Diabetologia (2011) 54:3071–3077
DOI 10.1007/s00125-011-2293-3

ARTICLE

Genetic variants at *CDC123/CAMK1D* and *SPRY2* are associated with susceptibility to type 2 diabetes in the Japanese population

M. Imamura · M. Iwata · H. Maegawa · H. Watada · H. Hirose · Y. Tanaka · K. Tobe · K. Kaku · A. Kashiwagi · R. Kawamori · Y. Nakamura · S. Maeda

Received: 22 June 2011 / Accepted: 29 July 2011 / Published online: 10 September 2011
© Springer-Verlag 2011

Abstract
Aims/hypothesis Recently, rs10906115 in *CDC123/CAMK1D*, rs1359790 near *SPRY2*, rs1436955 in *C2CD4A/C2CD4B* and rs10751301 in *ODZ4* were identified as genetic risk variants for type 2 diabetes by a genome-wide association study in a Chinese population. The aim of the present study was to ascertain the role of these four variants in conferring susceptibility to type 2 diabetes in the Japanese population.
Methods We genotyped 11,530 Japanese individuals (8,552 type 2 diabetes cases, 2,978 controls) for the above single nucleotide polymorphisms (SNPs) and used logistic regression analysis to determine whether they were associated with type 2 diabetes.
Results In accordance with the findings in a Chinese population, rs10906115 A, rs1359790 C and rs1436955 G were found to be risk alleles. Both rs10906115 and rs1359790 were significantly associated with susceptibility to type 2 diabetes in our study (rs10906115 OR 1.15, 95% CI 1.08, 1.22; $p=6.10\times10^{-6}$; rs1359790 OR 1.14, 95% CI 1.06, 1.21; $p=2.24\times10^{-4}$). Adjustment for age, sex and BMI had no significant effects on the association between

Electronic supplementary material The online version of this article (doi:10.1007/s00125-011-2293-3) contains peer-reviewed but unedited supplementary material, which is available to authorised users.

M. Imamura · S. Maeda (✉)
Laboratory for Endocrinology and Metabolism,
RIKEN Center for Genomic Medicine,
1-7-22 Suehiro-cho, Tsurumi-ku,
Yokohama, Kanagawa 230-0045, Japan
e-mail: smaeda@src.riken.jp

M. Iwata · K. Tobe
First Department of Internal Medicine, University of Toyama,
Toyama, Japan

H. Maegawa · A. Kashiwagi
Department of Medicine, Shiga University of Medical Science,
Otsu, Shiga, Japan

H. Watada
Department of Medicine, Metabolism and Endocrinology,
School of Medicine, Juntendo University,
Tokyo, Japan

H. Watada · R. Kawamori · S. Maeda
Sportology Center, Graduate School of Medicine,
Juntendo University,
Tokyo, Japan

H. Hirose
Health Center, Keio University School of Medicine,
Tokyo, Japan

Y. Tanaka
Department of Internal Medicine, Division of Metabolism and Endocrinology, St Marianna University School of Medicine,
Kawasaki, Kanagawa, Japan

K. Kaku
Division of Endocrinology and Metabolism,
Department of Internal Medicine, Kawasaki Medical School,
Kurashiki, Okayama, Japan

Y. Nakamura
Laboratory of Molecular Medicine, Human Genome Center,
Institute of Medical Science, University of Tokyo,
Tokyo, Japan

these variants and the disease. We did not observe any significant associations between the SNPs and any metabolic traits, e.g. BMI, fasting plasma glucose (determined for 1,332 controls), HOMA of beta cell function (900 controls) and HOMA of insulin resistance (900 controls; $p>0.05$).
Conclusions/interpretation The SNPs rs10906115 A and rs1359790 C are significantly associated with susceptibility to type 2 diabetes in the Japanese population, confirming that these alleles are common susceptibility variants for type 2 diabetes in East Asian populations.

Keywords Association study · Japanese · SNP · Type 2 diabetes

Abbreviations

FPG	Fasting plasma glucose
GWAS	Genome-wide association study
HOMA-B	HOMA of beta cell function
HOMA-IR	HOMA of insulin resistance
HWE	Hardy–Weinberg equilibrium
SNP	Single nucleotide polymorphism

Introduction

To date, approximately 40 type 2 diabetes susceptibility loci have been identified, mostly through genome-wide association studies (GWAS) [1]. The majority of genetic loci for type 2 diabetes have been initially detected in populations of European descent, except for *KCNQ1* [2, 3], *UBE2E2* [4] and *C2CD4A*/*C2CD4B* [4], which were first identified in Japanese GWAS. Among the type 2 diabetes susceptibility loci discovered in European studies, several loci, including *TCF7L2*, *CDKAL1*, *HHEX*, *SLC30A8*, *KCNJ11*, *CDKN2A/B*, *IGF2BP2* and *GCKR*, have been confirmed as type 2 diabetes risk loci in Japanese populations [4–8].

Recently, new genetic risk variants for type 2 diabetes, namely rs10906115 in *CDC123*/*CAMK1D,* and rs1359790 near *SPRY2*, have been identified by GWAS in Han Chinese, followed by in silico replication in three GWAS conducted among European Americans, Koreans and Singapore Chinese, and by de novo genotyping in Han Chinese samples [9]. Although the associations between these two variants and type 2 diabetes reached a genome-wide significance level ($p<5\times10^{-8}$) in combined analysis with 9,794 cases and 14,615 controls (rs10906115 OR 1.13, 95% CI 1.08, 1.18; $p=1.45\times10^{-8}$; rs1359790 OR 1.15, 95% CI 1.10, 1.20; $p=6.49\times10^{-9}$), these associations have not been extensively replicated in other populations.

Here, therefore, we aimed to evaluate the degree to which these new variants confer susceptibility to type 2 diabetes in the Japanese. We also evaluated two additional single nucleotide polymorphisms (SNPs) showing borderline association in a report by Shu et al [9], namely rs1436955 in *C2CD4A/C2CD4B* and rs10751301 in *ODZ4* (rs1436955 OR 1.13, 95% CI 1.08, 1.19; $p=7.14\times10^{-7}$; rs10751301 OR 1.10, 95% CI 1.05, 1.15; $p=1.31\times10^{-4}$).

Methods

Participants, DNA preparation and genotyping DNA samples were prepared from peripheral blood of Japanese participants with type 2 diabetes (n=8,552), who were enrolled in BioBank Japan or recruited from the outpatient clinics of the Shiga University of Medical Science, Otsu, Kawasaki Medical School, Kurashiki, St Marianna University, Kawasaki, the University of Toyama, Toyama and Juntendo University, Tokyo (all in Japan). We also examined 2,978 individuals (controls) who were enrolled from an annual health check conducted at Keio University, Tokyo or St Marianna University, from the outpatient clinics of Toyama University or from the Japanese general population registered in the Japanese SNP database. Control participants with HbA_{1c} ≥6.0% (4.2 mmol/mol), fasting plasma glucose (FPG) ≥7 mmol/l or self-reported diabetes were excluded from the present study.

Diabetes was diagnosed according to the criteria established by the World Health Organization [10]. Type 2 diabetes is clinically defined as a disease with gradual onset in adults. Individuals who tested positive for anti-GAD antibodies, and those diagnosed as having mitochondrial disease (mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes [MELAS]) or MODY were not included in this study. Written informed consent was obtained from all participants and DNA was extracted using the standard phenol-chloroform procedure. The study protocol was approved by the ethics committees of the RIKEN Yokohama Institute and each of the participating institutes.

The characteristics of participants in the present study are presented in the electronic supplementary material (ESM) Table 1. In brief, type 2 diabetes cases had a higher BMI (24.2±4.0 vs 22.8±3.2 kg/m^2, mean±SD) and were also older (63.6±11.2 vs 50.5±16.2 years, mean±SD) than the controls. These values were adjusted during subsequent analysis, if necessary.

Genotyping of each SNP was performed by a multiplex-PCR invader assay as described previously [11]. Genotype data on rs12779790 and rs7172432 are quoted from our previous study [4, 12].

Statistical analysis We performed Hardy–Weinberg equilibrium (HWE) tests according to the method described by Nielsen et al [13]. To test the additive model for each SNP,

we analysed the differences between the case and control groups in terms of the distribution of genotypes, scored using an additive model (0, 1 and 2 for homozygous for non-effect allele, and heterozygous and homozygous for effect allele, respectively). Logistic regression analysis was used for the above, with or without adjusting for age, sex and log-transformed BMI. Quantitative trait analyses for BMI, FPG (1,332 controls), HOMA of beta cell function (HOMA-B) (900 controls) and HOMA of insulin resistance (HOMA-IR) (900 controls) were performed by multiple linear regression analysis with or without adjusting for age, sex and log-transformed BMI. As the present Japanese samples have skewed distribution for BMI, FPG, HOMA-IR and HOMA-B values, we performed the analyses for the quantitative traits using log-transformed BMI, FPG, HOMA-IR and HOMA-B. HOMA-IR and HOMA-B were calculated based on FPG and fasting plasma insulin as described by Matthews et al. [14, 15]. These analyses were conducted using StatView software (SAS Institute, Cary, NC, USA). Power calculation was by Quanto (http://hydra.usc.edu/gxe/, accessed 8 June 2011) or CaTS power calculator (www.sph.umich.edu/csg/abecasis/CaTS/, accessed 31 March 2011). Combined meta-analysis was performed using the Mantel–Haenszel procedure with a fixed effect model or the DerSimonian–Laird method with a random effect model after testing for heterogeneity.

Results

The genotype distribution of rs10906115, rs1359790, rs1436955 and rs10751301 in the case and control groups did not deviate from HWE (Table 1). The first two of the above, rs10906115 and rs1359790, were significantly associated with susceptibility to type 2 diabetes in the present Japanese population (rs10906115 OR 1.15, 95% CI 1.08, 1.22; $p=6.10\times10^{-6}$; rs1359790 OR 1.14, 95% CI 1.06, 1.21; $p=2.24\times10^{-4}$). In accordance with the findings in a Chinese population [9], rs10906115 A and rs1359790 C were found to be risk alleles. Adjustment for age, sex and log-transformed BMI had no significant effects on the association between these SNPs and type 2 diabetes (rs10906115 OR 1.17, 95% CI 1.09, 1.25; $p=9.16\times10^{-6}$; rs1359790 OR 1.12, 95% CI 1.03, 1.21; $p=5.45\times10^{-3}$). The variant rs1436955 was nominally associated with susceptibility to type 2 diabetes (rs1436955 G OR 1.10, 95% CI 1.02, 1.19; $p=0.013$ adjusted); its risk allele was in accordance with the previous report [9]. We did not observe any significant association between rs10751301 and type 2 diabetes in the present Japanese population (OR 0.98, 95% CI 0.91, 1.05; $p=0.54$).

When we combined the original data by Shu et al. [9] with the present data, the associations of rs10906115, rs1359790 and rs1436955 with type 2 diabetes were further strengthened (Table 2), whereas that between rs10751301 and the disease was no longer significant and remarkable heterogeneity in its effect size ($I^2=87.2$) was observed (Table 2).

To examine whether these SNPs contribute to risk of obesity, as well as to risk of type 2 diabetes, the association between them and BMI was analysed. As shown in ESM Table 2, none of the above SNPs showed an association with log-transformed BMI.

The variant rs10906115 is located on chromosome 10p13, 13 kb from rs12779790, which has previously been implicated in type 2 diabetes by a GWAS meta-analysis in European populations [16]. Because of this, we did a conditional analysis, in which rs10906115 and rs12779790 were included in the same logistic regression model. We used 5,201 samples (2,798 type 2 diabetes cases, 2,403 controls) who had been genotyped for rs12779790 in a previous study [12]. As shown in Table 3, the association between rs10906115 and type 2 diabetes remained significant even after conditioning on rs12779790 ($p=0.001$ before conditioning, $p=0.0051$ after conditioning), whereas the modest association for rs12779790 was no longer significant after conditioning on rs10906115 ($p=0.036$ before conditioning, $p=0.19$ after conditioning).

The variant rs1436955 is also located in the confirmed type 2 diabetes locus, *C2CD4A*/*C2CD4B* [4]; we therefore evaluated its association with type 2 diabetes after conditioning on a previously reported variant, rs7172432 [4]. After conditioning on rs7172432, the association between rs1436955 and type 2 diabetes disappeared ($p=0.46$; ESM Table 3), whereas that between rs7172432 and the disease remained significant after conditioning on rs1436955 ($p=1.0\times10^{-3}$; ESM Table 3).

We also examined the association between the above SNPs and quantitative metabolic traits, such as FPG ($n=1,332$), HOMA-IR ($n=900$) and HOMA-B ($n=900$). However, no association between them and the four SNPs was observed (Table 4, ESM Table 4).

Discussion

In the present study, we identified significant associations between two variants (rs10906115 within *CDC123/CAMK1D* and rs1359790 near *SPRY2*) and susceptibility to type 2 diabetes in a Japanese population.

Recent advances in genotyping technology and accumulation of information about the human genome have facilitated GWAS worldwide, and nearly 40 susceptibility loci for type 2 diabetes have already been identified and confirmed in populations of European descent [1]. However, only ~10% of type 2 diabetes heritability can be explained

Table 1 Association of four SNPs with type 2 diabetes in the Japanese

SNP, region, gene	Type 2 diabetes (*n*)[a]	Control (*n*)[a]	Adjusted/unadjusted	OR (95% CI)	*p* value[b]
rs10906115 A[c]/G, 10p13, *CDC123/CAMK1D*					
AA	2,845	903			
AG	4,120	1,425			
GG	1,469	622			
Ratio AA:AG:GG	0.34:0.49:0.17	0.31:0.48:0.21	Unadjusted	1.15 (1.08, 1.22)	6.10×10^{-6}
RAF	0.582	0.548	Adjusted[e]	1.17 (1.09, 1.25)	9.16×10^{-6}
HWE test[d]	0.73	0.17			
rs1359790 C[c]/T, 13q31.1, *SPRY2*					
CC	4,609	1,512			
CT	3,265	1,206			
TT	515	221			
Ratio CC:CT:TT	0.55:0.39:0.06	0.51:0.41:0.08	Unadjusted	1.14 (1.06, 1.21)	2.24×10^{-4}
RAF	0.744	0.720	Adjusted[e]	1.12 (1.03, 1.21)	5.45×10^{-3}
HWE test[d]	0.046	0.36			
rs1436955 G[c]/A, 15q22.2, *C2CD4A/C2CD4B*					
GG	4,442	1,511			
GA	3,188	1,197			
AA	610	231			
Ratio GG:GA:AA	0.54:0.39:0.07	0.51:0.41:0.08	Unadjusted	1.08 (1.01, 1.15)	0.030
RAF	0.733	0.718	Adjusted[e]	1.10 (1.02, 1.19)	0.0130
HWE test[d]	0.25	0.78			
rs10751301 G/C[c], 11q14.1, *ODZ4*					
CC	607	220			
CG	3,252	1,157			
GG	4,266	1,533			
Ratio CC:CG:GG	0.07:0.40:0.53	0.07:0.40:0.53	Unadjusted	1.00 (0.94, 1.07)	0.95
RAF	0.275	0.274	Adjusted[e]	0.98 (0.91, 1.05)	0.54
HWE test[d]	0.71	0.93			

[a] Participant total n=8,552; control total n=2,978

[b] Calculated in logistic regression analysis with additive model

[c] Reported risk allele for type 2 diabetes

[d] p values for HWE test are presented

[e] For age, sex and log-transformed BMI

RAF, Risk allele frequency

by those genetic loci [1]; thus, the majority of type 2 diabetes heritability genes remain unknown for these populations, and this applies even more so for populations not of European origin. By combining the present results with the original findings of Shu et al [9], rs10906115 and rs1359790 can now be considered to be convincing susceptibility loci for type 2 diabetes across different ethnic groups.

With regard to rs10906115 within the *CDC123/CAMK1D* locus, this SNP exists in the same linkage disequilibrium block as that for rs12779790, which was previously identified as a type 2 diabetes susceptibility SNP by European GWAS [16]. However, the linkage disequilibrium coefficient between rs10906115 and rs12779790 is low, as derived from genotype data from the present study (r^2=0.11), as well as from HapMap Japanese in Tokyo (JPT) (r^2=0.12), HapMap Han Chinese in Beijing, China (CHB) (r^2=0.05) and HapMap Centre d'Etude du Polymorphisme (Utah residents with northern and western European ancestry; CEU) (r^2=0.19) data (http://hapmap.ncbi.nlm.nih.gov/, accessed 22 June 2011). Using conditional analysis, we showed that rs10906115 was associated with type 2 diabetes independently of rs12779790, whereas the association between rs12779790 and type 2 diabetes (p=0.036) was no longer significant after conditioning on rs10906115 in the present Japanese population; this confirms results previously reported by Shu et al. [9].

Table 2 Results of a meta-analysis for the present Japanese study and the previous study [9]

SNP, gene	Model	OR (95% CI)[a]	*p* value[a]	Heterogeneity test, Q[b]	Heterogeneity test, I^2 (%)
rs10906115 A[c]/G, *CDC123/CAMK1D*					
Present study		1.17 (1.09, 1.25)	9.16×10^{-6}		
Shu et al. [9]		1.13 (1.08, 1.18)	1.45×10^{-8}		
Both	Fixed	1.14 (1.10, 1.18)	8.81×10^{-13}	0.40	0
Both	Random	1.14 (1.10, 1.18)	8.81×10^{-13}		
rs1359790 C[c]/T, *SPRY2*					
Present study		1.12 (1.03, 1.21)	5.45×10^{-3}		
Shu et al. [9]		1.15 (1.10, 1.20)	6.49×10^{-9}		
Both	Fixed	1.14 (1.10, 1.19)	1.45×10^{-10}	0.58	0
Both	Random	1.14 (1.10, 1.19)	1.45×10^{-10}		
rs1436955 G[c]/A, *C2CD4A/C2CD4B*					
Present study		1.10 (1.02, 1.19)	0.013		
Shu et al. [9]		1.13(1.08, 1.19)	7.14×10^{-7}		
Both	Fixed	1.12 (1.08, 1.17)	3.52×10^{-8}	0.56	0
Both	Random	1.12 (1.08, 1.17)	3.52×10^{-8}		
rs10751301 G/C[c], *ODZ4*					
Present study		0.98 (0.91, 1.05)	0.54		
Shu et al. [9]		1.10 (1.05, 1.15)	1.31×10^{-4}		
Both	Fixed	1.05 (1.01, 1.10)	0.0073	0.0052	87.2
Both	Random	1.04 (0.93, 1.17)	0.49		

[a] Adjusted for age, sex and BMI; *p* values additive

[b] Cochran's Q statistic

[c] Reported risk allele for type 2 diabetes

Thus, at least in East Asian populations, rs10906115 is likely to be linked more directly to true causal variation(s) involved in conferring susceptibility to type 2 diabetes.

However, in European populations rs10906115 did not show significant association with type 2 diabetes by itself (p=0.11 in the Wellcome Trust Case Control Consortium/UK Type 2 Diabetes Genetics consortium [WTCCC/UKT2D] [www.wtccc.org.uk/info/access_to_data_samples.shtml, accessed 14 December 2007], p=0.5 in Diabetes Genetics Initiative [www.broadinstitute.org/diabetes/scandinavs/type2.html, accessed 27 January 2011]). Since conditional analysis for rs10906115 and rs12779790 has not been robustly

Table 3 Conditional analysis for rs10906115 and rs12779790

SNP	Region	Position[a]	Risk allele frequency		OR[b] (95% CI)	*p* value[b]
			Type 2 diabetes (n=2,798)	Control (n=2,403)		
rs10906115 A[c]/G	10p13	12314997	0.580	0.549	1.16 (1.06, 1.26)[d]	0.0010
					1.14 (1.04, 1.25)[e]	0.0051
rs12779790 A/G[c]	10p13	12328010	0.155	0.143	1.13 (1.01, 1.28)[f]	0.036
					1.09 (0.96, 1.24)[g]	0.19

[a] Indicates genomic position based on data from the National Center for Biotechnology Information database (Entrez SNP, Genome Reference Consortium Human Build 37.1; www.ncbi.nlm.nih.gov/sites/entrez?db=snp, accessed 22 June 2011)

[b] Data with adjustment for age, sex and log-transformed BMI are presented; *p* values are additive

[c] Reported risk allele for type 2 diabetes

[d] Without adjustment for rs12779790

[e] With adjustment for rs12779790

[f] Without adjustment for rs10906115

[g] With adjustment for rs10906115

Table 4 Association of four SNPs with quantitative metabolic traits

SNP	FPG[a]			HOMA-IR[a]			HOMA-B[a]		
	β[b]	SE	*p* value	β[b]	SE	*p* value	β[b]	SE	*p* value
rs10906115 A[c]/G	−0.003	0.004	0.43	0.021	0.023	0.35	0.034	0.024	0.15
rs1359790 C[c]/T	−0.00005	0.004	0.99	−0.001	0.025	0.98	−0.023	0.027	0.40
rs1436955 G[c]/A	0.005	0.004	0.19	0.005	0.025	0.85	−0.036	0.026	0.16
rs10751301 G/C[c]	−0.003	0.004	0.42	−0.009	0.025	0.73	0.005	0.026	0.84

All association data were adjusted for age, sex and log-transformed BMI

[a] Log-transformed values for FPG (mmol/l, n=1,332), HOMA-IR (n=900) or HOMA-B (n=900) were used as the dependent valuables in the linear regression models

[b] Regression coefficient

[c] Reported risk allele for type 2 diabetes

performed in European populations, it is not clear whether the effects of these two SNPs on susceptibility to type 2 diabetes reflect the consequence of an identical causal variant, which is linked more closely to rs12779790 in European populations, or whether they are associated, independently of each other, with the disease. Fine-mapping of this locus among different ethnic groups including Asians and Europeans will be necessary to answer this question.

In the report by Shu et al., two additional SNPs showing modest associations with type 2 diabetes were identified, namely rs1436955 and rs10751301 (rs1436955 $p=7.14\times10^{-7}$, rs10751301 $p=1.31\times10^{-4}$) [9]. We therefore also examined the association between these two and type 2 diabetes in the Japanese. The variant rs1436955 is located in the *C2CD4A*/*C2CD4B* locus, which is a confirmed type 2 diabetes locus [4] and also associated with type 2 diabetes in the present Japanese population (OR 1.10, 95% CI 1.02, 1.19; p=0.013 adjusted; Table 1). However, the association between rs1436955 and type 2 diabetes disappeared after conditioning on a previously reported variant, rs7172432 (p=0.46; ESM Table 3). Since rs7172432 showed stronger association in the present population ($p=8.86\times10^{-5}$; ESM Table 3) and the association remained significant even after conditioning on rs1436955, the association for rs1436955 is unlikely to be independent on the already confirmed signal. We did not observe a significant association between rs10751301 and type 2 diabetes in the Japanese population (OR 0.98, 95% CI 0.91, 1.05; p=0.54 adjusted; Table 1). Although the present Japanese study had sufficient power to replicate the association reported previously (91% for α=0.05), it cannot be completely ruled out that a small number of participants with impaired glucose tolerance were included in our control samples, as OGTTs were not always performed to select the control individuals, and this could have reduced the power of our study.

The mechanisms by which the variants evaluated contribute to susceptibility to type 2 diabetes are unknown. *CDC123* and *CAMK1D*, both genes in the vicinity of rs10906115, encode a protein involved in cell cycle regulation [17] and a member of the Ca^{2+}/calmodulin-dependent protein kinase 1 subfamily of serine threonine kinases [18], respectively. The variant rs1359790 is located 200 kb downstream of *SPRY2*, which encodes a protein belonging to the sprouty family and has been shown to inhibit growth factor-mediated, receptor tyrosine kinase-induced, mitogen-activated protein kinase signalling [19]. The roles of these genes in pancreatic beta cells or peripheral tissues involved in glucose metabolism have not yet been elucidated.

Impaired beta cell function in rs12779790 G allele carriers has been reported in European [20, 21] and Asian Indian populations. Grarup et al. reported that glucose-stimulated insulin secretion was decreased in homozygous carriers of rs12779790 G during OGTTs, without affecting fasting serum glucose or fasting serum insulin [20]. Simonis-Bik et al. also demonstrated a decreased second-phase insulin response in risk allele carriers during a 2-h hyperglycaemic clamp [21]. In Asian Indians, carriers of the rs12779790 G allele were shown to have decreased plasma insulin levels and lower HOMA-B [22], but these effects were more obvious in type 2 diabetes cases than in control participants.

We analysed the association of rs10906115 and rs1359790 with metabolic traits such as FPG, HOMA-IR and HOMA-B using control participants with no diabetes; however, we did not observe a significant correlation between the two variants and these metabolic traits, but

our sample size might not have been large enough (ESM Table 5). Differences in study design and/or experimental procedures may underlie the discrepancy between the results of the present study and those of previous studies indicating an association between the *CDC123*/*CAMK1D* locus and quantitative traits related to glucose metabolism [20–22]. Further studies are required to clarify the precise mechanisms of how variants in these loci confer susceptibility to type 2 diabetes.

In conclusion, we identified a significant association of rs10906115 and rs1359790 with type 2 diabetes in a Japanese population, thus confirming a role for these loci in conferring susceptibility to type 2 diabetes across East Asian populations.

Acknowledgements We thank M. Nakamura, R. Tsuzuki, R. Okumura and R. Kusano at the Laboratory for Endocrinology and Metabolism, RIKEN Center for Genomic Medicine, for their technical assistance. This work was partly supported by a grant from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

Contribution statement MIm contributed to analysis and interpretation of data, drafting the article. MIw, HM, HW, HH, YT, KT, KK, AK, RK and YN contributed to analysis and interpretation of data and revising the article critically for important intellectual content. SM designed the study, researched the data, contributed to critical discussion and reviewed/edited the manuscript. All authors have approved the final version of the manuscript to be published.

Duality of interest The authors declare that there is no duality of interest associated with this manuscript.

References

1. Billings LK, Florez LC (2010) The genetics of type 2 diabetes: what we learned from GWAS? Ann N Y Acad Sci 1212:59–77
2. Unoki H, Takahashi A, Kawaguchi T et al (2008) SNPs in *KCNQ1* are associated with susceptibility to type 2 diabetes in East Asian and European populations. Nat Genet 40:1098–1102
3. Yasuda K, Miyake K, Horikawa Y et al (2008) Variants in *KCNQ1* are associated with susceptibility to type 2 diabetes mellitus. Nat Genet 40:1092–1097
4. Yamauchi T, Hara K, Maeda S et al (2010) A genome-wide association study in the Japanese population identifies susceptibility loci for type 2 diabetes at *UBE2E2* and *C2CD4A-C2CD4B*. Nat Genet 42:864–868
5. Omori S, Tanaka Y, Takahashi A et al (2008) Association of *CDKAL1*, *IGF2BP2*, *CDKN2A/B*, *HHEX*, *SLC30A8*, and *KCNJ11* with susceptibility to type 2 diabetes in a Japanese population. Diabetes 57:791–795
6. Hayashi T, Iwamoto Y, Kaku K, Hirose H, Maeda S (2007) Replication study for the association of *TCF7L2* with susceptibility to type 2 diabetes in a Japanese population. Diabetologia 50:980–984
7. Horikoshi M, Hara K, Ito C, Nagai R, Froguel P, Kadowaki T (2007) A genetic variation of the transcription factor 7-like 2 gene is associated with the risk of type 2 diabetes in the Japanese population. Diabetologia 50:747–751
8. Onuma H, Tabara Y, Kawamoto R et al (2010) The *GCKR* rs780094 polymorphism is associated with susceptibility of type 2 diabetes, reduced fasting plasma glucose levels, increased triglycerides levels and lower HOMA-IR in Japanese population. J Hum Genet 55:600–604
9. Shu XO, Long J, Cai Q et al (2010) Identification of new genetic risk variants for type 2 diabetes. Plos Genet 6:e1001127
10. Alberti KG, Zimmet PZ (1998) Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. Diabet Med 15:539–553
11. Maeda S, Tsukada S, Kanazawa A et al (2005) Genetic variations in the gene encoding *TFAP2B* are associated with type 2 diabetes mellitus. J Hum Genet 50:283–292
12. Omori S, Tanaka Y, Horikoshi M et al (2009) Replication study for the association of new meta-analysis derived risk loci with susceptibility to type 2 diabetes in 6,244 Japanese individuals. Diabetologia 52:1554–1560
13. Nielsen DM, Ehm MG, Weir BS (1998) Detecting marker-disease association by testing for Hardy–Weinberg disequilibrium at a marker locus. Am J Hum Genet 63:1531–1540
14. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC (1985) Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 28:412–419
15. Wallace TM, Levy JC, Matthews DR (2004) Use and abuse of HOMA modeling. Diabetes Care 27:1487–1495
16. Zeggini E, Scott LJ, Saxena R et al (2008) Meta-analysis of genome-wide association data and large-scale replication identifies additional susceptibility loci for type 2 diabetes. Nat Genet 40:638–645
17. Bieganowski P, Shilinski K, Tsichlis PN, Brenner C (2004) Cdc123 and checkpoint forkhead associated with RING proteins control the cell cycle by controlling eIF2gamma abundance. J Biol Chem 279:44656–44666
18. Verploegen S, Ulfman L, van Deutekom HW et al (2005) Characterization of the role of CaMKI-like kinase (*CKLiK*) in human granulocyte function. Blood 106:1076–1083
19. Cabrita MA, Christofori G (2008) Sprouty proteins, masterminds of receptor tyrosine kinase signaling. Angiogenesis 11:53–62
20. Grarup N, Andersen G, Krarup NT et al (2008) Association testing of novel type 2 diabetes risk alleles in the *JAZF1*, *CDC123*/*CAMK1D*, *TSPAN8*, *THADA*, *ADAMTS9*, and *NOTCH2* loci with insulin release, insulin sensitivity, and obesity in a population-based sample of 4,516 glucose-tolerant middle-aged Danes. Diabetes 57:2534–2540
21. Simonis-Bik AM, Nijpels G, van Haeften TW et al (2010) Gene variants in the novel type 2 diabetes loci *CDC123*/*CAMK1D*, *THADA*, *ADAMTS9*, *BCL11A*, and *MTNR1B* affect different aspects of pancreatic beta-cell function. Diabetes 59:293–301
22. Sanghera DK, Been L, Ortega L et al (2009) Testing the association of novel meta-analysis-derived diabetes risk genes with type II diabetes and related metabolic traits in Asian Indian Sikhs. J Hum Genet 54:162–168