *PTPN11* (protein tyrosine phosphatase, nonreceptor type 11) as T1DM candidate genes [35-37]. In addition, multiple diverse effects have been reported for its association with 1-hour plasma glucose [38], waist hip ratio [20], metabolic traits [39], congenital heart defect [40], drinking behavior [41], and blood pressure [42,43] from current GWASs, which suggest its pleiotropic effects [44].

Furthermore, interactions between genetic variants and sex-specificity have been reported in the chromosome 12q24 region for T2DM [45] and obesity-related traits [32,34,46]. In this study, we observed male-specific associations in susceptibility to T2DM and T2DM-related traits, such as FPG and HOMA-B (Table 3). Male-specific genetic effects were reported to have strong associations with liver aminotransferase levels [47], alcohol consumption [48] and hypertension [49]. This sex-specific genetic architecture was further demonstrated by

sex-biased genetic effects on gene regulation [50].

In conclusion, our meta-analysis demonstrated multiple signals and significant sex differences for T2DM and T2DM-related traits as well as ethnic-specific characteristics in a Korean population. This information will be analyzed to gain further insight into gene-gene and gene-environment interaction. We propose that GWAS-based findings in a systematic consideration of potential confounding factors, such as genetic heterogeneity, ethnic predisposition, gender specificity, and pleiotropic effects, may provide predictive or prognostic genetic information to a wider clinical application.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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Appendix 1. Twenty-four type 2 diabetes mellitus-associated single nucleotide polymorphisms taken to the stage 2 replication study

SNP ID	CHR	Position (bp)	Gene	Risk allele	Stage 1 (KARE-GWAS) (1,042/2,943)			Stage 2 (replication) (1,216/1,352)			All Korean (stage 1+stage 2) (2,258/4,295)	
					RAF	OR	*P* value	RAF	OR (95% CI)	*P* value	OR (95% CI)	*P* value
rs6665139	1	38368797		C	0.87/0.83	1.4 (1.2–1.64)	2.71E-05	0.82/0.84	0.83 (0.70–0.99)	0.03414	1.11 (0.98–1.24)	8.95E-02
rs2791212	1	69382309		C	0.18/0.14	1.34 (1.16–1.56)	9.34E-05	0.15/0.16	0.88 (0.73–1.06)	0.16751	1.14 (1.01–1.28)	2.94E-02
rs360481	2	14129817		C	0.86/0.83	1.36 (1.17–1.59)	6.28E-05					
rs1156560	2	157845249	GALNT5	A	0.19/0.15	1.35 (1.17–1.56)	4.05E-05	0.2/0.2	0.94 (0.82–1.09)	0.41073	1.13 (1.02–1.25)	2.05E-02
rs2700396	3	125049031	MYLK	A	0.05/0.03	1.79 (1.36–2.36)	3.41E-05	0.03/0.04	0.98 (0.7–1.39)	0.92526	1.42 (1.14–1.76)	1.52E-03
rs6439472	3	135479558		A	0.15/0.12	1.41 (1.21–1.66)	1.73E-05					
rs4376068	3	186980329	IGF2BP2	C	0.32/0.28	1.27 (1.13–1.43)	6.56E-05	0.3/0.26	1.24 (1.07–1.44)	0.00486	1.26 (1.15–1.38)	1.08E-06
rs3821964	4	96259727	BMPR1B	G	0.55/0.5	1.27 (1.14–1.41)	2.29E-05	0.53/0.51	1.14 (1.00–1.31)	0.04912	1.22 (1.12–1.32)	6.13E-06
rs6882351	5	40517411		T	0.67/0.61	1.31 (1.16–1.47)	7.08E-06	0.64/0.61	1.16 (1.01–1.33)	0.03049	1.24 (1.14–1.35)	1.50E-06
rs7754840	6	20833402	CDKAL1	C	0.53/0.46	1.35 (1.21–1.51)	5.09E-08	0.51/0.46	1.22 (1.08–1.39)	0.00219	1.30 (1.19–1.41)	8.16E-10
rs10258075	7	154730440	INSIG1	A	0.16/0.12	1.39 (1.19–1.62)	3.46E-05	0.13/0.11	1.26 (1.03–1.55)	0.02724	1.34 (1.18–1.51)	3.66E-06
rs10811661	9	22124094	CDKN2A/B	T	0.6/0.55	1.28 (1.15–1.43)	7.26E-06	0.61/0.55	1.29 (1.13–1.48)	0.00022	1.29 (1.18–1.40)	6.14E-09
rs10115450	9	103425694	GRIN3A	T	0.69/0.64	1.27 (1.13–1.43)	4.99E-05	0.65/0.65	1.00 (0.87–1.15)	0.98872	1.15 (1.05–1.26)	1.79E-03
rs16911914	9	124373314	OR1L8	G	0.36/0.31	1.26 (1.12–1.41)	7.64E-05	0.33/0.34	0.94 (0.82–1.08)	0.40376	1.12 (1.02–1.22)	1.22E-02
rs11065756	12	109823177	CCDC63	G	0.85/0.81	1.42 (1.22–1.65)	4.47E-06	0.84/0.81	1.36 (1.14–1.63)	0.00054	1.40 (1.25–1.56)	9.43E-09
rs2074356	12	111129784	C12orf51	C	0.88/0.84	1.46 (1.24–1.72)	3.96E-06	0.88/0.84	1.40 (1.15–1.70)	0.00069	1.43 (1.27–1.62)	1.12E-08
rs2444728	15	34536722		A	0.18/0.15	1.35 (1.17–1.56)	5.38E-05	0.15/0.16	0.92 (0.77–1.09)	0.33507	1.15 (1.03–1.29)	1.28E-02
rs7163430	15	36310957		A	0.56/0.51	1.27 (1.14–1.42)	1.62E-05	0.52/0.55	0.94 (0.82–1.07)	0.32711	1.12 (1.03–1.22)	7.18E-03
rs4777379	15	69460667	THSD4	C	0.28/0.24	1.28 (1.13–1.45)	9.42E-05					
rs10492918	16	58201055		T	0.34/0.29	1.27 (1.13–1.43)	6.84E-05	0.31/0.31	0.99 (0.86–1.14)	0.90092	1.15 (1.05–1.26)	2.76E-03
rs2868088	20	42347066	GDAP1L1, HNF4A	G	0.59/0.54	1.25 (1.12–1.4)	7.37E-05	0.58/0.56	1.17 (1.02–1.34)	0.02598	1.22 (1.12–1.33)	7.52E-06
rs2236208	20	54401300	CSTF1,AURKA	G	0.12/0.09	1.48 (1.25–1.76)	8.33E-06	0.08/0.1	0.8 (0.57–1.12)	0.19686	1.31 (1.12–1.52)	6.95E-04
rs11086668	20	57218452	ZNF831	C	0.21/0.18	1.33 (1.16–1.52)	4.53E-05	0.2/0.2	1.15 (0.98–1.36)	0.09154	1.25 (1.13–1.39)	2.48E-05
rs6128654	20	57649177	PHACTR3	C	0.41/0.36	1.3 (1.17–1.46)	2.87E-06	0.39/0.38	1.07 (0.93–1.22)	0.34572	1.20 (1.10–1.31)	2.38E-05

SNP, single nucleotide polymorphism; CHR, chromosome; KARE, Korea Association Resource; GWAS, genome-wide association study; RAF risk allele frequency of case/control samples; OR, odds ratio; CI, confidence interval.