Polymorphisms in the *IDE-KIF11-HHEX* Gene Locus Are Reproducibly Associated with Type 2 Diabetes in a Japanese Population

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Context: A genome-wide association study in the French population has detected that novel single-nucleotide polymorphisms (SNPs) in the *IDE-KIF11-HHEX* gene locus and the *SLC30A8* gene locus are associated with susceptibility to type 2 diabetes.

Objective: We investigated whether SNPs in these loci were associated with type 2 diabetes in Japanese.

Design: Two SNPs, rs7923837 and rs1111875, in the *IDE-KIF11-HHEX* gene locus and one SNP, rs13266634, in the *SLC30A8* gene locus were genotyped in Japanese type 2 diabetic patients (n = 405) and in nondiabetic control subjects (n = 340) using the TaqMan genotyping assay system.

Results: The G allele of rs7923837 was associated with type 2 diabetes [odds ratio 1.66, 95% confidence interval (CI) 1.28–2.15; $P = 0.00014$], following the same tendency as in the French population of the previous report. Heterozygous and homozygous carriers of the risk allele had odds ratios of 1.57 (95% CI 1.15–2.16; $P = 0.0050$) and 3.16 (95% CI 1.40–7.16; $P = 0.0038$) relative to noncarriers. Although the G allele was a major allele (66.5%) in the French population, it was a minor allele (23.8%) in Japanese. The G allele of rs1111875 was also associated with type 2 diabetes (odds ratio 1.42, 95% CI 1.13–1.78; $P = 0.0024$). Heterozygous and homozygous carriers of the risk allele had odds ratios of 1.31 (95% CI 0.97–1.77; $P = 0.0810$) and 2.40 (95% CI 1.34–4.32; $P = 0.0028$) relative to noncarriers. A significant association with type 2 diabetes was not observed for rs13266634.

Conclusions: Polymorphisms in the *IDE-KIF11-HHEX* gene locus are associated with susceptibility to type 2 diabetes across the boundary of race. **(*J Clin Endocrinol Metab* 93: 310–314, 2008)**

Type 2 diabetes is a common disease caused by a combination of impaired insulin secretion and insulin resistance. In addition to environmental factors such as habitual overeating and physical inactivity, genetic factors play an important role in the pathogenesis of type 2 diabetes. To date, it has been reproducibly reported that two missense mutations, the Pro12Ala polymorphism in the peroxisome proliferator-activated receptor-γ (*PPARG*) gene (1) and the Glu23Lys polymorphism in the potassium inwardly rectifying channel subfamily J, member 11 (*KCNJ11*) gene (2), are associated with susceptibility to type 2 diabetes. Furthermore, several linkage studies have shown that noncoding genetic variants in the calpain 10 (*CAPN10*) (3), the hepatocyte nuclear factor 4α (*HNF4A*) (4), and the transcription factor 7-like 2 (*TCF7L2*) (5) genes are associated with type 2 diabetes. The strong association between type 2 diabetes and the *TCF7L2* gene, especially, has been consistently replicated in various populations including Japanese (6). On the other hand, the risk allele frequency of the *TCF7L2* gene in Japanese is nearly one

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Abbreviations: BMI, Body mass index; CI, confidence interval; GAD, glutamic acid decarboxylase; HbA1c, glycosylated hemoglobin; LD, linkage disequilibrium; SNP, single-nucleotide polymorphism.

tenth the frequency in white populations, which suggests a genetic heterogeneity among racial groups.

Recently, Sladek *et al.* (7) identified four novel risk loci for type 2 diabetes in a genome-wide association study of the French population and reported that the statistical significances of three single-nucleotide polymorphisms (SNPs) (rs7923837 and rs1111875 in the *IDE-KIF11-HHEX* gene locus and rs13266634 in the *SLC30A8* gene locus) were especially robust.

In the present study, we examined whether these SNPs were associated with increased risk of type 2 diabetes in Japanese subjects.

Subjects and Methods

Subjects

A total of 405 unrelated Japanese type 2 diabetic patients and 340 nondiabetic control subjects were recruited from among patients attending the outpatient clinic of Wakayama Medical University Hospital. Diabetes was diagnosed in accordance with the criteria of the World Health Organization (8), and patients who were glutamic acid decarboxylase (GAD) antibody positive and/or had started insulin therapy within 3 yr of the diagnosis of diabetes were excluded from this study. The age at diagnosis, body mass index (BMI), and the glycosylated hemoglobin (HbA1c) of the diabetic group were 47.3 ± 10.8 yr (mean ± SD), 23.9 ± 3.6 kg/m^2, and 7.4 ± 1.4%, respectively. Nondiabetic control subjects were chosen based on the following criteria: age at least 50 yr and HbA1c of at least 5.6%. In this group, the BMI and the HbA1c were 22.3 ± 3.3 kg/m^2 and 5.0 ± 0.4%, respectively. All the participants gave written informed consent before participating in the study. This study was approved by the ethics committee of Wakayama Medical University.

Genotyping

Genomic DNA was isolated from peripheral blood in accordance with standard procedures. Genotyping was undertaken using a TaqMan SNP genotyping assay system (Applied Biosystems, Foster City, CA). Assays were performed in accordance with the manufacturer's specification, and the genotypes were analyzed on an ABI PRISM 7700 sequence detector system (Applied Biosystems). To check for errors in genotyping, 20% of the samples were also genotyped by direct sequencing, reacted with a BigDye terminator (Applied Biosystems), and analyzed with an ABI 3100 capillary sequencer (Applied Biosystems); no discrepancy was observed. Distributions of genotype frequency did not deviate from Hardy-Weinberg equilibrium.

Statistical analysis

The genotype frequencies obtained were tested for Hardy-Weinberg equilibrium by χ^2 test. The allele and genotype frequencies were compared between diabetic and control subjects by χ^2 test. The association between the genotypes of SNPs and clinical characteristics was examined by χ^2 test (for sex), one-way ANOVA (for age, age at diagnosis, and HbA1c), and multiple linear regression analysis assuming an additive inheritance model adjusted for age and sex (for BMI and maximum BMI). Haplotype frequencies were separately estimated for case and control using the expectation-maximization algorithm. Statistical significance was estimated based on 100,000 permutations. P values of < 0.05 were considered to be statistically significant. All P values were not adjusted for multiple testing. Statistical analyses were performed using SNPAlzye version 5.1 (Dynacom, Yokohama, Japan) and StatView version 5.01 (SAS Institute, Cary, NC) software.

Results

The genotype and allele frequencies of two SNPs, rs7923837 (A/G) and rs1111875 (A/G), in the *IDE-KIF11-HHEX* gene locus, and one SNP, rs13266634 (C/T), in the *SLC30A8* gene locus, are listed in Table 1. The genotype distributions of these SNPs showed no deviation from the Hardy-Weinberg equilibrium. The G allele of rs7923837 was significantly more frequent in the diabetes patients than in the controls [odds ratio 1.66, 95% confidence interval (CI) 1.28–2.15; $P = 0.00014$], following the same tendency as in the French population of the previous report (7). Heterozygous and homozygous carriers of the risk allele had odds ratios of 1.57 (95% CI 1.15–2.16; $P = 0.0050$) and 3.16 (95% CI 1.40–7.16; $P = 0.0038$) relative to noncarriers. Homozygous carriers had odds ratios of 2.01 (95% CI 0.87–4.65; $P = 0.097$) relative to heterozygous carriers. The G allele was a minor allele (23.8%) in the Japanese population, although it was a major allele (66.5%) in the French population.

The G allele of rs1111875 was also significantly more frequent in the diabetes patients than in the controls (odds ratio

TABLE 1. Genotype and allele frequencies of three SNPs in the type 2 diabetic patients and the control subjects

Genotypes	Diabetes	Control	Odds ratio (95% CI)	*P* value	Alleles	Diabetes	Control	Odds ratio (95% CI)	*P* value
HHEX									
rs7923837									
AA (%)	237 (58.5)	240 (70.6)	1.00						
AG (%)	143 (35.3)	92 (27.1)	1.57(1.15–2.16)	0.0050	A (%)	617 (76.2)	572 (84.1)	1.00	
GG (%)	25 (6.2)	8 (2.3)	3.16(1.40–7.16)	0.0038	G (%)	193 (23.8)	108 (15.9)	1.66 (1.28–2.15)	0.00014
rs1111875									
AA (%)	185 (45.7)	186 (54.7)	1.00						
AG (%)	177 (43.7)	136 (40.0)	1.31(0.97–1.77)	0.0810	A (%)	547 (67.5)	508 (74.7)	1.00	
GG (%)	43 (10.6)	18 (5.3)	2.40(1.34–4.32)	0.0028	G (%)	263 (32.5)	172 (25.3)	1.42 (1.13–1.78)	0.0024
SLC30A8									
rs13266634									
TT (%)	57 (14.1)	58 (17.1)	1.00						
TC (%)	197 (48.6)	161 (47.3)	1.25(0.82–1.90)	0.3573	T (%)	311 (38.4)	277 (40.7)	1.00	
CC (%)	151 (37.3)	121 (35.6)	1.27(0.82–1.97)	0.2834	C (%)	499 (61.6)	403 (59.3)	1.10 (0.90–1.36)	0.3573

Data are presented as n (%) unless otherwise indicated.

1.42, 95% CI 1.13–1.78; $P = 0.0024$), in agreement with Sladek *et al.* (7). For rs1111875, heterozygous and homozygous carriers of the risk allele had odds ratios of 1.31 (95% CI 0.97–1.77; $P = 0.081$) and 2.40 (95% CI 1.34–4.32; $P = 0.0028$) relative to noncarriers. Homozygous carriers had odds ratios of 1.84 (95% CI 1.01–3.32; $P = 0.043$) relative to heterozygous carriers. The G allele was a minor allele (32.5%) in the Japanese population, but a major allele (64.2%) in the French population.

The rs7923837 was in moderate linkage disequilibrium with rs1111875 in both, case ($D' = 0.71$; $r^2 = 0.33$) and control subjects ($D' = 0.68$; $r^2 = 0.26$). The GG haplotype carrying the risk alleles of both of the SNPs was more common among diabetes patients than control subjects (19.1 *vs.* 12.1%, $P = 0.00039$), and the AA haplotype carrying the protective alleles of both of the SNPs was less common among patients than control subjects (62.8 *vs.* 71.0%, $P = 0.0011$).

On the other hand, the genotype and allele frequencies for the rs13266634 in the *SLC30A8* gene locus did not show significant differences between type 2 diabetic patients and control subjects, although the C allele, which was a risk allele in the French population, was slightly more frequent in case subjects than in control subjects in our Japanese population.

We next examined the association of three SNPs with age at diagnosis, BMI, and maximum BMI in the diabetic patients group (Table 2). The G allele of rs7923837 was associated with a lower maximum BMI in an additive inheritance model adjusted for age and sex ($P = 0.028$). Homozygous carriers of the G allele of rs1111875 had an earlier age at diagnosis of diabetes relative to heterozygous carriers and noncarriers ($P = 0.016$ and $P = 0.008$ by Fisher's *post hoc* test, respectively). On the other hand, no significant association with age at diagnosis was observed for rs7923837. There were no associations with any characteristics for rs13266634. We also examined the association between rs7923837 and BMI in control subjects, but no association was observed (mean BMI values of homozygous carriers, heterozygous carriers, and noncarriers of the G allele were 20.8 ± 2.8, 22.3 ± 3.3, and 22.3 ± 3.3 kg/m^2, respectively; $P = 0.777$).

Discussion

In the present study, we confirmed that two SNPs (rs7923837 and rs1111875) in the *IDE-KIF11-HHEX* gene locus on chromosome 10q23-q24 were strongly associated with susceptibility to type 2 diabetes in Japanese subjects, even though the frequencies of risk alleles were much lower in Japanese than those reported in the French population. The rs7923837 yielded a stronger association than rs1111875, and the risk of type 2 diabetes was even stronger, with an increased number of risk alleles for each SNP. The association between rs1111875 and susceptibility to type 2 diabetes has recently been confirmed in other Caucasian populations (9–12). The allele-specific odds ratios observed in these studies and the original French study (7) ranged from 1.08–1.21, which were lower than that observed in this study. The effect of gene polymorphisms in the *IDE-KIF11-HHEX* gene locus on susceptibility to type 2 diabetes may be larger in Japanese than in Caucasians.

Sladek *et al.* (7) showed that rs7923837 and rs1111875 are located near the telomeric end of a 270-kb linkage disequilibrium (LD) block in the French population. A similar LD block was observed in the HapMap data (HapMap Data Rel no. 20/phaseII Jan06) of Japanese subjects. This LD block contains three genes: insulin-degrading enzyme (*IDE*), kinesin family member 11 (*KIF11*), and hematopoietically expressed homeobox (*HHEX*). These genes are located, in that order, from the centromeric side to the telomeric side of the LD block. The *IDE* gene is a metallopeptidase that can degrade a number of peptides, including insulin and amylin. Amylin is the chief component of the islet amyloid found in type 2 diabetic patients, and *IDE* inhibition by a pharmacological inhibitor impaired amylin degradation, in-

TABLE 2. Association between each SNP and clinical characteristics in the type 2 diabetic patients

Genotypes	n (M/F)	Age (yr)	Age at diagnosis (yr)	BMI (kg/m^2)	Maximum BMI (kg/m^2)	HbA1c (%)
HHEX						
rs7923837						
AA	123/114	64.8 ± 12.3	48.0 ± 10.7	24.1 ± 3.7	27.4 ± 4.2	7.5 ± 1.6
AG	84/59	64.3 ± 11.8	46.6 ± 10.8	23.8 ± 3.6	26.9 ± 3.9	7.4 ± 1.3
GG	16/9	65.2 ± 10.2	45.5 ± 11.6	22.8 ± 2.7	25.5 ± 2.5	7.3 ± 1.1
P value		0.891	0.356	0.133[a]	0.028[a]	0.238
rs1111875						
AA	104/81	65.2 ± 12.5	48.0 ± 10.7	23.9 ± 4.0	27.1 ± 4.2	7.4 ± 1.4
AG	97/80	64.1 ± 10.9	47.6 ± 10.6	24.0 ± 3.3	27.4 ± 3.8	7.4 ± 1.4
GG	22/21	64.0 ± 12.2	43.2 ± 11.6	23.4 ± 3.1	26.3 ± 4.0	7.8 ± 1.6
P value		0.620	0.027	0.461[a]	0.425[a]	0.663
SLC30A8						
rs13266634						
CC	82/69	65.1 ± 11.3	47.6 ± 10.3	24.2 ± 3.5	27.5 ± 4.1	7.4 ± 1.4
CT	109/88	63.7 ± 12.2	46.8 ± 11.4	23.7 ± 3.7	26.7 ± 4.0	7.4 ± 1.4
TT	32/25	66.5 ± 11.1	48.4 ± 10.3	23.8 ± 3.4	27.3 ± 3.8	7.6 ± 1.5
P value		0.797	0.866	0.283[a]	0.381[a]	0.668

Data are presented as number or means ± SD. Comparisons were performed by one-way ANOVA or multiple linear regression analysis (see below). *P* values of BMI and maximum BMI were calculated assuming an additive inheritance model adjusted for age and sex. F, Female; M, male.

[a] Comparisons performed by multiple linear regression analysis.

creased amyloid formation, and increased amylin-induced cytotoxicity in a pancreatic β-cell line (13). Furthermore, mice with homozygous deletions of the *Ide* gene had glucose intolerance (14). However, it has been reported that genetic variants in the human *IDE* gene did not contribute to susceptibility of type 2 diabetes in a well-designed large-scale study (15). The *KIF11* gene is a member of microtubule-dependent molecular motors that are involved in the formation of bipolar spindles and the proper segregation of sister chromatids during cell mitosis (16). The *KIF11* gene has received attention as a target for cancer treatment recently (17), but no evidence of association with glucose homeostasis has been reported. The *HHEX* gene is a transcription factor required for organogenesis of the ventral pancreas (18) and the liver (19) and is the nearest gene to rs7923837 and rs1111875. The SNPs, however, do not reside within the coding or putative regulatory regions of any one of the three genes. Furthermore, we genotyped only two SNPs in a large LD block containing three genes in this study. Therefore, it is difficult from our results to explain which gene may be the susceptibility gene.

On the other hand, we did not observe a significant association with susceptibility to type 2 diabetes for rs13266634 in the *SLC30A8* gene locus. Our sample size, however, was smaller than that of the French study (7). Assuming a risk allele frequency and genotypic relative risks of heterozygote and homozygote carriers (0.70, 1.18, and 1.53, respectively) using the French study as a basis, the power of our study was 59% at an α-level of 0.05 (20). The association between rs13266634 in the *SLC30A8* gene locus and susceptibility to type 2 diabetes has recently been confirmed in other Caucasian populations (9–12). Further study in a large sample set, therefore, will be needed to clarify the role of the *SLC30A8* gene locus in Japanese subjects.

In the present study, the association between two SNPs in the *IDE-KIF11-HHEX* locus and susceptibility to type 2 diabetes was replicated in Japanese subjects, which suggests that genetic variants in the *IDE-KIF11-HHEX* gene locus are associated with type 2 diabetes across the boundary of race.

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