Implication of Genetic Variants Near *TCF7L2*, *SLC30A8*, *HHEX*, *CDKAL1*, *CDKN2A/B*, *IGF2BP2*, and *FTO* in Type 2 Diabetes and Obesity in 6,719 Asians

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OBJECTIVE—Recent genome-wide association studies have identified six novel genes for type 2 diabetes and obesity and confirmed *TCF7L2* as the major type 2 diabetes gene to date in Europeans. However, the implications of these genes in Asians are unclear.

RESEARCH DESIGN AND METHODS—We studied 13 associated single nucleotide polymorphisms from these genes in 3,041 patients with type 2 diabetes and 3,678 control subjects of Asian ancestry from Hong Kong and Korea.

RESULTS—We confirmed the associations of *TCF7L2*, *SLC30A8*, *HHEX*, *CDKAL1*, *CDKN2A/CDKN2B*, *IGF2BP2*, and *FTO* with risk for type 2 diabetes, with odds ratios ranging from 1.13 to 1.35 ($1.3 \times 10^{-12} < P_{\text{unadjusted}} < 0.016$). In addition, the A allele of rs8050136 at *FTO* was associated with increased BMI in the control subjects ($P_{\text{unadjusted}} = 0.008$). However, we did not observe significant association of any genetic variants with surrogate measures of insulin secretion or insulin sensitivity indexes in a subset of 2,662 control subjects. Compared with subjects carrying zero, one, or two risk alleles, each additional risk allele was associated with 17% increased risk, and there was an up to 3.3-fold increased risk for type 2 diabetes in those carrying eight or more risk alleles. Despite most of the effect sizes being similar between Asians and Europeans in the meta-analyses, the ethnic differences in risk allele frequencies in most of these genes lead to variable attributable risks in these two populations.

CONCLUSIONS—Our findings support the important but differential contribution of these genetic variants to type 2 diabetes and obesity in Asians compared with Europeans. ***Diabetes* 57: 2226–2233, 2008**

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Received 8 November 2007 and accepted 30 April 2008.

Published ahead of print at http://diabetes.diabetesjournals.org on 13 May 2008. DOI: 10.2337/db07-1583.

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Type 2 diabetes is a major health problem affecting more than 170 million people worldwide. In the next 20 years, Asia will be hit hardest, with the diabetic populations in India and China more than doubling (1). Type 2 diabetes is characterized by the presence of insulin resistance and pancreatic β-cell dysfunction, resulting from the interaction of genetic and environmental factors. Until recently, few genes identified through linkage scans or the candidate gene approach have been confirmed to be associated with type 2 diabetes (e.g., *PPARG*, *KCNJ11*, *CAPN10*, and *TCF7L2*). Under the common variant–common disease hypothesis, several genome-wide association (GWA) studies on type 2 diabetes have been conducted in large-scale case-control samples. Six novel genes (*SLC30A8*, *HHEX*, *CDKAL1*, *CDKN2A* and *CDKN2B*, *IGF2BP2*, and *FTO*) with modest effect for type 2 diabetes (odds ratio [OR] 1.14–1.20) had been reproducibly demonstrated in multiple populations of European ancestry. Moreover, *TCF7L2* was shown to have the largest effect for type 2 diabetes (1.37) in the European populations to date (2–8). Although many of these genes may be implicated in the insulin production/secretion pathway (*TCF7L2*, *SLC30A8*, *HHEX*, *CDKAL1*, *CDKN2A/B*, and *IGF2BP2*) (6,9–11), *FTO* is associated with type 2 diabetes through its regulation of adiposity (8,12,13). Moreover, two adjacent regions near *CDKN2A/B* are associated with type 2 diabetes and cardiovascular diseases risks, respectively (7,14–16). Despite the consistent associations among Europeans, the contributions of these genetic variants in other ethnic groups are less clear. Given the differences in environmental factors (e.g., lifestyle), risk factor profiles (body composition and insulin secretion/resistance patterns), and genetic background (linkage disequilibrium pattern and risk allele frequencies) between Europeans and Asians, it is important to understand the role of these genes in Asians. A recent case-control study in 1,728 Japanese subjects revealed nominal association to type 2 diabetes for variants at the *SLC30A8*, *HHEX*, *CDKAL1*, *CDKN2B*, and *FTO* genes but not *IGF2BP2* (17). In the present large-scale case-control replication study of 6,719 Asians, we aimed to test for the association of six novel genes from GWA studies and *TCF7L2*, which had the largest effect in Europeans, and their joint effects on type 2 diabetes risk and metabolic traits.

RESEARCH DESIGN AND METHODS

All subjects were recruited from Hong Kong and Korea and of Asian ancestry. The subjects in the Hong Kong case-control study were of southern Han Chinese ancestry residing in Hong Kong. Participants for the case cohort consisting of 1,481 subjects with type 2 diabetes were selected from two

sources. From the Hong Kong Diabetes Registry (18), we selected 556 patients (age 40.4 ± 8.3 years [mean ± SD], 33.2% men) with early-onset diabetes (age at diagnosis [AAD] ≤40 years) and with positive family history of diabetes in first-degree relatives. An additional 763 case subjects (age 58.2 ± 11.7 years, 40.9% men) were randomly selected from the same registry irrespective of age at diagnosis (AAD). From the Hong Kong Family Diabetes Study, 162 unrelated type 2 diabetic patients (age 41.8 ± 11.6 years, 38.9% men), of whom 115 had early-onset familial diabetes, were also selected as case subjects (19). Patients with classic type 1 diabetes with acute ketotic presentation or continuous requirement of insulin within 1 year of diagnosis were excluded. The inclusion of young diabetic patients with familial history may increase genetic loading of the study population. Despite our previous findings suggesting up to 14% presence of monogenic diabetes in the young patients (20), 50% of these young patients were obese, mimicking the predominant feature of type 2 diabetes. The control subjects consisted of 1,530 subjects with normal glucose tolerance (fasting plasma glucose [FPG] <6.1 mmol/l). Of these, 589 (age 41.4 ± 10.5 years, 44.7% men) were recruited from the general population participating in a community-based cardiovascular risk screening program and from hospital staff. We recruited 941 subjects (age 15.3 ± 1.9 years, 46.8% men) from a population-based cardiovascular risk screening program for adolescents (21). Informed consent was obtained for each participating subject. This study was approved by the Clinical Research Ethics Committee of the Chinese University of Hong Kong.

The Korea Seoul National University Hospital (SNUH) case-control population consisted of 761 unrelated patients with type 2 diabetes registered at the Diabetes Clinic of SNUH and 632 nondiabetic control subjects. Type 2 diabetes was diagnosed using the World Health Organization (WHO) criteria (22). Subjects positive for glutamic acid decarboxylase antibodies were excluded. Nondiabetic control subjects were selected according to the following criteria: ≥60 years old, no history of diabetes, no first-degree relatives with diabetes, FPG <6.1 mmol/l, and A1C <5.8%. The Institutional Review Board of the Clinical Research Institute in SNUH approved the study protocol, and informed consent for genetic analysis was obtained from each subject.

The Korean Health and Genome Study (KHGS) case-control population were selected from a prospective community-based epidemiology study in the Ansung (rural) and Ansan (urban) communities (23). In this study, eligible subjects aged between 40 and 69 years were examined at baseline in 2001–2002 for demographic and glucose tolerance and then followed up biannually. At baseline, 799 subjects who were on treatment for type 2 diabetes or with FPG ≥7 mmol/l or 2-h plasma glucose ≥11.1 mmol/l during a 75-g oral glucose tolerance test (OGTT) were selected as case subjects using the WHO criteria (22). For each case subject, approximately two sex-matched subjects without family history of diabetes and with normal glucose level at OGTT (FPG <7 mmol/l and 2-h plasma glucose <7.8 mmol/l) at both baseline and follow-up visits were selected as control subjects (n = 1,516). The case and control groups were frequency matched for age. The study protocol was approved by the Ethics Committee of the KHGS and Ajou University Medical Center.

In all studies, general obesity was defined as BMI ≥25 kg/m^2, which was modified for Asian populations (24). Among the control subjects, 434 subjects from Hong Kong and 1,516 subjects from KHGS studies underwent a 75-g OGTT to exclude diabetes (22). Moreover, 548, 609 and 1,505 subjects from the Hong Kong, SNUH, and KHGS studies, respectively, were measured for both FPG and insulin to derive surrogate indexes for insulin secretion and sensitivity.

Clinical studies. All study subjects were examined in the morning after an overnight fast. Anthropometric parameters and blood pressure were measured. Fasting blood samples were collected for measurement of plasma glucose, insulin, and lipids. Using the homeostasis model assessment (HOMA), insulin resistance index (HOMA-IR) was assessed as fasting insulin (mU/l) × FPG (mmol/l)/22.5; and β-cell function (HOMA-β) was assessed as fasting insulin × 20/(FPG − 3.5) (25).

Gene and single nucleotide polymorphism selection. Six novel genes identified through recent GWA studies and *TCF7L2* showing reproducible association to type 2 diabetes in Europeans were selected for replication study (Supplementary Table 1, which is detailed in the online appendix [available at http://dx.doi.org/10.2337/db07-1583]) (3–8). For genes with multiple associated single nucleotide polymorphisms (SNPs), the pairwise linkage disequilibrium D′ and r^2 were assessed using Haploview (v.3.32) (26). Only representative SNPs with r^2 <0.8 based on HapMap Han Chinese and Japanese data were selected for genotyping. Two representative SNPs (rs1333040 and rs10757278) close to *CDKN2A/B* that were associated with coronary heart disease and myocardial infraction were also selected (7,14–16). Genotyping of rs13266634 at *SLC30A8* failed in the KHGS samples and was replaced by rs3802177, which is in complete linkage disequilibrium (r^2 = 1) with rs13266634. The genotyping method and quality control for the 13 studied SNPs were shown in the online appendix.

Statistical analyses. For disease association analyses, genotype frequencies for case and control subjects in each of the three study population were compared using logistic regression under a log additive model in PLINK (v.0.99, http://pngu.mgh.harvard.edu/~purcell/plink). ORs with 95% CIs are presented with respect to the risk allele in the combined samples. For genes with multiple SNPs, haplotypes with frequencies >5% were compared in case-control samples using omnibus test implemented in PLINK. Possible independent SNP effect was assessed by conditional omnibus analysis after controlling for a significant SNP. An insignificant test suggests the presence of a single- rather than multiple-association signal at the haplotype.

Meta-analysis of type 2 diabetes association for the combined samples from the three study populations was performed by the fixed effects Cochran-Mantel-Haenszel (CMH) test implemented in PLINK to estimate a summary allelic OR, using study population as a strata. To correct for multiple comparisons, 10,000 permutations of case-control labels were performed in PLINK to assess for experiment-wise empirical P values. The effect of additional covariates on type 2 diabetes association was tested using logistic regression with adjustment for BMI, age, and sex in individual samples and further adjustment for study population in combined samples.

Continuous data were expressed as means ± SD. BMI, insulin, and HOMA indexes were transformed by natural logarithm to normality. Each trait was winsorized at ±4 SD from the mean to reduce the impact of outliers, which represented 0–0.5% of the data. The values were further transformed to Z scores with adjustment for age and sex and then combined and analyzed under an additive model using linear regression. For quantitative trait association analyses in the combined control samples, trait values from four groups, including the adolescents and adults from Hong Kong, Korea SNUH, and KHGS populations, were transformed separately before merging to account for population differences in trait distributions. For each trait, 5,000 permutations were performed to assess for experiment-wise empirical P values using PLINK.

We tested for model fit for type 2 diabetes association tests by comparing additive, dominant, and recessive models using logistic regression (1 degree of freedom [df] tests) in the combined samples. Deviations from the additive model were assessed by testing the significance of dominance effect in a general (2 df) model that include an additive effect. To test for joint and interaction effects of the seven genes, a representative significant SNP from each gene was selected. Each pairwise SNP interaction was then tested in a logistic regression model that included the main effects of all seven SNPs under an additive model (except *TCF7L2* for a dominant model due to the small number of homozygous risk allele carriers). By assuming similar effect size, the joint effect of the seven SNPs for type 2 diabetes risk was assessed by calculating the OR with respect to the number of risk alleles carried under an additive model (except *TCF7L2* for a dominant model). The significance of the trend was assessed by logistic regression for type 2 diabetes using the categories of risk allele carried as an independent variable.

We also compared the effect size of these risk alleles between Asians and Europeans. For type 2 diabetes association, genotype counts for SNPs in the seven genes in type 2 diabetic case and control subjects were directly obtained or estimated from the five European GWA studies and a Japanese replication study (3–8,17). Meta-analyses of type 2 diabetes association for the five European samples, four Asian samples (including three samples from the current study), and the combined European and Asian samples were performed by the CMH test. Attributable risk was calculated as $(x - 1)/x$. The study assumed a log additive model, $x = (1 - f)^2 + 2f(1 - f)\gamma + f^2\gamma^2$ where γ is the estimated OR and f is the risk allele frequency.

For meta-analysis for the association of *FTO* and BMI, the A allele of rs9939609 and G allele of rs9930506 were used as surrogates for the risk A allele of rs8050136 in Europeans because they are in strong linkage disequilibrium (r^2 = 0.84–1) in a HapMap population of Utah residents with northern and western European ancestry (CEU population). Means and SDs were directly obtained for rs9939609 or estimated for rs9930506 genotypes from two European studies (nondiabetic control subjects and adult and older adult populations from Frayling et al. [12] and Sardinia and European American populations from Scuteri et al. [13], respectively) and for the rs8050136 genotypes from two Asian studies (17,27) and the present four samples (adolescents and adults from Hong Kong, Korea SNUH, and KHGS control subjects). Standardized mean difference (SMD), the difference between two genotypic means divided by the pooled SD, and the 95% CI for the Europeans, Asians, and combined samples were calculated with the Hedges g statistic under the fixed effects model using MedCalc for Windows, version 9.2.0.0 (MedCalc Software, Mariakerke, Belgium).

In both disease and quantitative trait analyses, heterogeneity of ORs or SMDs among studies or populations was assessed by Cochran's Q statistic (28) using MedCalc (online appendix). In case of significant heterogeneity (Q

TABLE 1
Clinical characterization of study populations

	Hong Kong		Korea SNUH		Korea KHGS	
	Type 2 diabetes	Control subjects	Type 2 diabetes	Control subjects	Type 2 diabetes	Control subjects
n	1,481	1,530	761	632	799	1,516
Men/women	598/883	703/827	354/407	287/345	428/371	805/711
Age (year)	49.7 ± 13.7	25.3 ± 14.4	59.2 ± 9.9	64.7 ± 3.6	56.1 ± 8.6	55.8 ± 8.7
AAD (year)	43.6 ± 13.7	—	50.0 ± 10.1	—	52.8 ± 9.2	—
BMI (kg/m^2)	25.1 ± 4.2	21.0 ± 3.7	24.5 ± 2.9	23.6 ± 3.1	25.5 ± 3.3	24.2 ± 3.2
Fasting glucose (mmol/l)	—	4.8 ± 0.4	—	4.9 ± 0.5	—	4.6 ± 0.4
Glucose at 120 min (mmol/l)	—	5.6 ± 1.2	—	—	—	5.8 ± 1.2
Fasting insulin (pmol/l)	—	39.0 (37.6–40.4)	—	41.7 (40.1–43.3)	—	39.3 (38.2–40.5)
Insulin at 120 min (pmol/l)	—	236.7 (228.1–245.5)	—	—	—	100.4 (95.8–105.1)
HOMA-IR	—	1.4 (1.3–1.4)	—	1.5 (1.5–1.6)	—	1.3 (1.3–1.4)
HOMA-β	—	103.1 (99.3–107.0)	—	102.9 (98.5–107.5)	—	125.6 (121.4–130)
Obesity (%)	46.8	13.3	38.2	33.1	54.3	39.0
Metabolic syndrome (%)	57.9	2.4	68.6	23.7	67.1	21.6

Data are means ± SD, geometric mean (95% CI), or percent.

statistic $P < 0.1$), the effect size calculated from the random effects model (DerSimonian and Laird for disease analyses) using MedCalc was also reported.

All statistical tests were performed by PLINK or SAS v.9.1 (SAS Institute, Cary, NC) unless specified otherwise. Because the studied genes are well replicated and posterior power calculations (online appendix) demonstrated that the present sample size had sufficient power to detect the observed effect sizes at α-level of 0.05 but insufficient power at a corrected α-level of 0.0038 for some cases of modest effects (e.g., *FTO*) or rare at-risk allele frequency (e.g., *TCF7L2*), a nominal *P* value <0.05 was considered significant in this study.

RESULTS

We genotyped 13 representative SNPs from 7 genes implicated in type 2 diabetes in recent GWA studies in 3,041 type 2 diabetic case subjects and 3,678 nondiabetic control subjects from a Chinese population in Hong Kong and two Korean populations. The clinical characteristics of the subjects are summarized in Table 1. Table 2 showed the meta-analyses of type 2 diabetes association under a log additive model. There was no heterogeneity of ORs among the three study populations except for *CDKN2A/B* (rs10811661) (Q statistic $P = 0.03$), with a random effect OR of 1.32 (1.15–1.52). Apart from two SNPs at *CDKN2A/B* (rs564398 and rs1333040), all other 11 SNPs were significantly associated with type 2 diabetes, with ORs ranging from 1.09 to 1.35 ($1.3 \times 10^{-12} < P < 0.016$) in the combined samples (Table 2). Eight of the 11 SNPs remained significant after adjustment for multiple comparison by permutation ($1.0 \times 10^{-4} < P_{empirical} < 0.012$) (Table 2) despite nonsignificance of *CDKN2A/B* (rs10757278), *TCF7L2* (rs7903146), and *FTO* (rs8050136). Because multiple SNPs with little or moderate linkage disequilibrium at *CDKAL1* ($r^2 = 0.56$), *CDKN2A/B* ($r^2 = 0.002–0.31$), and *HHEX* ($r^2 = 0.25–0.55$) were studied (Supplementary Table 2), we examined haplotype associations but did not reveal more significant association than single marker analyses (Supplementary Table 3). Further haplotype analyses by conditioning rs7756992 on *CDKAL1* haplotypes and rs7923837 on *HHEX* haplotypes revealed no significant residual associations ($P > 0.05$; data not shown), suggesting that these two SNPs are sufficient to explain the respective multiple associations at *CDKAL1* and *HHEX*. Although residual association was observed after conditioning rs10811661 on *CDKN2A/B* haplotypes ($P = 0.023$), the much stronger single marker association of rs10811661 compared with rs10757278 ($P = 1.3 \times 10^{-12}$ vs. 0.015; Table 2) suggests the former is the key associated SNP. Taken together, seven key SNPs from these genes were significant without correction for multiple comparisons. In this regard, *TCF7L2* (rs7903146) showed the strongest effect on type 2 diabetes risk (OR 1.35), followed by *CDKN2A/B* (rs10811661), *CDKAL1* (rs7756992), *HHEX* (rs7923837), *IGF2BP2* (rs4402960), *SLC30A8* (rs13266634), and *FTO* (rs8050136). These seven SNPs were further examined in the subsequent analyses.

The association for type 2 diabetes was also tested by adjustment for BMI, age, sex, and/or study population in both individual and combined samples. Most SNPs showed similar effect sizes with or without adjustment for covariates in both individual (data not shown) and combined samples. However, the association for type 2 diabetes was lost for *FTO* (rs8050136) after covariate adjustment (OR 1.13, $P = 0.016$ vs. 1.09, $P = 0.13$ with or without adjustment in the combined samples) (Table 2; Supplementary Table 4).

We further examined the association of the seven SNPs with quantitative traits in the combined control samples. The risk A allele of *FTO* was significantly associated with increased BMI ($P = 0.008$) (Table 3) and obesity defined as BMI ≥25 kg/m^2 (OR [95% CI] 1.18 [1.01–1.39]). In addition, the risk alleles at *SLC30A8* and *TCF7L2* were associated with increased FPG ($P = 0.023$) and decreased insulin at 120 min during the OGTT ($P = 0.038$), respectively (Table 3). However, only *FTO* (rs8050136) showed trend of association after multiple comparison correction ($P_{empirical} = 0.057$). None of the SNPs showed significant associations with insulin secretion (HOMA-β) or insulin sensitivity (HOMA-IR).

When we tested for the best fit model, all seven SNPs did not show significant dominance effects (Supplementary Table 5); thus, the joint and interaction effects analyses were performed using an additive/multiplicative model (except the dominant model for *TCF7L2*). None of the pairwise SNP interactions was significant (data not shown). However, there was a significant increase in risk for type 2 diabetes with increasing number of risk alleles ($P < 0.001$) in gene-dosage analysis. Compared with 9% of subjects carrying zero, one, or two risk alleles, each additional risk allele was associated with 17% increased

TABLE 2
Associations of seven genes with type 2 diabetes in Chinese and Korean populations

Gene	SNP	Chr	Position (bp)	Risk/ non-risk alleles*	Hong Kong				Korea SNUH				Korea KHGS				Combined (95% CI)†	
					Case risk AF	Control risk AF	OR (95% CI)†	*P* value	Case risk AF	Control risk AF	OR (95% CI)†	*P* value	Case risk AF	Control risk AF	OR (95% CI)†	*P* value	OR (95% CI)†	$P_{empirical}$ value
Total *n*					3,011				1,393				2,315				6,719	
Case/control subjects					1,481/1,530				761/632				799/1,516				3,041/3,678	
IGF2BP2	rs4402960	3	186994381	T/G	0.255	0.245	1.05 (0.93–1.18)	0.413	0.331	0.296	1.18 (1.00–1.39)	0.049	0.318	0.273	1.24 (1.09–1.42)	0.001	1.14 (1.06–1.23)	8.1×10^{-4}	0.012
CDKAL1	rs7754840	6	20769229	C/G	0.420	0.358	1.29 (1.17–1.43)	1.0×10^{-6}	0.519	0.464	1.24 (1.07–1.44)	0.005	0.529	0.468	1.27 (1.13–1.44)	1.0×10^{-4}	1.28 (1.19–1.37)	4.6×10^{-12}	1.0×10^{-4}
CDKAL1	rs7756992	6	20787688	G/A	0.517	0.462	1.24 (1.12–1.37)	2.9×10^{-5}	0.586	0.526	1.26 (1.09–1.47)	0.002	0.601	0.530	1.33 (1.17–1.50)	8.2×10^{-6}	1.28 (1.19–1.37)	3.9×10^{-12}	1.0×10^{-4}
SLC30A8§	rs13266634	8	118253964	C/T	0.572	0.532	1.17 (1.06–1.3)	0.002	0.627	0.585	1.18 (1.02–1.38)	0.029	0.590	0.582	1.03 (0.91–1.17)	0.636	1.13 (1.05–1.21)	6.5×10^{-4}	0.010
CDKN2A/B	rs564398	9	22019547	C/T	0.108	0.102	1.07 (0.91–1.27)	0.407	0.156	0.128	1.24 (1.01–1.54)	0.044	0.127	0.135	0.93 (0.77–1.11)	0.421	1.06 (0.95–1.18)	0.284	0.978
CDKN2A/B	rs1333040	9	22073404	T/C	0.692	0.675	1.08 (0.97–1.21)	0.154	0.664	0.684	0.91 (0.77–1.07)	0.250	0.690	0.680	1.05 (0.92–1.20)	0.477	1.03 (0.96–1.11)	0.402	0.998
CDKN2A/B	rs10757278	9	22114477	G/A	0.524	0.495	1.12 (1.01–1.24)	0.030	0.449	0.453	0.98 (0.85–1.14)	0.834	0.477	0.449	1.12 (0.99–1.27)	0.069	1.09 (1.02–1.17)	0.015	0.167
CDKN2A/B	rs10811661	9	22124094	T/C	0.614	0.568	1.21 (1.09–1.34)	3.5×10^{-4}	0.619	0.512	1.55 (1.33–1.81)	2.0×10^{-8}	0.601	0.546	1.25 (1.10–1.41)	4.4×10^{-4}	1.29 (1.20–1.38)	1.3×10^{-12}	1.0×10^{-4}
HHEX	rs1111875	10	94452862	C/T	0.305	0.288	1.09 (0.97–1.21)	0.144	0.347	0.305	1.21 (1.03–1.43)	0.019	0.352	0.309	1.23 (1.08–1.41)	0.002	1.16 (1.07–1.24)	1.6×10^{-4}	0.003
HHEX	rs5015480	10	94455539	C/T	0.185	0.172	1.09 (0.95–1.25)	0.228	0.219	0.186	1.22 (1.02–1.47)	0.034	0.227	0.183	1.32 (1.13–1.54)	3.7×10^{-4}	1.20 (1.09–1.31)	9.0×10^{-5}	0.002
HHEX	rs7923837	10	94471897	G/A	0.205	0.176	1.20 (1.06–1.37)	0.005	0.262	0.210	1.33 (1.12–1.59)	0.002	0.252	0.224	1.17 (1.01–1.35)	0.033	1.22 (1.12–1.33)	3.3×10^{-6}	3.0×10^{-4}
TCF7L2	rs7903146	10	114748339	T/C	0.030	0.023	1.30 (0.95–1.76)	0.099	0.037	0.025	1.53 (0.98–2.39)	0.063	0.031	0.024	1.29 (0.90–1.87)	0.169	1.35 (1.10–1.67)	0.005	0.058
FTO	rs8050136	16	52373776	A/C	0.156	0.136	1.18 (1.02–1.37)	0.028	0.138	0.122	1.15 (0.92–1.44)	0.228	0.124	0.118	1.06 (0.88–1.28)	0.535	1.13 (1.02–1.25)	0.016	0.177

AF, allele frequency; Chr, chromosome. *All alleles were indexed to the forward strand of NCBI Build 36. Risk alleles were defined according to association results from combined samples. †ORs (95% CI) were reported with respect to the risk allele using a log additive model in logistic regression. ‡Fixed effects Cochran-Mantel-Haenszel test was shown for meta-analysis in the combined samples. §Rs13266634 assay was failed in the Korea KHGS samples and was replaced by rs3802177.

risk and up to 3.3-fold increased risk for type 2 diabetes in those 4% subjects carrying eight or more risk alleles (Supplementary Fig. 1).

We examined for ethnic differences of SNP association with type 2 diabetes and BMI using the current data and published studies (3–8,12,13,17,27). Although *TCF7L2* demonstrated the strongest effect on type 2 diabetes in both Europeans (OR 1.44) and Asians (1.44), other genes had modest effect in Europeans (1.11–1.23) and Asians (1.12–1.27) (Table 4; Supplementary Fig. 2). Moreover, *CDKAL1* (rs7756992) showed stronger effect sizes in Asians than in Europeans (1.26 vs. 1.14) (Table 4).

In the meta-analysis of *FTO* (rs8050136) and BMI in Europeans, AC and AA genotypes were associated with an increase of 0.09 (0.07–0.11) and 0.19 (0.17–0.21) SMD of BMI, respectively, when compared with CC genotype (Supplementary Fig. 3). The respective effect was weaker in Asians, corresponding to an increase of 0.05 (−0.006 to 0.10) and 0.10 (−0.07 to 0.26) SMD of BMI, respectively, for AC and AA genotypes. The difference reached significance when comparing AC+AA with CC genotypes (SMD 0.05 [0.0001–0.11]). Although the SMDs of BMI between AC+AA and CC groups were similar in study groups within both Europeans and Asians, the effect of rs8050136 on BMI was significantly stronger in Europeans than in Asians (Q statistic $P = 0.02$).

DISCUSSION

Our study provides important insights for the impact of the new type 2 diabetes genes identified through GWA studies. To our knowledge, this is the largest replication study in Asians up to now. We confirm the type 2 diabetes association of seven representative risk alleles for these seven genes found in Europeans (3–8), suggesting many of the variants associated with type 2 diabetes in Europeans are also associated in Asians. These genetic effects seem to be additive. Despite differences in effect size of each gene, a crude estimate suggests up to 3.3-fold increased type 2 diabetes risk in subjects carrying eight or more risk alleles compared with those carrying two or fewer risk alleles (Supplementary Fig. 1). Two adjacent regions near *CDKN2A/B* have been reported to be associated with type 2 diabetes and cardiovascular diseases. Our data confirm the association of type 2 diabetes for rs10811661, found in the European type 2 diabetes studies (3,4,8), but not rs564398, found only in the Wellcome Trust Case Control Consortium Study (8). In addition, we found that the cardiovascular disease risk loci (rs1333040 and rs10757278) (14–16) were not associated with type 2 diabetes.

Our findings are further supported by a recent Japanese study on 864 case subjects and 864 control subjects that demonstrated nominal association to type 2 diabetes for variants at the *SLC30A8*, *HHEX*, *CDKAL1*, *CDKN2B*, and *FTO* genes with similar ORs (1.19–1.46) compared with our data (17). The lack of association at *IGF2BP2* in their study was partly due to the smaller sample size. Meta-analyses of the Japanese and our data confirmed the significant associations to type 2 diabetes in all seven genes (Supplementary Fig. 2). It is of note that different ascertainment criteria were used in the present three populations. These differences in phenotypes and environmental exposure and the use of the same statistics for both matched and unmatched samples may bias the estimation of the actual effect size in the general population. For

TABLE 3
Associations of seven genes with metabolic traits in the combined Chinese and Korean control samples

Trait	n	β (95% CI)†	P value	$P_{empirical}$ value	β (95% CI)†	P value	$P_{empirical}$ value
		IGF2BP2: rs4402960 (T/G)*			*CDKAL1*: rs7756992 (G/A)*		
BMI (kg/m^2)	3,667	−0.022 (−0.074 to 0.029)	0.394	0.969	−0.014 (−0.060 to 0.031)	0.532	0.996
Fasting glucose (mmol/l)	3,678	0.008 (−0.044 to 0.060)	0.763	1.000	0.030 (−0.015 to 0.075)	0.196	0.775
Glucose at 120 min (mmol/l)	1,950	−0.015 (−0.086 to 0.056)	0.671	1.000	−0.042 (−0.105 to 0.021)	0.190	0.776
Fasting insulin (pmol/l)	2,662	0.049 (−0.011 to 0.109)	0.111	0.563	−0.014 (−0.068 to 0.040)	0.609	0.998
Insulin at 120 min (pmol/l)	1,947	0.006 (−0.065 to 0.077)	0.868	1.000	−0.011 (−0.073 to 0.052)	0.739	1.000
HOMA-IR	2,662	0.052 (−0.008 to 0.112)	0.090	0.479	−0.011 (−0.064 to 0.043)	0.698	1.000
HOMA-β	2,662	0.026 (−0.035 to 0.086)	0.406	0.976	−0.014 (−0.068 to 0.039)	0.600	0.998
		SLC30A8: rs13266634 (C/T)*			*CDKN2A/B*: rs10811661 (T/C)*		
BMI (kg/m^2)		0.010 (−0.036 to 0.057)	0.662	1.000	−0.016 (−0.062 to 0.029)	0.483	0.992
Fasting glucose (mmol/l)		0.055 (0.008–0.102)	0.023	0.139	0.034 (−0.012 to 0.08)	0.152	0.673
Glucose at 120 min (mmol/l)		0.046 (−0.019 to 0.111)	0.162	0.718	0.017 (−0.046 to 0.08)	0.603	0.998
Fasting insulin (pmol/l)		−0.030 (−0.085 to 0.026)	0.291	0.909	−0.002 (−0.055 to 0.052)	0.947	1.000
Insulin at 120 min (pmol/l)		0.054 (−0.010 to 0.119)	0.100	0.521	−0.023 (−0.086 to 0.040)	0.476	0.990
HOMA-IR		−0.022 (−0.077 to 0.034)	0.443	0.983	0.00002 (−0.05352 to 0.05356)	0.999	1.000
HOMA-β		−0.052 (−0.107 to 0.004)	0.067	0.389	−0.011 (−0.065 to 0.043)	0.695	1.000
		HHEX: rs7923837 (G/A)*			*TCF7L2*: rs7903146 (T/C)*		
BMI (kg/m^2)		−0.033 (−0.090 to 0.024)	0.259	0.878	0.015 (−0.133 to 0.162)	0.846	1.000
Fasting glucose (mmol/l)		0.025 (−0.032 to 0.082)	0.393	0.968	0.051 (−0.096 to 0.199)	0.494	0.991
Glucose at 120 min (mmol/l)		0.013 (−0.064 to 0.089)	0.748	1.000	−0.090 (−0.29 to 0.110)	0.377	0.967
Fasting insulin (pmol/l)		0.005 (−0.061 to 0.071)	0.881	1.000	0.052 (−0.123 to 0.226)	0.560	0.996
Insulin at 120 min (pmol/l)		−0.053 (−0.130 to 0.023)	0.174	0.744	−0.211 (−0.411 to 0.012)	0.038	0.230
HOMA-IR		0.003 (−0.064 to 0.069)	0.932	1.000	0.056 (−0.119 to 0.230)	0.533	0.996
HOMA-β		0.017 (−0.049 to 0.084)	0.606	0.998	0.032 (−0.143 to 0.206)	0.722	1.000
		FTO: rs8050136 (A/C)*					
BMI (kg/m^2)		0.094 (0.024–0.164)	0.008	0.057			
Fasting glucose (mmol/l)		−0.004 (−0.074 to 0.066)	0.910	1.000			
Glucose at 120 min (mmol/l)		0.024 (−0.072 to 0.120)	0.621	0.999			
Fasting insulin (pmol/l)		−0.011 (−0.093 to 0.071)	0.786	1.000			
Insulin at 120 min (pmol/l)		0.034 (−0.063 to 0.131)	0.491	0.992			
HOMA-IR		−0.007 (−0.089 to 0.075)	0.871	1.000			
HOMA-β		−0.011 (−0.093 to 0.071)	0.798	1.000			

*Risk alleles/non-risk alleles are indicated in the parentheses as defined according to Table 2. †Analyses were performed by combining Z scores of age- and sex-adjusted metabolic traits in the control subjects of four populations separately and then analyzed for association by linear regression. β values, 95% CI, and asymptotic P values (t statistic) are shown. β value represents the difference of Z score in the trait value associated with each copy of the risk allele.

example, the Hong Kong population consisted of young-onset diabetic patients who may be contaminated by monogenic diabetes, whereas some adolescent control subjects may develop diabetes in the future. Removal of these young case and control subjects (Supplementary Table 6) resulted in similar effect sizes in both the Hong Kong and combined samples compared with Table 2.

In this study, we also confirmed the association of *FTO* with obesity, which indirectly modulates type 2 diabetes risk as found in Europeans (8,12,13). Interestingly, both the Japanese study (17) and a Chinese study (n = 3,210) (27) failed to demonstrate association of *FTO* (rs8050136) with obesity or BMI. The discrepancy might be due to population-specific bias and/or insufficient power. Our meta-analysis demonstrated significant association of *FTO* (AC+AA vs. CC) with BMI in Asians, although their risk allele frequency and effect size were lower compared with Europeans.

We were unable to demonstrate association of any genes with insulin secretion capacity in nondiabetic subjects as assessed by HOMA-β index, in contrast with the significant findings at *CDKAL1* (rs7756992) and *CDKN2A/B* (rs10811661) in Japanese subjects (17). HOMA-β index is a less sensitive surrogate for β-cell function compared with insulinogenic index derived from OGTT or hyperglycemic clamp. This will compromise the study power, which could be further reduced by the relatively low minor allele frequency in Asians for some of the genes, such as *TCF7L2*.

Europeans and Asians are different in their environmental risk profiles, body composition, and genetic backgrounds. In particular, Asians are at risk for type 2 diabetes at a lower level of obesity, partly due to their increased predisposition to visceral adiposity (29) and reduced pancreatic β-cell function (30). In the meta-analyses, *TCF7L2* rs7903146 showed the strongest effect (OR 1.44) in both Europeans and Asians. Moreover, the effect sizes of most risk alleles are similar in the two populations except for *CDKAL1* rs7756992 (Table 4; Supplementary Fig. 2). In addition to the consistent

TABLE 4
Meta-analysis of seven genes for type 2 diabetes association in European and Asian populations

				Europeans*			Asians†			Europeans versus Asians	All populations‡
Gene	Chr	SNP	Risk/non-risk alleles	Control risk AF	OR (95% CI)	AR (%)	Control risk AF	OR (95% CI)	AR (%)	*P* for heterogeneity of OR	OR (95% CI)
Maximum *n*					55,826			8,447			64,273
Case/control subjects					21,733/34,093			3,905/4,542			25,638/38,635
IGF2BP2	3	rs4402960	T/G	0.30	1.14 (1.11–1.18)	8.2	0.27	1.12 (1.05–1.20)	6.5	0.653	1.14 (1.11–1.17)
CDKAL1	6	rs7756992	G/A	0.29	1.14 (1.11–1.17)	7.9	0.50	1.26 (1.19–1.34)	21.6	0.003	1.16 (1.13–1.19)
SLC30A8	8	rs13266634	C/T	0.67	1.16 (1.13–1.20)	18.6	0.56	1.13 (1.07–1.21)	13.5	0.501	1.16 (1.13–1.19)
CDKN2A/B	9	rs10811661	T/C	0.84	1.19 (1.14–1.25)	25.8	0.55	1.27 (1.20–1.36)	24.5	0.130	1.22 (1.18–1.26)
HHEX	10	rs7923837	G/A	0.60	1.23 (1.16–1.30)	22.5	0.20	1.25 (1.16–1.34)	9.2	0.722	1.23 (1.18–1.29)
TCF7L2	10	rs7903146	T/C	0.27	1.44 (1.40–1.49)	20.2	0.03	1.44 (1.21–1.72)	2.2	1.000	1.44 (1.40–1.49)
FTO	16	rs8050136	A/C	0.39	1.11 (1.08–1.15)	8.3	0.14	1.16 (1.07–1.27)	4.4	0.375	1.12 (1.08–1.15)

AF, allele frequency; AR, attributable risk. *Meta-analysis in Europeans was performed by fixed effects Cochran-Mantel-Haenszel test based on available SNPs in all European populations reported in the five genome-wide association studies. The SNPs included from the French study were rs13266634, rs7923837, and rs7903146 (5). The SNPs included from the Icelandic study were rs7756992, rs13266634, rs7923837, and rs7903146 (6). The SNPs included from the DGI, FUSION, and WTCCC studies were rs4402960, rs7754840, rs13266634, rs10811661, rs7903146/rs7901695, and rs8050136 (3,4,8). DerSimonian and Laird random effects OR (95% CI) for SNPs with heterogeneous between-group effects were 1.14 (1.09–1.20) for rs7756992, 1.17 (1.10–1.23) for rs13266634, 1.44 (1.30–1.59) for rs7903146, and 1.12 (1.00–1.26) for rs8050136. †Meta-analysis from this study and Horikoshi et al. (17). DerSimonian and Laird random effects OR (95% CI) for SNPs with heterogeneous between-group effects was 1.29 (1.16–1.43) for rs10811661. ‡Meta-analysis by combining European and Asian data.

association of *PPARG* Pro12Ala (ORs for Ala allele 1.14 and 1.76, respectively) and *KCNJ11* Glu23Lys (OR for Lys allele 1.14 and 1.23, respectively) polymorphisms to type 2 diabetes in both Europeans (3,4,8) and Asians (31,32), many of these genes are believed to play important roles in insulin secretion (3,6,10,33). This is in keeping with the prevailing view that abnormalities in β-cell function play a critical role in defining the risk and development of type 2 diabetes in different populations (34). On the other hand, ethnic differences in risk allele frequencies for genes, such as *CDKAL1*, *CDKN2A/B*, *HHEX*, *TCF7L2*, and *FTO*, may lead to differences in attributable risks (e.g., 7.9 vs. 21.6% for *CDKAL1*, 22.5 vs. 9.2% for *HHEX*, and 20.2 vs. 2.2% for *TCF7L2*, in Europeans vs. Asians, respectively) and thus alter their impacts on different populations (Table 4). Our previous work and that of others suggest the presence of additional risk loci at *TCF7L2* for type 2 diabetes in Chinese compared with Europeans (35,36). Given the differences in linkage disequilibrium pattern and risk allele frequencies, it will be valuable to further examine these genes thoroughly to search for population-specific and/or shared culprit disease loci and the associated phenotypes in different ethnic groups.

ACKNOWLEDGMENTS

The Hong Kong study was supported by the Research Grant Council Central Allocation Scheme (CUHK 1/04C) and the Chinese University of Hong Kong Direct Grant (2006.1.041). The Korea SNUH study was supported by a grant from the Korea Health 21 R&D Project, Ministry of Health & Welfare, Republic of Korea (00-PJ3-PG6-GN07-001). The KHGS study work was supported by the intramural grant and the extramural grant of the National Institute of Health, Korea (2001: 2003-347-6111-221, 2004: 347-6111-213, and 2005: 347-24002-440-215).

We thank all study subjects participating in these three studies. For the Hong Kong study, we thank Cherry Chiu and Dr. Ying Wang for recruitment of study subjects and Lunan Chow, Kevin Yu, and Patty Tse for computing and laboratory support. We thank the Centre for Clinical Trials and the Information Technology Services Centre for computing resources support. We thank all nursing and medical staff at the Prince of Wales Hospital Diabetes and Endocrine Centre for their dedication and professionalism. For the Korea SNUH study, we thank In Suk Ha and Hyun Jung Lim for recruitment of study subjects and Mi Ok Kang for laboratory support. We thank all the staff at the Genome Research Center for Diabetes and Endocrine Disease at SNUH for their dedication and professionalism. For the KHGS study, we thank Dr. Younjhin Ahn for epidemiological study design and Seung Hun Cha, Hye Ree Han, and Min Hyung Ryu for laboratory support. We thank all staff at the Center for Clinical Epidemiology, Ajou University Medical Center for their dedication for the project.

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