Association of *CDKAL1*, *IGF2BP2*, *CDKN2A/B*, *HHEX*, *SLC30A8*, and *KCNJ11* With Susceptibility to Type 2 Diabetes in a Japanese Population

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OBJECTIVE—Recently, several genes have been shown to be associated with an increased risk of type 2 diabetes by genome-wide association studies in white populations. To further investigate the involvement of these polymorphisms in conferring susceptibility to type 2 diabetes, we examined the association of 14 single nucleotide polymorphisms (SNPs) within 11 candidate loci with type 2 diabetes in a Japanese population.

RESEARCH DESIGN AND METHODS—We analyzed 14 SNPs (rs4402960 in *IGF2BP2*, rs10811661 in *CDKN2A/B*, rs1111875 and rs7923837 in *HHEX*, rs13266634 in *SLC30A8*, rs1113132 and rs11037909 in *EXT2*, rs9939609 and rs8050136 in *FTO*, rs7756992 in *CDKAL1*, rs1801282 in *PPARG* Pro12Ara, rs5219 in *KCNJ11* Glu23Lys, rs7480010 in *LOC387761*, and rs9300039 in Ch11) in 1,630 Japanese subjects with type 2 diabetes and in 1,064 control subjects by using an invader assay or a TaqMan assay.

RESULTS—Among the 11 loci examined, 6 were significantly associated with type 2 diabetes in our population by a logistic regression analysis, similar to previously reported results (rs4402960, $P = 0.00009$; rs10811661, $P = 0.0024$; rs5219, $P = 0.0034$; rs1111875, $P = 0.0064$; rs13266634, $P = 0.0073$; rs7756992, $P = 0.0363$). In this population, the remaining five loci were not significantly associated with type 2 diabetes. In addition, we identified significant association of the SNPs in FTO gene with BMI in the control subjects.

CONCLUSIONS—We have identified 6 of the 11 loci that were identified by genome-wide association studies in white populations, and these loci are considered strong candidates for type 2 diabetes susceptibility across different ethnicities. ***Diabetes* 57: 791–795, 2008**

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SNP, single nucleotide polymorphism.

Type 2 diabetes affects >200 million individuals worldwide, and its prevalence continues to increase in many countries, including Japan. Although the precise mechanisms underlying the development and progression of type 2 diabetes have not been elucidated, a combination of multiple genetic and/or environmental factors is considered to contribute to the pathogenesis of the disease (1).

Recently, genome-wide association studies conducted by several independent European and American groups have identified multiple susceptible variants in white populations including *TCF7L2* variants, which had been originally identified by a genome-wide linkage study (2) and confirmed in several replication studies across different ethnicities (3–7). Sladek et al. (8) additionally identified the solute carrier family 30 member 8 (*SLC30A8*), homeobox hematopoietically expressed (*HHEX*), *LOC387761*, and exostosin 2 (*EXT2*) genes, and the WTCCC/UKT2D, FUSION, and DGI study groups identified the insulin-like growth factor 2 mRNA binding protein 2 (*IGF2BP2*), cyclin-dependent kinase 5 regulatory subunit associated protein 1–like 1 (*CDKAL1*), cyclin-dependent kinase inhibitor-2A/B (*CDKN2A/B*), fat mass– and obesity-associated (*FTO*) genes, and the rs9300039 locus as additional loci that were strongly associated with the susceptibility to this disease (9–11). The latter study also confirmed the association between the susceptibility to type 2 diabetes and the peroxisome proliferators–activated receptor-γ (*PPARG*) Pro12Ala or potassium inwardly rectifying channel subfamily J member 11 (*KCNJ11*) Glu23Lys polymorphism that had already been reported as strong candidates. The associations among single nucleotide polymorphisms (SNPs) within *CDKAL1* and *SLC30A8* were also identified by a genome-wide association study conducted for the Icelandic population (12).

These additional loci are also considered to be strong candidates for conferring susceptibility to type 2 diabetes in white populations. However, the contributions of these new loci should be evaluated in other ethnic populations, because it is well known that there are significant differences in the frequencies of some genetic variations among different ethnic groups (6,7,13).

The aim of the present study is to determine whether the variations identified by the genome-wide association studies in white populations are associated with the susceptibility to type 2 diabetes in a Japanese population.

TABLE 1
Clinical characteristics of the subjects

	Type 2 diabetic subjects	Control subjects	*P**
n	1,630	1,064	
Sex (M/F)	978/652	638/426	0.9845
Age (years)	61.5 ± 11.6	45.5 ± 9.5	<0.0001
BMI (kg/m^2)	23.7 ± 3.9	22.9 ± 3.0	<0.0001
FPG (mmol/l)	9.1 ± 3.5	5.1 ± 0.5	<0.0001
A1C (%)	7.4 ± 1.6	4.7 ± 0.4	<0.0001
Duration of diabetes (years)	11.5 ± 13.9	—	—

Data are means ± SE unless otherwise indicated. *Pearson's χ^2 test.

RESEARCH DESIGN AND METHODS

Subject and DNA preparation. DNA samples were obtained from the peripheral blood samples of 1,630 type 2 diabetic patients recruited from the outpatient clinic of the Shiga University of Medical Science, Kawasaki Medical School (978 men and 652 women; age 61.5 ± 11.6 years; duration of diabetes 11.5 ± 13.9 years; A1C 7.4 ± 1.6%; fasting plasma glucose 9.1 ± 3.5 mmol/l; BMI 23.7 ± 3.9 kg/m^2 [all values are expressed as means ± SD], Table 1). Diabetes was diagnosed according to the WHO criteria. Type 2 diabetes is clinically defined as a disease with gradual adult onset. Subjects who tested positive for anti-GAD antibodies and those diagnosed as mitochondrial disease (mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes [MELAS]) or maturity-onset diabetes of young (MODY) were not included in the case group. We also examined 1,064 control subjects who were enrolled from an annual health check conducted either at the Juntendo University or Keio University (Tokyo, Japan; 638 men and 426 women; age 45.5 ± 9.5 years; A1C 4.7 ± 0.4%; fasting plasma glucose 5.1 ± 0.5 mmol/l; BMI 22.9 ± 3.0 kg/m^2; Table 1).

Written informed consent was obtained from all the participants, and DNA was extracted using the standard phenol-chloroform procedure. The protocol was approved by the ethics committee of the Institute of Physical and Chemical Research (RIKEN).

Genotyping. Each SNP genotyping was performed by the TaqMan assay (Applied Biosystems, Foster City, CA) or by the multiplex-PCR invader assay as described previously (13). The success rates of these assays were >95%, and there was almost a 100% agreement between the results of genotyping and direct sequencing.

Statistical analysis. Statistical methods for determining associations and to calculate linkage disequilibrium (LD) coefficients (r^2) were described previously (14). We performed the Hardy-Weinberg equilibrium (HWE) test according to the method described by Nielsen et al. (15). Although the genotype distributions of all the SNPs were within the Hardy-Weinberg equilibrium ($P \geq 0.01$), some of them had borderline results for HWE test (rs5219 in control, rs7480010 in case, rs8050136 in case; see supplementary Table 1 at http://dx.doi.org/10.2337db07–0979). Therefore, we performed Wright's *F* statistics (16) to evaluate the difference in the population structure between our case and control groups using randomly selected 96 SNPs. The result indicated that the population structures of our case and control groups were almost the same in view of a very small F_{ST} value between the two groups (F_{ST} = 0.001556).

The differences between the case and control groups in terms of genotype distribution were analyzed using a logistic regression analysis. To test the additive model of each SNP after adjusting for sex, age, and log-transformed BMI, the analysis was performed using StatView software. In addition, χ^2 test to evaluate the additive, dominant, and recessive models of each SNP were also performed by the method of Sladek et al. (8).

The difference in the BMI according to the genotypes was analyzed using a multiple linear regression with log-transformed BMI as the dependent variable and genotype as the independent variable with sex as a covariate for log-transformed BMI (17).

RESULTS

As shown in Table 2, six SNPs within six distinct loci (rs4402960, rs10811661, rs5219, rs1111875, rs13266634, and rs7756992) were found to be significantly associated with type 2 diabetes in our Japanese population. No significant association was observed between the remaining five loci and type 2 diabetes in this population ($P \geq 0.05$; Table 2). We also evaluated the association of the 14 SNP loci with type 2 diabetes using χ^2 test by the method of Sladek et al. (8) (supplementary Table 2) and identified almost consistent results with those obtained by a logistic regression analysis even after selecting control subjects whose age was >50 years old (n = 382, supplementary Table 3). Since *FTO* variants have been reported to be associated with BMI, we also examined the association of these polymorphisms with BMI in our control subjects, and we found that the polymorphisms within *FTO* and *HHEX* were modestly associated with BMI (Table 3).

TABLE 2
Association of candidate SNP loci with type 2 diabetes

SNP	Gene	*P**	Odds ratio (95% CI)
rs4402960	*IGF2BP2*	0.00009	1.368 (1.169-1.600)
rs10811661	*CDKN2A/B*	0.0024	1.255 (1.084-1.454)
rs5219	*KCNJ11*	0.0034	1.254 (1.078-1.459)
rs1111875†	*HHEX*	0.0064	1.243 (1.063-1.453)
rs7923837†	*HHEX*	0.3773	1.083 (0.907-1.293)
rs13266634	*SLC30A8*	0.0073	1.225 (1.056-1.420)
rs7756992	*CDKAL1*	0.0363	1.164 (1.010–1.342)
rs9939609	*FTO*	0.2376	1.114 (0.931-1.332)
rs8050136	*FTO*	0.3520	1.089 (0.910–1.302)
rs1801282	*PPARG*	0.4137	0.843 (0.559-1.270)
rs7480010	*LOC387761*	0.4393	1.073 (0.898-1.281)
rs1113132	*EXT2*	0.4728	1.056 (0.910-1.225)
rs11037909	*EXT2*	0.5365	1.048 (0.903-1.216)
rs9300039	41871942‡	0.6966	1.034 (0.874-1.222)

**P* value is calculated on logistic regression with additive model (sex, age, BMI adjusted, and BMI were log transformed for the analysis); †r^2 = 0.50 (this study), 0.346 (HapMap-JPT), and 0.698 (HapMap-CEU), respectively. ‡Position on the chromosome is indicated.

TABLE 3
Association of the SNP loci with BMI in control subjects

SNP/gene	Genotype (number of subjects)/BMI*			*P*
rs9939609	TT (676)	AT (331)	AA (37)	
FTO	22.2 (21.9–22.4)	23.0 (22.7–23.4)	23.1 (22.5–23.8)	0.0271
rs8050136	CC (678)	CA (331)	AA (35)	
FTO	22.2 (22.0–22.4)	23.0 (22.7–23.3)	23.2 (22.5–23.9)	0.0436
rs7923837	AA (653)	AG (333)	GG (46)	
HHEX	22.4 (22.2–22.6)	22.5 (22.2–22.8)	22.7 (21.9–23.5)	0.032
rs1111875	TT (529)	CT (419)	CC (84)	
HHEX	22.5 (22.2–22.7)	22.5 (22.2–22.7)	22.3 (21.7–22.9)	0.05
rs5219	CC (421)	CT (509)	TT (118)	
KCNJ11 Glu23Lys	22.4 (22.1–22.7)	22.6 (22.3–22.8)	22.1 (21.6–22.6)	0.0777
rs1801282	CC (2)	CG (53)	GG (995)	
PPARG Pro12Ala	24.4	23.1 (22.4–23.9)	22.4 (22.2–22.6)	0.1039
rs11037909	CC (141)	CT (471)	TT (425)	
EXT2	22.4 (21.9–22.9)	22.7 (22.4–22.9)	22.3 (22.0–22.6)	0.1243
rs1113132	CC (143)	CG (467)	GG (427)	
EXT2	22.4 (21.9–22.9)	22.6 (22.4–22.9)	22.3 (22.0–22.6)	0.1315
rs9300039	AA (68)	AC (370)	CC (592)	
41871942†	22.7 (21.9–23.5)	22.5 (22.2–22.8)	22.4 (22.2–22.6)	0.4153
rs13266634	TT (173)	CT (491)	CC (376)	
SLC30A8	22.6 (22.1–23.1)	22.5 (22.2–22.7)	22.4 (22.2–22.7)	0.6014
rs10811661	CC (200)	CT (518)	TT (326)	
CDKN2A/B	22.3 (21.9–22.7)	22.5 (22.2–22.7)	22.5 (22.2–22.8)	0.6185
rs7480010	AA (684)	AG (317)	GG (42)	
LOC387761	22.4 (22.1–22.6)	22.8 (22.5–23.1)	22.3 (21.5–23.2)	0.7183
rs7756992	AA (289)	AG (508)	GG (236)	
CDKAL1	22.4 (22.0–22.7)	22.6 (22.4–22.9)	22.3 (22.0–22.7)	0.7985
rs4402960	GG (520)	GT (433)	TT (88)	
IGF2BP2	22.5 (22.3–22.8)	22.4 (22.1–22.7)	22.5 (21.8–23.1)	0.9313

*Data are presented as geometric means, and values for 95% CI are in parentheses; †position on the chromosome is indicated.

DISCUSSION

In the present study, we identified significant associations of SNPs within the *CDKAL1*, *IGF2BP2*, *CDKN2A/B*, *HHEX*, *SLC30A8* and *KCNJ11* genes with the susceptibility to type 2 diabetes in a Japanese population. We also found that the SNPs in the *FTO* gene and the *HHEX* gene were significantly associated with BMI in our control group.

Recent advances in human genetic research have facilitated the identification of genes conferring susceptibility to common diseases such as type 2 diabetes from across the entire human genome by using a large number of subjects, and genome-wide association studies have been conducted worldwide (8–12). Although the importance of *TCF7L2* as a susceptibility gene for type 2 diabetes has been well established, its polymorphism could account for ~20% of all cases for type 2 diabetes in white populations (2,4,5). The population-attributable risk of the *TCF7L2* polymorphism in the Japanese was ~2% because the risk allelic frequency in a previously studied Japanese population was very low (6,7). Further, many important genes for the disease remain to be identified, especially in East Asian populations.

Several groups have independently performed genome-wide association studies for type 2 diabetes in white populations (8–12). All these studies have demonstrated that the *TCF7L2* polymorphism is most strongly associated with the susceptibility to type 2 diabetes, and from a large set of replication studies, they have identified additional candidate loci also associated with the disease. The results of these genome-wide association studies are also considered highly consistent with regard to white populations. However, there are considerable differences in phenotype between Japanese (lean and less hyperinsulinemic Asian type 2 diabetes) and white (European descent) type 2 diabetes, and these differences might affect the genetic contribution of each gene to conferring susceptibility to type 2 diabetes. Therefore, the new candidates should also be evaluated in different ethnic groups because there are clear ethnic differences in terms of genetic contribution to diseases (13,18).

In the present study, we also identified the six SNPs within the *CDKAL1*, *IGF2BP2*, *CDKN2A/B*, *HHEX*, *SLC30A8*, and *KCNJ11* genes that were significantly associated with type 2 diabetes in our Japanese population. Since the risk alleles for these variations in the tested population were entirely consistent with those in white populations (8–12), the contribution of these polymorphisms to type 2 diabetes susceptibility is highly convincing across the different ethnicities, although there are considerable differences in allele frequencies between the Japanese and white populations (Table 4 and supplementary Table 4). Regarding the *HHEX* locus, only rs1111875 had significant association with type 2 diabetes in the present study, whereas both rs1111875 and rs7923837 were associated with the disease in white populations. The risk allele frequencies of SNPs in the *HHEX* gene were significantly different between our population and white populations (rs1111875 28.4 vs. 56.1%, rs7923837 20.6 vs. 60.1% in Japanese and white populations, respectively; supplementary Table 4), and there were some differences in the LD coefficients (r^2) between rs1111875 and rs7923837 among those populations (0.5 in the Japanese and 0.698 in the white population). Therefore, these dif-

TABLE 4
The comparison of risk allele frequency and population-attributable risk (PAR) between Japanese and white populations

SNP	Gene	Risk allele frequency (%)			PAR (%)	
		This study	White populations	*P**	This study	White populations†
rs4402960	*IGF2BP2*	29.3	31.3	0.1439	11.1	4.8
rs10811661	*CDKN2A/B*	56.1	84.1	2.2×10^{-183}	13.4	18.1
rs5219	*KCNJ11*	35.5	46.4	1.9×10^{-16}	9.1	5.7
rs1111875	*HHEX*	28.4	57.7	3.2×10^{-146}	7.3	19.0
rs7923837	*HHEX*	20.6	62.3	3.6×10^{-218}	—	20.0
rs13266634	*SLC30A8*	60.0	63.4	0.0097	12.5	14.6
rs7756992	*CDKAL1*	47.4	23.2	3.0×10^{-114}	7.7	6.1
rs9939609	*FTO*	19.4	38.5	1.3×10^{-19}	—	—
rs8050136	*FTO*	19.3	39.0	6.0×10^{-67}	—	—
rs1801282	*PPARG*	97.3	82.4	4.2×10^{-63}	—	14.2
rs7480010	*LOC387761*	19.1	30.1	9.5×10^{-21}	—	8.0
rs1113132	*EXT2*	63.6	73.3	1.8×10^{-16}	—	19.0
rs11037909	*EXT2*	63.6	72.9	2.6×10^{-14}	—	25.0
rs9300039	41871942‡	75.3	89.2	2.5×10^{-46}	—	30.6

*P values for χ^2 test for genotype distribution (2×3 contingency table); †combined data from WTCCC, UKRS, FUSION, French, and Icelandic studies; ‡position on the chromosome is indicated.

ferences might explain the discrepancies in the results for the association of SNPs in the *HHEX* gene with type 2 diabetes, although the possibility of insufficient study power in the present study could not be excluded.

We also found that the SNPs within *FTO* (rs9939609 and rs8050136) and *HHEX* (rs1111875 and rs7923837) were modestly associated with BMI in our control subjects (Table 3). The association of the SNPs in *FTO* with type 2 diabetes was not significant in our population (Table 2 and supplementary Tables 2 and 3). Therefore, the variations in the *FTO* gene might directly affect body weight rather than type 2 diabetes itself; this finding is also consistent with that in white populations (17,19).

Among the other four loci, the association of the Pro12Ala polymorphism in the *PPARG* gene with type 2 diabetes has been well established (20,21), and this association was also observed in Japanese populations (22,23), although we could not determine whether the association of this polymorphism with type 2 diabetes was significant. Because the frequencies of the Ala allele or its carrier (X/Ala) found in the present study (three and 6%, respectively) are consistent with those in previous studies on Japanese populations, the frequencies of the Ala allele can be considered very low in the Japanese as compared to those in white populations. Because an estimated power to detect the association of the SNP with type 2 diabetes in the present study is ~20%, the results do not appear strong enough to determine the association between the *PPARG* Pro12Ala polymorphism and type 2 diabetes.

With regard to the remaining three loci, the results for *EXT2*, *LOC387761*, and rs930039 were not always in agreement with those of the genome-wide association studies in white populations. In addition, the allele frequencies of those SNPs were also significantly different between the Japanese and the white populations (Table 4 and supplementary Table 4). Because the estimated powers of the present study were >90%, >90%, and >70% for rs1113132 (*EXT2*), rs7480010 (*LOC387761*), and rs930039, respectively, the contribution of these three loci in the Japanese populations is considered minor, if present at all; however, more replication studies are required for the precise evaluation of these loci.

In conclusion, we identified significant associations between SNPs within the *CDKAL1*, *IGF2BP2*, *CDKN2A/B*, *HHEX*, *SLC30A8*, and *KCNJ11* genes and type 2 diabetes in a Japanese population. These loci are considered strong candidates for conferring susceptibility to type 2 diabetes across different ethnicities. However, further studies are required to elucidate the association of other loci with the susceptibility to type 2 diabetes and the biological significance of these genes and gene polymorphisms.

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