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ORIGINAL ARTICLE

Association of *TCF7L2* polymorphisms with susceptibility to type 2 diabetes in 4,087 Japanese subjects

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Abstract Transcription factor 7-like 2 (*TCF7L2*) has been shown to be associated with type 2 diabetes mellitus in multiple ethnic groups. Regarding the Asian population, Horikoshi et al. (Diabetologia 50:747–751, 2007) and Hayashi et al. (Diabetologia 50:980–984, 2007) reported that single nucleotide polymorphisms (SNPs) in *TCF7L2* were associated with type 2 diabetes in the Japanese population, while contradictory results were reported for Han Chinese populations. The aim of this study was to investigate the associations of the *TCF7L2* gene with type 2 diabetes using a relatively large sample size: 2,214 Japanese individuals with type 2 diabetes and 1,873 normal controls. The minor alleles of rs7903146, rs11196205, and rs12255372 showed significant associations with type 2

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Table 1 Clinical characteristics of each sample set. Data are means ± SD. *BMI* Body mass index

	Kobe		Gunma		Consortium	
	Diabetes	Control	Diabetes	Control	Diabetes	Control
n	465	323	576	576	1,173	974
Male participants (%)	59.6	45.8	56.1	40.4	56.6	43.1
Age at study (years)	60.5 ± 10.7	75.6 ± 8.1	60.2 ± 11.5	67.3 ± 6.5	62.5 ± 8.8	69.2 ± 7.0
BMI	24.3 ± 3.9	21.4 ± 3.5	23.9 ± 4.2	23.0 ± 2.9	23.1 ± 2.9	22.6 ± 3.0
HbA_{1c} (%)	8.1 ± 2.0	5.0 ± 0.4	7.8 ± 3.5	5.0 ± 0.4	7.5 ± 1.5	4.9 ± 0.4

diabetes (OR = 1.48, $P = 2.7 \times 10^{-4}$; OR = 1.39, $P = 4.6 \times 10^{-4}$; OR = 1.70, $P = 9.8 \times 10^{-5}$, respectively) in the combined sample sets. However, neither rs11196218 nor rs290487 showed a significant association. These results indicate that *TCF7L2* is an important susceptibility gene for type 2 diabetes in the Japanese population.

Keywords Type 2 diabetes · Polymorphism · β-cell function · Transcription factor 7-like 2 (*TCF7L2*) · Association study

Introduction

The transcription factor 7-like 2 gene (*TCF7L2*) is one of the most convincing susceptibility genes for type 2 diabetes. Following the initial report (Grant et al. 2006), there have been a number of association studies in various ethnic groups (Florez et al. 2006; Zhang et al. 2006; Saxena et al. 2006). Regarding the Asian population, Horikoshi et al. (2007) reported that a single nucleotide polymorphism (SNP), rs7903146, in *TCF7L2* is associated with type 2 diabetes in the Japanese population but that other SNPs (rs7895340, rs11196205, rs12255372) are not. The minor allele frequencies of these SNPs in Japanese were also found to be much lower than those of Caucasians. Hayashi et al. (2007) replicated the association of *TCF7L2* with type 2 diabetes in Japanese. Contradictory results were reported for Han Chinese populations (Ng et al. 2007; Chang et al. 2007), but these two reports found that other common SNPs (rs11196218 and rs290487, respectively) were associated with type 2 diabetes. This apparent difference between Asian populations could be due to the relatively small sample sizes involved. Recently, variants in the *TCF7L2* gene also were reported to be associated with β-cell function (Schäfer et al. 2007; Lyssenko et al. 2007) and response to sulfonylureas in Caucasians (Pearson et al. 2007). To clarify the association of the *TCF7L2* gene with type 2 diabetes and β-cell function in an Asian population, we have performed association studies using a relatively large Japanese sample set: 2,214 Japanese individuals with type 2 diabetes and 1,873 normal controls.

Subjects and methods

Subjects

Three sample sets were involved. The Kobe set and the Gunma set samples were recruited from hospitals in Hyogo and Gunma prefecture, respectively. The Consortium set samples were recruited from seven districts in Japan by the Study Group of the Millennium Genome Project for Diabetes Mellitus. The Kobe, Gunma, and Consortium sets were independent of one another. The inclusion criteria for normal, control subjects of the Consortium set were as follows: (1) >60 years of age; (2) HbA_{1c} values <5.8%; and (3) no family history of type 2 diabetes in first- or second-degree relatives. In the Kobe and Gunma control samples, the inclusion criteria were (1) no past history of diabetes and (2) HbA_{1c} values < 5.8%. The control subjects were hospital patients for annual medical checkup or unrelated disorders. Type 2 diabetes was diagnosed in accordance with WHO criteria. Other forms of diabetes were excluded based on the clinical data. The clinical and laboratory characteristics of the study subjects are shown in Table 1. Written, informed consent was obtained from all participants. The study was approved by the ethics committee of each participating institute.

Genotyping

Five SNPs (rs7903146, rs11196205, rs12255372, rs11196218, rs290487) were genotyped using TaqMan SNP Genotyping Assays (Applied Biosystems, Foster City,

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CA) or SSP-FCS (sequence specific primer-fluorescence correlation spectroscopy) Assays (Bannai et al. 2004). Of the original five SNPs (rs7903146, rs11196205, rs12255372, rs7901695, rs7895340) in the first report (Grant et al. 2006), we selected three SNPs (rs7903146, rs11196205, rs12255372) for the following reasons: the original five SNPs are located in one linkage disequilibrium (LD) block surrounding exon 4 in the Japanese population (Supplementary Figure 1), which is similar to the case in Caucasians (Grant et al. 2006); rs7901695 and rs7895340 are in almost complete LD with rs7903146 ($r^2 = 1$) and rs11196205 ($r^2 = 0.90$), respectively, in the Japanese population (Horikoshi et al. 2007); there is no common (minor allele frequency > 10%) SNP in this LD block (HapMap JPT data). We also genotyped rs11196218 and rs290487, which were associated with type 2 diabetes in Han Chinese, to replicate this association in Japanese. To evaluate our genotyping, 180 samples in the Consortium set were genotyped by both TaqMan SNP Genotyping Assays and SSP-FCS Assays. The concordance rate between these two assays was 100%: genotypes determined by TaqMan or SSP-FCS methods were identical to those determined by direct sequencing for 48 samples.

The genotyping success rates in the three sample sets were all >93%. All five SNPs were in Hardy–Weinberg equilibrium (HWE; $P > 0.05$ in the Exact test) in both case and control groups of all sample sets.

Clinical assessment

The clinical profile of each subject was directly determined at the time of entry. HOMA-IR and HOMA-β were calculated as follows: HOMA-IR = (fasting insulin [pmol/l]) × glucose [mmol/l])/22.5 × 6 and HOMA-β = (fasting insulin [pmol/l]) × 2)/(glucose [mmol/l] − 3.5) × 6. Diabetic subjects treated with insulin were excluded from analysis of HOMA-IR and HOMA-β. Assessments were performed with the combined three sample sets. Data are expressed as means ± SD.

Statistical analysis

The differences for SNPs or estimated haplotypes between type 2 diabetic and non-diabetic subjects were compared using Chi-square test under an allelic model. We also performed multiple logistic regression analysis adjusted for age, sex, and BMI under a dominant model. Statistical analysis was performed with the Stat-View program (version 5.0-J; SAS Institute, Cary, NC). The relation of the variants in *TCF7L2* with BMI and Homeostasis model assessment (HOMA-IR and HOMA-β) by *t* test under the dominant model for each SNP was then assessed. The HOMA-IR and HOMA-β data were log-transformed for normality. LD and haplotype analyses were performed with SNPAlyze version 5.1 pro software (Dynacom, Mobara, Japan). We considered statistical significance at *P* values of < 0.01 and < 0.017 in the association study for SNPs and for clinical parameters, respectively, after Bonferroni correction. The prevalence of type 2 diabetes in the Japanese population was assumed to be 0.07. Population attributable risk (PAR) was calculated as PAR = p(RR-1)/[p(RR-1) + 1], where p and RR are the risk allele frequency in the general population and the relative risk, respectively, estimated by the prevalence. When the frequency of risk allele, OR, and type I error probability are assumed to be 0.03 (Horikoshi et al. 2007), 1.46 (Cauchi et al. 2007), and 0.05, respectively, based upon the previous study, the power of our combined samples (2,214 cases and 1,873 controls) to detect association between SNP rs7903146 and type 2 diabetes is 0.92. In the case of OR assumed to be 1.69 (Horikoshi et al. 2007), the power of our study is 0.99.

Results

We performed association analyses using three independent sample sets. Regarding three SNPs (rs7903146, rs11196205, and rs12255372), which originally showed association with type 2 diabetes, the minor alleles showed a trend toward association with type 2 diabetes in the Kobe set. These SNPs also showed a marginally significant association in the Gunma set and in the Consortium set when multiple testing was considered. In the combined three sample sets (Combined set), the minor alleles of rs7903146, rs11196205, and rs12255372 showed a significant association with susceptibility to the disease (OR = 1.48, $P = 2.7 \times 10^{-4}$; OR = 1.39, $P = 4.6 \times 10^{-4}$; OR = 1.70, $P = 9.8 \times 10^{-5}$, respectively). These associations remained significant after adjustment for age, sex, and BMI (Table 2). As in a previous report (Horikoshi et al. 2007), the MAF and PAR in our study were much lower (MAF: 0.022−0.072, PAR: ∼0.02 in the Combined set) than those in Caucasians. Neither rs11196218 nor rs290487 showed a significant association in any sample set (Table 2).

LD among the five SNPs in 974 control subjects in the Consortium set was then analyzed. The D' and r^2 values are shown in Table 3. As reported previously for Japanese, three SNPs (rs7903146, rs11196205, and rs12255372) were found to be in modest to strong LD ($D' = 0.56$–1.0). Haplotypes then were constructed with these SNPs in the Combined set and assessed for association with type 2 diabetes. A haplotype comprising the risk allele of each

Table 2 Association analyses for five single nucleotide polymorphisms (SNPs) in the *TCF7L2* gene. *P* values and OR were calculated with allele data by the Chi-square test. Adjusted *P* values were calculated by multiple logistic regression (dominant model) with adjustment for age, sex and BMI. *MAF* minor allele frequency, *OR* odds ratio, *CI* confidence interval

dbSNP ID	Position on Chr10		Kobe							Gunma						
			n		MAF		OR	*P*	Adjusted *P*	*n*		MAF		OR	*P*	Adjusted *P*
			Case	Control	Case	Control	(95% CI)			Case	Control	Case	Control	(95% CI)		
rs7903146	114748339	CC	426	305	0.043	0.028	1.56	0.12	0.046	475	512	0.060	0.038	1.63	0.015	0.012
		CT	38	18			(0.89–2.76)			63	42			(1.09–2.42)		
		TT	1	0						1	0					
rs11196205	114797037	GG	408	292	0.063	0.047	1.39	0.16	0.093	455	485	0.084	0.055	1.58	0.007	0.023
		GC	55	30			(0.83–2.18)			77	58			(1.13–2.21)		
		CC	2	0						7	1					
rs12255372	114798892	GG	436	312	0.032	0.017	1.92	0.062	0.018	509	538	0.047	0.024	1.99	0.004	0.005
		GT	28	11			(0.96–3.87)			48	27			(1.24–3.20)		
		TT	1	0						2	0					
rs11196218	114830484	GG	271	194	0.23	0.23	1.01	0.92	0.23	317	334	0.22	0.22	1.04	0.72	0.84
		GA	170	106			(0.80–1.29)			184	185			(0.85–1.27)		
		AA	23	21						25	25					
rs290487	114899721	TT	181	124	0.37	0.38	0.94	0.57	0.90	209	236	0.37	0.34	1.18	0.072	0.13
		TC	226	141			(0.76–1.16)			228	235			(0.99–1.41)		
		CC	57	49						78	61					

Consortium							Combined						
n		MAF		OR	*P*	Adjusted *P*	*n*		MAF		OR	*P*	Adjusted *P*
Case	Control	Case	Control	(95% CI)			Case	Control	Case	Control	(95% CI)		
1,020	879	0.058	0.041	1.43	0.014	0.06	1,921	1,696	0.055	0.038	1.48	2.7×10^{-4}	0.0011
127	77			(1.07–1.90)			228	137			(1.20–1.84)		
3	1						5	1					
1,011	863	0.071	0.054	1.32	0.031	0.12	1,874	1,640	0.072	0.053	1.39	4.6×10^{-4}	0.0053
153	99			(1.02–1.70)			285	187			(1.16–1.67)		
6	3						15	4					
1,068	906	0.035	0.023	1.52	0.026	0.12	2,013	1,756	0.037	0.022	1.70	9.8×10^{-5}	7.0×10^{-4}
76	42			(1.05–2.21)			152	80			(1.30–2.22)		
2	1						5	1					
728	584	0.20	0.22	0.87	0.076	0.11	1,331	1,115	0.21	0.22	0.94	0.26	0.56
370	321			(0.75–1.01)			730	617			(0.85–1.05)		

Table 2 continued

Consortium						Combined					
n		MAF		OR	*P*	Adjusted *P*	*n*		MAF		OR	*P*	Adjusted *P*
Case	Control	Case	Control	(95% CI)			Case	Control	Case	Control	(95% CI)		
45	54						93	100					
476	381	0.37	0.37	0.99	0.91	0.50	873	744	0.37	0.36	1.04	0.45	0.46
507	448			(0.88–1.13)			977	824			(0.95–1.14)		
169	129						306	239					

SNP, T-C-T, was significantly associated with type 2 diabetes ($P = 5.3 \times 10^{-5}$) (Table 4).

The relation of rs7903146, rs11196205, and rs12255372 to BMI, HOMA-IR, and HOMA-β in the combined cases and controls were then compared. There was no association with BMI in cases or controls. The risk allele of rs7903146 was associated with lower HOMA-β (CC ($n = 789$) versus CT/TT ($n = 83$); 52.0 ± 87.6 versus 35.7 ± 35.9, $P = 0.009$) and lower HOMA-IR (CC vs. CT/TT; 3.2 ± 4.5 vs. 2.2 ± 1.6, $P = 0.01$) in the combined diabetic subjects. However, these associations disappeared after adjustment for age, sex, and BMI. No association was found for HOMA-β or HOMA-IR in the combined control subjects.

Discussion

We have found that three SNPs (rs7903146, rs11196205, rs12255372) of *TCF7L2* are associated with susceptibility to type 2 diabetes in the Japanese population. Our results are consistent with previous reports for Japanese populations (Horikoshi et al. 2007; Hayashi et al. 2007), but not with other reports for Han Chinese populations (Ng et al. 2007; Chang et al. 2007). The apparent difference in the association of these SNPs in Asians could be due to the low frequencies of the SNPs and the relatively small sample sizes used in the previous studies. Since we did not detect any association of rs11196218 or rs290487 in the present study, the associations of the two SNPs in the previous reports for Chinese might be specific to that population. In this study, rs7903146, rs11196205, and rs12255372 were in modest to strong LD. Based on HapMap data (JPT), the LD block surrounding exon 4 of *TCF7L2* in Asians does not exceed the gene (Supplementary Figure 1), which is consistent with findings in Caucasians (Grant et al. 2006). Previous reports (Ng et al. 2007; Chang et al. 2007) also found that the three SNPs were in a single LD block while the other two (rs11196218 and rs290487) were not. According to meta-analysis by Cauchi et al. (2007), *TCF7L2* is the most reproducible susceptibility gene for type 2 diabetes in various ethnic groups. *TCF7L2* also was one of the most significantly associated genes in recent genome-wide association studies (Sladek et al. 2007; WTCCC 2007). While the risk alleles of this gene are not common in East Asians, including Japanese, and the population attributable risk is much lower, *TCF7L2* is nevertheless a risk gene for type 2 diabetes in East Asians as well as in other populations. On the other hand, in a very recent online report, polymorphisms in the *TCF7L2* gene were found not to be associated with type 2 diabetes in a relatively large study of Pima Indians (Guo et al. 2007). Further investigation is required to

Table 3 Pairwise linkage disequilibrium (LD) for five SNPs in the *TCF7L2* gene. Values of D' (left lower) and of r^2 (upper right) for pairwise LD analysis in 974 control subjects of the Consortium set

	rs7903146	rs11196205	rs12255372	rs1196218	rs290487
rs7903146		0.24	0.49	0.002	0.0036
rs11196205	0.56		0.44	0.012	0.0037
rs12255372	0.93	1.00		0.007	0.0036
rs1196218	0.45	0.87	1.00		0.0002
rs290487	0.22	0.19	0.30	0.02	

Table 4 Association analysis for haplotypes with three SNPs (rs7903146, rs11196205, rs12255372). *P* values were calculated by the chi-square test with estimated haplotype data from the Combined set

Haplotype	Case	Control	*P*
C-G-G	0.91	0.93	1.5×10^{-4}
C-C-G	0.032	0.031	0.72
T-C-T	0.032	0.018	5.3×10^{-5}
T-G-G	0.020	0.017	0.30

elucidate the differences in the contribution of the *TCF7L2* gene to type 2 diabetes among various populations.

TCF7L2 regulates expression of the proglucagon gene (*GCG*), which encodes the precursor of glucagon, glucagon-like peptide 1 (GLP-1) (Yi et al. 2005). Several reports have found that polymorphisms of *TCF7L2* are associated with β-cell function (Florez et al. 2006; Saxena et al. 2006; Schäfer et al. 2007; Lyssenko et al. 2007). In this study, the association between the *TCF7L2* gene and HOMA-β was found to disappear after adjustment for the various factors. Although the relationship of this gene to β-cell function is not clear in this study, our results suggest that *TCF7L2* is an important susceptibility gene for type 2 diabetes in Japanese. The pathophysiological mechanism of this gene in susceptibility to type 2 diabetes remains to be elucidated.

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