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Association Study of the Effect of *WFS1* Polymorphisms on Risk of Type 2 Diabetes in Japanese Population

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Mutations of WFS1 gene cause Wolfram syndrome, which is a rare autosomal recessive disorder characterized by juvenile diabetes mellitus, optic atrophy, deafness and diabetes insipidus. The product encoded by *WFS1* gene, wolframin, could be involved in ER stress response causing β-cell loss through impaired cell cycle progression and increased apoptosis. Recently, polymorphisms in the *WFS1* gene were strongly associated with type 2 diabetes in Caucasians. The aim of the present study was to examine whether the variants of *WFS1* are associated with risk of type 2 diabetes in Japanese individuals. Four single nucleotide polymorphisms, rs6446482, rs12511742, rs1801208 (R456H) and rs734312 (H611R) were genotyped in a total of 536 diabetic patients and 398 nondiabetic control subjects. Among the four variants, rs12511742 showed a marginal association with susceptibility to type 2 diabetes (odds ratio = 1.32, 95% confidence interval = 1.02-1.71, *P* = 0.033). Carriers of the risk allele at rs12511742 exhibited lower pancreas β-cell function (*P* = 0.017). However, this association disappeared after adjustment for sex, age and BMI (Adjusted *P* = 0.24). Although we found no evidence for a substantial effect of *WFS1* polymorphisms on risk of type 2 diabetes or clinical characteristics of diabetic subjects in Japanese population, this gene is still a good candidate for a type 2 diabetes susceptibility gene, potentially, through impaired insulin secretion.

Genome-wide association studies (GWASs) have successfully revealed novel susceptibility genes for type 2 diabetes in Caucasians since 2007 [2, 5, 16, 18, 19, 21]. Some of these genes have been replicated in other ethnic groups including Japanese [7, 14, 23]. Meanwhile, the candidate-gene approach is still an effective strategy to identify susceptibility genes for common diseases when the study is sufficiently powered. Recently, the Wolfram syndrome 1 (*WFS1*) gene was identified as a novel type 2 diabetes susceptibility genes by the latter approach [15]. In that report, 1,536 single nucleotide polymorphisms (SNPs) in 84 candidate genes including *WFS1* were genotyped in the association study of 9,533 cases and 11,389 controls. Four common SNPs (rs10010131, rs6446482, rs752854 and rs734312 (H611R)) in the *WFS1* locus were shown to be convincingly associated with type 2 diabetes, where odds ratios (ORs) and *P* values ranged 0.90 ~ 0.92 and $1.3 \times 10^{-4} \sim 1.4 \times 10^{-7}$, respectively [15]. In Japanese subjects, Kawamoto et al. reported that a haplotype with rs1801208 (R456H) and rs734312 (H611R) in *WFS1* showed a nominal association with type 2 diabetes ($P = 0.013$) [11]. *WFS1* encodes wolframin, a transmembrane protein predominantly localized in the

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endoplasmic reticulum. Mutations of this gene cause Wolfram syndrome (OMIM 222300), which is a rare autosomal recessive disorder characterized by juvenile diabetes mellitus, optic atrophy, deafness and diabetes insipidus [8]. Mice with disruption of *WFS1* exhibited impaired glucose homeostasis accompanied by progressive reduction of β-cell mass [9]. In this study, we attempt to replicate the association between *WFS1* and type 2 diabetes by analyzing SNPs and haplotypes in the Japanese population. We also examined whether a variation of this gene is associated with clinical characteristics of type 2 diabetes.

SUBJECTS AND METHODS

Subjects

A total of 536 unrelated individuals with type 2 diabetes and 398 unrelated nondiabetic control subjects were enrolled in the study. We excluded samples that were subjected to an independent study, the Study Group of the Millennium Genome Project for Diabetes Mellitus. In our sample panel, the mean ± SD of age, body mass index (BMI), and HbA_{1c} were 63.6 ± 11.5 years, 23.6 ± 3.8 kg/m^2, and 7.9 ± 1.7 %, respectively, for the diabetic subjects and 72.4 ± 9.7 years, 21.8 ± 3.5 kg/m^2, and 5.0 ± 0.4 %, respectively, for the control subjects. The diagnosis of type 2 diabetes was based on the criteria of WHO (1998). The nondiabetic subjects were selected if they had no past history of glucose intolerance. The study was performed with written informed consent from all subjects and was approved by the Ethics Committee of Kobe University Graduate School of Medicine.

Clinical assessment

The BMI of each individual was directly measured at the time of collection of blood samples. The fasting plasma glucose concentration (FPG), fasting serum immunoreactive insulin concentration (FIRI) and HbA_{1c} level were determined by standard laboratory techniques calibrated with uniform standards. Indices of basal insulin secretion and resistance were derived by homeostasis model assessment (HOMA). The HOMA of β-cell function (HOMA-β) was calculated as {FIRI (pmol/l) × 20}/{FPG (mmol/l) − 3.5} ×6, and that of insulin resistance (HOMA-IR) was calculated as {FPG (mmol/l) × FIRI (pmol/l)}/22.5×6 [13]. Among the diabetic subjects, the individuals who were not treated with insulin were evaluated for HOMA-IR and HOMA-β. Some of the diabetic subjects were evaluated for the intramyocellular lipid content (IMCL), hepatic lipid content (HLC), visceral fat (VF) and an index of insulin sensitivity. IMCL and HLC were determined by ^{1}H-MRS on a 1.5-T magnetic resonance machine (Signa Echo Speed; GE Yokogawa Medical Systems, Hino, Japan) as described previously [20]. Areas of visceral fat were acquired from a region extending from 4 cm above to 4 cm below the fourth and fifth lumbar interspace (16 slices, each with a thickness of 10 mm) and measured with NIH Image software. The hyperinsulinemic-euglycemic clamp test was performed as described previously [20]. Regular human insulin was infused intravenously at 1.46 mU/kg/min to achieve serum insulin concentration of 600 pmol/l, and plasma glucose concentration was maintained at 5.5 mmol/l by a variable infusion of glucose. The rate of glucose infusion (GIR), expressed in milligrams per kilogram per minute, required to maintain euglycemia during hyperinsulinemia was evaluated as an index of insulin sensitivity.

DNA analysis

Genomic DNA was extracted from blood with the use of a QIAamp DNA Blood Maxi Kit (Qiagen, Valencia, CA), and genotypes for the SNPs were determined with the TaqMan procedure (Applied Biosystems, Foster City, CA). The polymerase chain reaction was

performed with ABsolute QPCR ROX Mixes (ABgene, Epsom, UK) and an ABI PRISM 7700 Sequence Detector System (Applied Biosystems); the amplification protocol included incubation at 95°C for 15 min followed by 40 cycles of 92°C for 15 s and 60°C for 1 min.

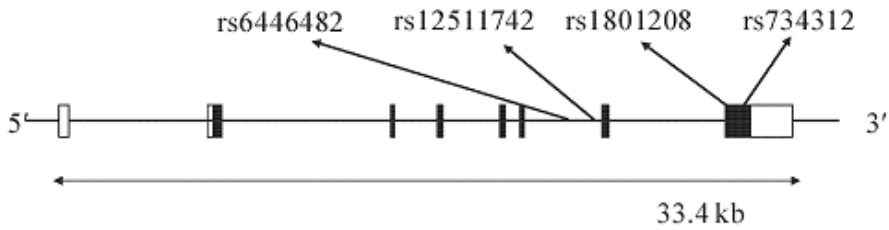
Statistical analysis

We assessed association and Hardy-Weinberg equilibrium with the chi-square test. Linkage disequilibrium (LD) and haplotype analyses were performed with SNPAlyze version 5.1 pro software (Dynacom, Mobara, Japan). Averaged data are presented as means ± SD, and differences between groups were analyzed by *t*-test; if necessary, data were log transformed. Adjusted *P* values were obtained by ANCOVA with adjustment for sex, age and BMI. Statistical analysis was performed with StatView software version 5.0-J (SAS Institute, Cary, NC). A *P* value of <0.05 was considered statistically significant.

RESULTS

Minor allele frequencies (MAF) of rs10010131, rs6446482, rs752854, rs734312 (H611R) [15] and rs1801208 (R456H) [11] are 0.00, 0.01, 0.00, 0.11 and 0.07, respectively, in the HapMap (http://www.hapmap.org/index.html.ja) Japanese data. We selected rs6446482, rs734312 (H611R) and rs1801208 (R456H) based on this information. Additionally, rs12511742 was selected from the HapMap database because of its MAF (= 0.15) and LD information. These four SNPs were genotyped in 536 diabetic subjects and 398 nondiabetic control subjects (Figure 1A).

A.



B.

	rs6446482	rs12511742	rs1801208	rs734312
rs6446482		**0.001**	**0.003**	**0.112**
rs12511742	-0.50		**0.024**	**0.016**
rs1801208	-1	-1		**0.808**
rs734312	0.92	-0.74	1	

Figure 1. Genomic organization of *WFS1* and pairwise LD analysis of SNPs. (**A**) Schematic representation of the *WFS1* genomic region showing the locations of SNPs. Coding and noncoding sequences of exons are shown as closed and open boxes, respectively. Details of the SNPs are provided in Table I. (**B**) Values of D' (non-bold type) and of r^2 (bold type) for pairwise LD analysis in 398 control subjects.

All of 536 cases were genotyped successfully. Meanwhile, typing results of 398, 391, 398 and 396 controls were obtained for rs6446482, rs12511742, rs1801208 (R456H) and rs734312 (H611R), respectively (Table I). The average of genotyping success rates was 0.998. All SNPs were in Hardy-Weinberg equilibrium. The *D*' and r^2 values in the 398 controls are shown in Figure 1B. The recent paper [15] and HapMap data show that the entire *WFS1* gene on chromosome 4 is contained in a single LD block of 39 kb in Caucasians. Given that the genotyped SNPs were high LD by *D*', these four SNPs were within a LD block in Japanese, which was believed to be similar to that of Caucasians. Among four SNPs, only rs12511742 was associated with susceptibility to type 2 diabetes (Table I, odds ratio = 1.32, 95% confidence interval = 1.02-1.71, $P = 0.033$). However, this association was marginal when multiple testing was considered ($P < 0.05 / 4$ SNPs = 0.0125).

Table I. Association analysis for SNPs of *WFS1* and type 2 diabetes.
MAF, minor allele frequency. *P* values for the difference in the minor allele frequency between cases and controls were calculated by the chi-square test; the odds ratio (OR) and 95% confidence interval (CI) were also calculated for the minor allele. Bold type indicates *P* value of <0.05.

SNP	allele 1	allele 2	Case (*n*)			Control (*n*)			MAF /case	MAF /control	*P* value	OR	95% CI
			11	12	22	11	12	22					
rs6446482	G	C	517	19	0	380	18	0	0.018	0.023	0.453	0.78	0.41-1.50
rs12511742	**G**	**T**	**364**	**155**	**17**	**291**	**91**	**9**	**0.176**	**0.139**	**0.033**	**1.32**	**1.02-1.71**
rs1801208 (R456H)	G	A	433	99	4	307	82	9	0.100	0.126	0.079	0.77	0.58-1.03
rs734312 (H611R)	A	G	406	123	7	289	95	12	0.128	0.150	0.164	0.83	0.64-1.08

Next, we performed haplotype analyses with the combination of two SNPs. As shown in Table II, haplotype analyses including rs12511742 showed marginally significant associations with type 2 diabetes as much as that of rs12511742 alone. Although a haplotype with rs1801208 (R456H) and rs734312 (H611R) was previously associated with type 2 diabetes in Japanese [11], we did not detect such a case (Table II).

Table II. Association analysis for haplotypes with the indicated combination of two SNPs. *P* values for the difference in the estimated haplotype frequency between cases and controls were calculated by the chi-square test. Haplotypes with a frequency of less than 0.01 were excluded. Bold type indicates *P* values of <0.05.

Combination of SNPs	Haplotype	Frequency /case	Frequency /control	*P* value
rs6446482 - rs12511742	G-G	0.808	0.839	0.086
	G-T	**0.174**	**0.138**	**0.035**
	C-G	0.016	0.021	0.345
rs12511742 - rs1801208 (R456H)	G-G	0.724	0.733	0.674
	T-G	**0.176**	**0.139**	**0.033**
	G-A	0.100	0.128	0.058
rs12511742 - rs734312 (H611R)	G-A	0.706	0.713	0.767
	T-A	0.166	0.135	0.063
	G-G	0.118	0.147	0.059
rs1801208 (R456H) - rs734312 (H611R)	G-A	0.872	0.850	0.163
	A-G	0.100	0.125	0.086
	G-G	0.028	0.025	0.722

Table III shows the result of the association analysis between rs12511742 and clinical characteristics in the diabetic subjects. Carriers of T allele, the risk allele, at rs12511742 exhibited lower values of HOMA-β, which suggested lower pancreas β-cell function. However, this association disappeared after adjustment for sex, age and BMI (Table III). No associations of this polymorphism were observed with indexes of insulin resistance (HOMA-IR and GIR) and fat distribution (VF, IMCL and HLC).

Table III. Clinical characteristics of diabetic subjects according to genotype for rs12511742 of *WFS1*. Data are means ± SD. *P* values were calculated by *t*-test. Adjusted *P* values were obtained by ANCOVA with adjustment for sex, age and BMI. *These parameters were log transformed before analysis. GIR: glucose infusion rate during the hyperinsulinemic-euglycemic clamp. VF: visceral fat area. IMCL: intramyocellular lipid content. HLC: hepatic lipid content.

Parameter	GG	GT + TT	*P* value	Adjusted *P*
Age (years)	64 ± 11 (*n* = 364)	64 ± 11 (*n* = 172)	0.78	
BMI (kg/m^2)	23.7 ± 3.8 (*n* = 358)	23.5 ± 3.6 (*n* = 170)	0.54	
HOMA-IR*	3.1 ± 2.8 (*n* = 133)	2.8 ± 2.6 (*n* = 74)	0.18	
HOMA-β*	74.8 ± 144.0 (*n* = 133)	47.2 ± 48.8 (*n* = 74)	**0.017**	0.24
HbA_{1c} (%)*	7.8 ± 1.7 (*n* = 363)	7.8 ± 1.8 (*n* = 170)	0.63	
GIR (mg/kg/min)*	5.5 ± 1.8 (*n* = 42)	6.4 ± 2.3 (*n* = 27)	0.23	
VF (cm^2)	112 ± 44 (*n* = 44)	117 ± 61 (*n* = 29)	0.69	
IMCL (arbitrary units)*	8.2 ± 4.1 (*n* = 44)	7.5 ± 3.2 (*n* = 29)	0.36	
HLC (arbitrary units)	8.9 ± 6.2 (*n* = 44)	7.0 ± 5.5 (*n* = 29)	0.18	

DISCUSSION

We found no evidence for a substantial effect of *WFS1* SNPs on susceptibility to type 2 diabetes or clinical characteristics of diabetic subjects in a Japanese population. Only a marginal association between the SNP rs12511742 of *WFS1* and type 2 diabetes was observed (P = 0.033). It is noteworthy that the risk allele of this polymorphism was associated with lower β-cell function in the crude analysis with the diabetic subjects. The association between rs6446482 and type 2 diabetes, which was recently reported in Caucasian [15], was not apparent in this Japanese case-control study, although the odds ratio was still in the same direction as that in Caucasians. This discrepancy may be due to much lower MAF of the SNP in Japanese (0.02 in Japanese and 0.33~0.42 in Caucasians [15]). Our result of the haplotype analysis with rs1801208 (R456H) and rs734312 (H611R) was not consistent with a previous report, which showed that the G-A (R456-H611) haplotype was protective for type 2 diabetes [11].

Disruption of *WFS1* gene in mice causes glucose intolerance due to progressive β-cell loss [9]. β-cells were selectively absent from the islets of Langerhans in postmortem specimens from two patients with Wolfram's syndrome [10]. The product encoded by *WFS1* gene, wolframin, could be involved in ER stress response causing β-cell loss through impaired cell cycle progression and increased apoptosis [22]. These various observations suggest that *WFS1* may confer susceptibility to type 2 diabetes through β-cell dysfunction. In the present study, the risk allele of rs12511742 was associated with lower β-cell function, although this association disappeared after adjustment for sex, age and BMI.

Genes causing rare monogenic disorders might also confer susceptibility to similar conditions with a multifactorial etiology. For example, genes responsible for maturity-onset diabetes of the young (MODY), an autosomal dominant monogenic diabetes, have been associated with type 2 diabetes [1, 6, 12, 17]. Very recently, a meta-analysis in Caucasians for the *WFS1* gene showed strong evidence of statistical association [4]. Another report by the Diabetes Prevention Program showed that carriers of the protective variants in *WFS1* exhibited a trend towards increased insulin secretion [3]. The marginal association between *WFS1* gene and risk of type 2 diabetes in the present study may be due to the lack of analytical power with our relatively small sample size. In order to clarify the effect of *WFS1* gene on the common form of diabetes as well as its clinical characteristics, further studies will be required with a larger sample size, especially in Asian populations.

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