Replication of Genome-Wide Association Studies of Type 2 Diabetes Susceptibility in Japan

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Background: In Europeans and populations of European origin, several groups have recently identified novel type 2 diabetes susceptibility genes, including *FTO*, *SLC30A8*, *HHEX*, *CDKAL1*, *CDKN2B*, and *IGF2BP2*, none of which were in the list of functional candidates.

Objective and Design: The aim of this study was to replicate in a Japanese population previously identified associations of single nucleotide polymorphisms (SNPs) within 10 candidate loci with type 2 diabetes using a relatively large sample size: 1921 subjects with type 2 diabetes and 1622 normal controls.

Results: A total of 15 SNPs were genotyped. Eight SNPs in five loci were found to be associated with type 2 diabetes: rs3802177 [odds ratio (OR) = 1.16 (95% confidence interval (CI) 1.05–1.27); $P = 4.5 \times 10^{-3}$] in *SLC30A8*; rs1111875 [OR = 1.27 (95% CI 1.14–1.40); $P = 1.4 \times 10^{-5}$] and rs7923837 [OR = 1.27 (95% CI 1.13–1.43); $P = 1.0 \times 10^{-4}$] in *HHEX*; rs10811661 [OR = 1.27 (95% CI 1.15–1.40); $P = 1.9 \times 10^{-6}$] in *CDKN2B*; rs4402960 [OR = 1.23 (95% CI 1.11–1.36); $P = 8.1 \times 10^{-5}$] and rs1470579 [OR = 1.18 (95% CI 1.07–1.31); $P = 8.3 \times 10^{-4}$] in *IGF2BP2*; and rs7754840 [OR = 1.28 (95% CI 1.17–1.41); $P = 4.5 \times 10^{-7}$] and rs7756992 [OR = 1.27 (95% CI 1.15–1.40); $P = 9.8 \times 10^{-7}$] in *CDKAL1*. The first and second strongest associations were found at variants in *CDKAL1 and CDKN2B*, both of which are involved in the regenerative capacity of pancreatic β-cells.

Conclusion: Some of these variants represent common type 2 diabetes-susceptibility genes in both Japanese and Europeans. (***J Clin Endocrinol Metab* 93: 3136–3141, 2008**)

Type 2 diabetes is a complex disease with several genes and environmental factors involved in onset and development. To date, a number of genes have been reported to be associated with type 2 diabetes. Most of these were investigated because of their assumed relevance to the pathogenesis of type 2 diabetes based on their functions. However, because the pathogenesis of

0021-972X/08/$15.00/0

Printed in U.S.A.

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doi: 10.1210/jc.2008-0452 Received February 27, 2008. Accepted May 2, 2008.

First Published Online May 13, 2008

Abbreviations: BMI, Body mass index; *CDKAL1*, cyclin-dependent kinase inhibitor 5 regulatory subunit associated protein 1-like 1 gene; *CDKN2B*, cyclin-dependent kinase inhibitor 2B gene; CI, confidence interval; *EXT2*, exostosin 2; *FTO*, fat mass and obesity associated gene; *GCKR*, glucokinase regulatory protein gene; *HHEX*, hematopoietically expressed homeobox gene; HOMA, homeostasis model assessment; HOMA-β, homeostasis model assessment of β-cell function; HOMA-IR, homeostasis model assessment of insulin resistance; *IGF2BP2*, IGF2 mRNA binding protein 2 gene; LD, linkage disequilibrium; OR, odds ratio; *SLC30A8*, zinc transporter gene; SNP, single nucleotide polymorphism; TG, triglyceride.

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type 2 diabetes is yet to be elucidated completely, the candidate-gene approach is limited in power to detect novel disease-susceptibility genes. A strongly associated type 2 diabetes gene, transcription factor 7-like 2, has been identified by a genome-wide linkage study (1). Several groups confirmed a significant association between type 2 diabetes and this gene in various populations, with some noteworthy exceptions (2–7). Genome-wide association studies using 300,000–500,000 single nucleotide polymorphisms (SNPs) and high throughput technology overcome the limitation of function-based investigation, and novel susceptibility genes for type 2 diabetes, including zinc transporter (*SLC30A8*), hematopoietically expressed homeobox (*HHEX*), cyclin-dependent kinase inhibitor 2B (*CDKN2B*), IGF2 mRNA binding protein 2 (*IGF2BP2*), and CDK5 regulatory subunit associated protein 1-like 1 (*CDKAL1*), have recently been identified. In addition, the fat mass and obesity associated gene (*FTO*) and glucokinase regulatory protein gene (*GCKR*) were associated with body mass index (BMI) and serum triglyceride (TG) level, respectively (8–13). All of these proven genes for type 2 diabetes have been reproducibly associated in multiple studies (14). Meanwhile, exostosin 2 (*EXT2*), *LOC387761* (11), and an intergenic signal (rs9300039) (9) were identified in a single study and have not been replicated. However, most of the populations analyzed were of European ancestry, except in the case of *CDKAL1*, which was replicated in subjects from Hong-Kong. To distinguish variants that are common and reproducible susceptibility genes, it is important to replicate the associations of candidate SNPs with type 2 diabetes in various ethnic groups. In this study we examined the association of recently identified risk SNPs in 10 candidate loci with type 2 diabetes in a relatively large sample set of Japanese subjects.

Subjects and Methods

Subjects

Three sample sets were involved. The Kobe set and the Gunma set subjects were recruited from hospitals in Hyogo and Gunma prefecture, respectively. The Consortium set subjects were recruited from seven districts in Japan by the Study Group of the Millennium Genome Project for Diabetes Mellitus. The inclusion criteria for normal, control subjects of these three sets were as follows: 1) older than 60 yr, 2) glycosylated hemoglobin A_{1c} values less than 5.8%, and 3) no past history of type 2 diabetes. Type 2 diabetes was diagnosed in accordance with World Health Organization criteria. Other forms of diabetes were excluded based on the clinical data. The clinical and laboratory characteristics of the study subjects are shown in supplemental Table 1, which is published as supplemental data on The Endocrine Society's Journals Online web site at http://jcem.endojournals.org. Written, informed consent was obtained from all participants. This study was approved by the ethics committee of each participating institute (6).

Genotyping

There were 15 SNPs genotyped using TaqMan SNP Genotyping Assays (Applied Biosystems, Foster City, CA). These SNPs were selected based on previous reports (8–13) and HapMap linkage disequilibrium (LD) data of Japanese. Departures from Hardy Weinberg Equilibrium were defined as $P < 0.001$ in cases and controls (11). Because SNP rs13266634 in *SLC30A8* was deviated from Hardy Weinberg Equilibrium, SNP rs3802177 in the same gene, which is in strong LD with rs13266634 ($r^2 = 0.96$, HapMap LD data of Japanese), was also examined. The genotyping success rate in the three sample sets was more than 96%. The genotypes determined by TaqMan methods were identical to those determined by direct sequencing for 48 samples. The risk allele of each SNP is shown in supplemental Table 2.

Clinical assessment

The clinical profile of each subject was directly determined at entry. Association studies were performed between the candidate SNPs and BMI, homeostasis model assessment (HOMA) [HOMA of insulin resistance (HOMA-IR) and HOMA of β-cell function (HOMA-β)], or serum TG level. Subjects who had not been treated with insulin were evaluated for HOMA-IR and HOMA-β. Data are expressed as means ± SD.

Statistical analysis

The differences in SNPs between type 2 diabetic and nondiabetic subjects were compared using χ^2 test and multiple logistic regression analysis under additive, dominant, and recessive models for SNPs. The Cochran-Armitage trend test was also performed with the additive model. There was no heterogeneity among the samples in regard to the recruiting districts. We considered statistical significance at P values less than 0.0033 (0.05/15) in the association study for SNPs after Bonferroni correction. The relation of the variants in these genes with BMI, HOMA-IR, HOMA-β, and TG was assessed by ANOVA for each SNP. The HOMA-IR, HOMA-β, and TG data were log transformed for normality. Statistical analysis was performed with the StatView program (version 5.0-J; SAS Institute Inc., Cary, NC). LD analysis was performed with Haploview (http://www.broad.mit.edu/personal/jcbarret/haploview).

Results

There were 15 SNPs from 10 candidate loci examined for association with type 2 diabetes with a criterion of significance of P value less than 0.05/15 = 0.0033 after Bonferroni adjustment. Eight SNPs in five loci, *SLC30A8* (rs3802177), *HHEX* (rs1111875, rs7923837), *CDKN2B* (rs10811661), *IGF2BP2* (rs4402960, rs1470579), and *CDKAL1* (rs7754840, rs7756992), were found to be associated with the occurrence of type 2 diabetes (Tables 1 and 2). The P values of association for *CDKN2B* (rs10811661) and *CDKAL1* (rs7754840 and rs7756992) were about 1.9×10^{-6}, 4.5×10^{-7}, and 9.8×10^{-7}, respectively. The next strongest association was found for *IGF2BP2* (rs4402960 and rs1470579) and *HHEX* (rs1111875 and rs7923837) at a P value of 10^{-4}–10^{-5}. SNP rs3802177 of *SLC30A8* showed a nominal association, which disappeared after adjustment for age, sex, and BMI. No association of the other SNPs with type 2 diabetes was detected.

Association studies were also performed between *FTO* and BMI and *GCKR* and serum TG level using the samples with serum data according to previous reports. A nominal association of *GCKR* (rs780094) with serum TG level both in case and control subjects was found in our samples, as previously reported in Caucasians (10). In control subjects the mean values of serum TG were 1.07 ± 0.53, 1.13 ± 0.49, and 1.18 ± 0.55 mmol/liter for CC, CT, and TT genotype, respectively ($P = 0.097$). In cases, these values were 1.32 ± 0.73, 1.43 ± 1.57, and 1.56 ± 1.05 mmol/liter for CC, CT, and TT genotype, respectively ($P = 0.063$). Association of the SNP of *FTO* (rs9939609) with BMI

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TABLE 1. Association results between 15 SNPs in 10 candidate loci and type 2 diabetes in Japanese

Gene	SNP ID	Genotype T2DM			Genotype CONT			RAF		*P* value	Armitage trend	*P* value[a]	OR	95% CI		RAF-C	OR -C
		RR	Rr	rr	RR	Rr	rr	T2DM	CONT					Upper	Lower		
SLC30A8	rs13266634	690	806	334	522	725	327	0.60	0.56	3.2×10^{-3}	4.5×10^{-3}	0.17	1.16	1.05	1.27	0.65	1.12
SLC30A8	rs3802177	649	885	306	473	808	291	0.59	0.56	3.2×10^{-3}	3.0×10^{-3}	0.065	1.16	1.05	1.27		
HHEX	rs1111875	212	784	852	132	603	828	0.33	0.28	9.6×10^{-6}	1.4×10^{-5}	8.4×10^{-5}	1.27	1.14	1.40	0.53	1.13
HHEX	rs7923837	98	633	1113	60	467	1049	0.22	0.19	8.8×10^{-5}	1.0×10^{-4}	6.7×10^{-3}	1.27	1.13	1.43	0.62	1.22
LOC387761	rs7480010	1226	556	68	1018	481	67	0.81	0.80	0.33[a]	0.33[a]	0.29	1.06	0.94	1.20		
EXT2	rs3740878	260	842	731	211	738	629	0.37	0.37	0.73[a]	0.74[a]	0.63	1.02	0.92	1.12		
CDKN2B	rs10811661	683	891	283	486	770	326	0.61	0.55	1.7×10^{-6}	1.9×10^{-6}	5.8×10^{-6}	1.27	1.15	1.40	0.83	1.20
CDKN2B	rs564398	1342	482	47	1122	416	41	0.85	0.84	0.67[a]	0.67[a]	0.65	1.03	0.90	1.17	0.56	1.12
GCKR	rs7800944	421	903	534	312	782	492	0.47	0.44	0.029[a]	0.030[a]	0.017	1.11	1.01	1.22		
Inter gene	rs9300039	1068	684	105	903	565	111	0.76	0.75	0.41[a]	0.42[a]	0.15	1.05	0.94	1.17		
IGF2BP2	rs4402960	230	835	787	143	675	759	0.35	0.30	7.9×10^{-5}	8.1×10^{-5}	9.4×10^{-4}	1.23	1.11	1.36	0.29	1.14
IGF2BP2	rs1470579	260	874	738	165	735	694	0.37	0.33	9.0×10^{-4}	8.3×10^{-4}	2.8×10^{-3}	1.18	1.07	1.31	0.30	1.17
CDKAL1	rs7754840	446	881	543	262	781	538	0.47	0.41	3.2×10^{-7}	4.5×10^{-7}	3.5×10^{-7}	1.28	1.17	1.41	0.31	1.12
CDKAL1	rs7756992	537	876	442	330	818	438	0.53	0.47	8.0×10^{-7}	9.8×10^{-7}	3.9×10^{-6}	1.27	1.15	1.40	0.26	1.20
FTO	rs9939609	88	596	1165	63	520	995	0.21	0.20	0.68[a]	0.68[a]	0.74	1.03	0.91	1.15		

ORs, 95% CIs, and *P* values are given for 15 SNPs identified in French, decode, Diabetes Genetics Initiative, Wellcome Trust Case Control Consortium, and Finland-United States Investigation of Noninsulin-Dependent Diabetes Mellitus Genetics studies. SNPs are shown with the risk allele (R) and risk allele frequency (RAF) and the exact count of each genotype in type 2 diabetic (T2DM) patients and controls (CONT). Risk allele-specific ORs and *P* values were calculated using an additive genetic model that in logistic regression is multiplicative on the OR scale. $r^2 = 0.83$ (rs13266634 and rs3802177), 0.22 (rs1111875 and rs7923837), 0.001 (rs10811661 and rs10811661), 0.87 (rs4402960 and rs1470579), and 0.69 (rs7754840 and rs7756992) in controls of this study. ID, Identification; OR-C, OR in Caucasians; r, nonrisk allele; RAF-C, risk allele frequency in Caucasian controls.

[a] *P* values adjusted for age, sex, and BMI.

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TABLE 2. Association results between 15 SNPs in 10 candidate loci and type 2 diabetes in Japanese

		Dominant model					Recessive model				
					95% CI					95% CI	
Gene	SNP ID	*P* value	*P* value[a]	OR	Lower	Upper	*P* value	*P* value[a]	OR	Lower	Upper
SLC30A8	rs13266634	0.063	0.24	1.17	0.99	1.39	5.8×10^{-3}	0.074	1.22	1.06	1.40
SLC30A8	rs3802177	0.15	0.36	1.14	0.95	1.36	1.3×10^{-3}	0.020	1.27	1.10	1.46
HHEX	rs1111875	6.4×10^{-5}	1.6×10^{-5}	1.32	1.15[a]	1.51	3.5×10^{-3}	0.083	1.40	1.12	1.77
HHEX	rs7923837	1.8×10^{-4}	1.9×10^{-3}	1.31	1.14[a]	1.50	0.036	0.15	1.42	1.02	1.97
LOC387761	rs7480010	0.37	0.16	1.17	0.83[a]	1.65	0.44	0.28	1.06	0.92	1.22
EXT2	rs3740878	0.99	0.66	1.00	0.87[a]	1.15	0.49	0.50	1.07	0.88	1.30
CDKN2B	rs10811661	4.0×10^{-5}	2.3×10^{-5}	1.44	1.21[a]	1.72	1.9×10^{-4}	1.8×10^{-4}	1.31	1.14	1.51
CDKN2B	rs564398	0.88	0.51	1.03	0.68[a]	1.58	0.66	0.65	1.03	0.89	1.20
GCKR	rs7800944	0.14	0.34	1.12	0.96[a]	1.29	0.033	4.2×10^{-3}	1.20	1.01	1.41
Inter gene	rs9300039	0.098	0.20	1.26	0.96[a]	1.66	0.85	0.32	1.01	0.88	1.16
IGF2BP2	rs4402960	9.5×10^{-4}	0.018	1.26	1.10[a]	1.44	1.7×10^{-3}	4.9×10^{-4}	1.42	1.14	1.77
IGF2BP2	rs1470579	0.014	0.063	1.18	1.03[a]	1.36	1.6×10^{-3}	9.2×10^{-4}	1.40	1.13	1.72
CDKAL1	rs7754840	1.6×10^{-3}	1.6×10^{-3}	1.26	1.09[a]	1.46	1.3×10^{-7}	1.5×10^{-7}	1.58	1.33	1.87
CDKAL1	rs7756992	0.01	0.022	1.22	1.05[a]	1.42	4.2×10^{-8}	7.4×10^{-7}	1.55	1.32	1.82
FTO	rs9939609	0.98	0.60	1.00	0.87[a]	1.15	0.28	0.70	1.20	0.86	1.67

ORs, 95% CIs, and *P* values under a dominant or recessive model of each risk allele are given for 15 SNPs identified in French, decode, Diabetes Genetics Initiative, Wellcome Trust Case Control Consortium, and Finland-United States Investigation of Noninsulin-Dependent Diabetes Mellitus Genetics studies. ID, Identification.

[a] *P* values adjusted for age, sex, and BMI.

was found only in control subjects. In addition, subjects with the risk A allele tended to show a larger BMI, as previously reported in Caucasians (13), although it did not reach the level of statistical significance. The mean values of BMI were 22.4 ± 3.2 (TT) and 22.7 ± 3.1 kg/m^2 (AA + AT) for controls ($P = 0.051$). On the other hand, these values were 23.6 ± 3.4 (TT) and 23.8 ± 3.8 kg/m^2 (AA + AT) for cases ($P = 0.306$). Although *HHEX*, *CDKN2B*, *IGF2BP2*, and *CDKAL1* were associated with pancreatic β-cell function in recent reports (15–17), we failed to detect an association with HOMA-β in this study. There was also no evidence of association between HOMA-IR and the risk alleles of these genes.

Discussion

Recent reports have revealed novel type 2 diabetes-susceptibility genes such as *SLC30A8*, *HHEX*, *CDKN2B*, *IGF2BP2*, and *CDKAL1* in the European population (8, 9, 11, 12). In addition, *FTO* and *GCKR* were associated with BMI and serum TG level, respectively (10, 13). In this study we confirmed that all of the proven genes found in Caucasians are replicated in Japanese. The strongest association by *P* value at the 10^{-6}–10^{-7} level was found at *CDKN2B* (rs10811661) and *CDKAL1* (rs7754840, rs7756992), followed by *HHEX* (rs1111875, rs7923837) and *IGF2BP2* (rs4402960, rs1470579). The odds ratio (OR) values of the first three SNPs were 1.27, 1.28, and 1.27, respectively, an even stronger association than that found in the original genome-wide association study in Europeans (10, 14). There were considerable differences in the frequencies of the risk alleles (Table 1), resulting in difficulty of replication due to decreased power of the study in addition to that due to population difference. According to the previous report in Japanese, the SNPs in *HHEX* showed the strongest association with type 2 diabetes, although the frequencies of risk alleles of SNPs in *HHEX* were even lower in the Japanese samples than European populations (15, 18). The previous report showed significant association with both SNPs in *HHEX* but not with the SNPs in *IGF2BP2* (15). This discrepancy cannot be explained by the small sample number because the risk allele frequencies of *IGF2BP2* are higher in Japanese than Europeans, in contrast to those of *HHEX*.

Although the previous study did not detect association of *IGF2BP2* with type 2 diabetes (15), the gene was detected as a diabetes-susceptibility gene in the present study. The absence of significant association in the previous study may be due to the lack of power deriving mainly from the small sample number. Recently, another study in Japanese has reported that rs4402960 in *IGF2BP2* showed the strongest association with type 2 diabetes, using a larger number of samples (19). The present study had 86% power to detect an OR of 1.20 when the frequency of a risk allele was 35% (rs4402960) and the *P* value was less than 0.0033. However, it is important to note that association study is dependent on discrimination of case and control subjects. It also has been reported that lifestyle changes can reduce the risk of type 2 diabetes, even in individuals carrying the type 2 diabetes-susceptibility variant of *TCF7L2* (20).

CDKAL1 and *CDKN2B* showed a nominal association with type 2 diabetes in a previous report in Japanese (15, 19). SNP rs7756992 in *CDKAL1* has been associated with type 2 diabetes in Han Chinese individuals from Hong Kong (12). A strong association between this SNP and type 2 diabetes [OR = 1.27 (95% confidence interval (CI) 1.15–1.40); $P = 9.8 \times 10^{-7}$] was detected in this study. Because type 2 diabetes in Asians is characterized primarily by β-cell dysfunction, these two genes might well be involved in transduction of glucose toxicity or regenerative capacity of pancreatic β-cells and, thus, are possible susceptibility genes for Japanese type 2 diabetes.

We found a nominal association of *GCKR* (rs780094) with the serum TG level both in case and control subjects, as previously reported in Caucasians (10). A nominal association of the

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SNP of *FTO* (rs9939609) with BMI was found only in control subjects. In addition, the subjects with risk A allele showed somewhat larger BMI values, as has been reported in Caucasians (13). *FTO* was identified as a type 2 diabetes-susceptibility variant that predisposes to diabetes in the United Kingdom population through its effect on BMI. The lack of association between BMI and the *FTO* SNPs in Japanese could be due to the fact that our samples were from a less obese population.

In conclusion, we were able to replicate a significant association with the largest number of samples so far in Japanese between type 2 diabetes and SNPs in *SLC30A*, *HHEX*, *CDKN2B*, *IGF2BP2*, and *CDKAL1*, which suggests that these variants represent common type 2 diabetes-susceptibility genes in both Japanese and Europeans. Further investigation is required to identify the most likely functional variants.

Acknowledgments

We thank Drs. Hideichi Makino, Kishio Nanjo, Takashi Kadowaki, Kazuo Hara, Haruhiko Osawa, Hiroto Furuta, Sumio Sugano, and Shoji Tsuji for their contributions and helpful discussion throughout the project.

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This work was supported by Grant-in-Aid for Scientific Research on Priority Areas (C), "Medical Genome Science (Millennium Genome Project)," "Applied Genomics," and "Comprehensive Genomics" by the Ministry of Education, Culture, Sports, Science, and Technology of Japan, and in part by a New Energy and Industrial Technology Development Organization grant (to Y.Ho.).

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Disclosure Statement: The authors have nothing to disclose.

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