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Genotype risk score of common susceptible variants for prediction of type 2 diabetes mellitus in Japanese: the Shimanami Health Promoting Program (J-SHIPP study)

Development of type 2 diabetes mellitus and genotype risk score

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ABSTRACT

Recent genomewide association studies have successfully identified several genotypes susceptible to type 2 diabetes mellitus (T2DM). However, only a few studies have investigated whether these variations confer a risk of the future development of T2DM. We conducted a longitudinal genetic epidemiological study to clarify the prognostic significance of the T2DM-associated variants. The sample population consisted of 2037 middle-aged to elderly community residents. Personal health records were obtained from a clinical database administered by the local government. Genotype risk score was calculated by the following variants, namely, KCNQ1, TCF7L2, CDKAL1, HHEX, IGF2BP2, CDKN2AB, SLC30A8, KCNJ11, PPARG, and GCKR. Susceptibility of these variants in Japanese has been confirmed by association analysis. Among the 1824 subjects who did not have T2DM at baseline, 95 cases of T2DM were newly diagnosed during the 9.4-year follow-up period. Mean genotype risk score in these subjects was significantly higher than that in the subjects who remained nondiabetic (9.5 ± 1.8 vs 9.1 ± 2.0, $P = .042$). Although the initial mean body mass index (24.7 ± 3.2 vs 23.0 ± 2.8, $P < .001$) and initial glucose (106 ± 18 vs 90 ± 13, $P < .001$) were also significantly higher in those subjects who developed T2DM, the genotype risk score remained an independent determinant of the development of T2DM even after adjustment for these parameters and possible

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confounding factors. Per-allele odds ratio for the development of T2DM was 1.12 (95% confidence interval, 1.00-1.25; $P = .049$). Type 2 diabetes mellitus–susceptible genetic variants identified by a cross-sectional genomewide association study were significantly associated with the future development of T2DM in a general population sample.

1. Introduction

Recent genomewide association studies (GWASs) have successfully identified several genotypes conferring susceptibility to type 2 diabetes mellitus (T2DM) [1]. These associations have been replicated in various populations, including East Asians [2-7]. Our previous meta-analysis also confirmed the disease susceptibility of the initially identified TCF7L2, CDKAL1, HHEX, CDKN2AB, IGF2BP2, SLC30A8, and KCNJ11 in Japanese [8]. In contrast to the accumulated evidence for a cross-sectional association, however, only a few studies have investigated whether these variations confer a risk of the future development of T2DM [9-13]. Here, to clarify the prognostic significance of these T2DM-associated variants, we conducted a longitudinal genetic epidemiological study in a community-dwelling general population. Furthermore, we also investigated the cross-validity and prognostic significance of the additionally identified susceptible genes, including MTNR1B, TSPAN8, CDC123, ADAMTS9, THADA, JAZF1, PANK1, HK1, WFS1, and TCF2 [14-21], as well as KCNQ1, which was identified by a Japanese GWAS [22].

2. Subjects and methods

2.1. T2DM case and control subjects

All T2DM subjects (n = 506) were in- or outpatients evaluated by diabetes specialists at Ehime University Hospital and Ehime Prefectural Hospital in Japan. Diabetes mellitus was diagnosed based on the 1998 American Diabetes Association criteria. Nondiabetic control subjects (n = 402) were chosen based on the absence of a history of diabetes in the subject and first-degree relatives, as well as either normal glucose tolerance, confirmed by a 75-g oral glucose tolerance test, or hemoglobin A_{1c} levels less than 5.6, with fasting plasma glucose levels less than 110 mg/dL. All case and control subjects were ethnic Japanese. Selection criteria details have been described in a previous study [23].

2.2. General population sample

Study subjects were selected from the residents of a community of 11 000 inhabitants in Ehime Prefecture, a largely rural area located in western Japan [8]. Subjects were recruited through a community-based annual medical checkup process in 2002 for self-employed individuals and included farmers and foresters, employees of small companies, and elderly persons without fixed employment. The sample population consisted of 2895 middle-aged to elderly residents. Of these, 2037 subjects with available overnight fasting plasma samples for the measurement of insulin were enrolled in the cross-sectional analysis. The homeostasis model assessment of insulin resistance (HOMA-IR) ([fasting plasma insulin (microunits per milliliter) × glucose (milligrams per deciliter)]/405) was used as an index of insulin resistance. Insulin secretion was evaluated by the homeostasis model assessment of β-cell function (HOMA-β) ([fasting plasma insulin (microunits per milliliter) × 360]/[glucose (milligrams per deciliter) – 63]). Baseline clinical characteristics were obtained from personal health records evaluated during the medical checkup. *Type 2 diabetes mellitus* was defined as the presence of any or all of the following: plasma fasting glucose more than 126 mg/dL, nonfasting glucose more than 200 mg/dL, and oral antidiabetic medication. All study procedures were approved by the ethics committee of Ehime University Graduate School of Medicine, and informed consent was obtained from each participating subject.

2.3. Retrospective study

Personal health records evaluated at previous medical checkups were obtained from a clinical database administered by the local government. For each subject, the oldest data available between 1992 and 1996 were obtained. Among 2895 subjects, those for whom retrospective data were available (n = 1897) and who were regarded as nondiabetic at initial measurement (n = 1824) were included in the analysis. Mean duration of follow-up was 9.4 ± 1.0 years.

2.4. Genotyping

Genomic DNA was extracted from peripheral blood (QIAamp DNA blood kit, QIAGEN, Hilden, Germany). All single nucleotide polymorphisms (SNPs) were analyzed by TaqMan probe assay (Applied Biosystems, Foster City, CA) using commercially available primers and probes purchased from the Assay-on-Demand system.

2.5. Statistical analysis

Values are expressed as mean ± standard deviation. Frequency differences in each genotype were assessed by the χ^2 test. Associations between plasma markers and genotype risk score were assessed by linear regression analysis. Adjusted odds ratio for T2DM, as well as coefficients and standard errors for plasma markers, were calculated using logistic and linear multiple regression analysis with adjustment for sex, age, and body mass index (BMI). Genotype risk score was calculated by adding the risk allele number of the following 10 SNPs: KCNQ1 rs2237892, TCF7L2 rs12255372, CDKAL1 rs7754840, HHEX rs7923837, IGF2BP2 rs4402960, CDKN2AB rs10811661, SLC30A8 rs13266634, KCNJ11 rs5219, PPARG rs1801282, and GCKR rs780094. We previously reported the

Table 1 – Association of candidate SNPs with T2DM in case-control analysis (n = 908)

Gene	rs no. (MAF)	Risk allele	Genotype frequency		Allelic		Recessive		Dominant		Additive
			Genotype	T2DM Control	Odds (95% CI)	P	Odds (95% CI)	P	Odds (95% CI)	P	P
KCNQ1	rs2237892 (0.348)	C	CC/CT/TT	243/206/44 136/193/65	**1.63 (1.34-1.99)**	**$9.9^{*}\ 10^{-7}$**	**1.84 (1.40-2.42)**	**$1.1^{*}\ 10^{-5}$**	**2.02 (1.34-3.03)**	**0.001**	**$6.4^{*}\ 10^{-6}$**
MTNR1B	rs1387153 (0.390)	T	TT/TC/CC	73/226/196 65/195/139	0.88 (0.72-1.06)	.175	0.89 (0.62-1.28)	.526	0.82 (0.62-1.07)	.144	.339
MTNR1B	rs10830963 (0.406)	G	GG/GC/CC	77/230/181 72/192/134	0.89 (0.73-1.07)	.222	0.85 (0.60-1.21)	.360	0.86 (0.65-1.14)	.290	.478
MTNR1B	rs1447352 (0.359)	G	GG/GA/AA	68/235/193 48/174/176	1.16 (0.96-1.41)	.127	1.16 (0.78-1.72)	.466	1.24 (0.95-1.63)	.109	.270
WFS1	rs10010131 (0.007)	G	GG/GA/AA	487/7/0 388/6/0	1.08 (0.36-3.21)	.897	1.08 (0.36-3.23)	.896			
TCF2	rs4430796 (0.377)	G	GG/GA/AA	65/240/192 65/174/159	0.96 (0.79-1.16)	.675	0.77 (0.53-1.12)	.171	1.06 (0.81-1.38)	.688	.258
TSPAN8	rs7961581 (0.211)	C	CC/CT/TT	26/170/300 20/115/261	1.18 (0.94-1.49)	.149	1.04 (0.57-1.89)	.898	1.26 (0.96-1.66)	.096	.231
CDC123	rs12779790 (0.146)	G	GG/GA/AA	10/126/359 7/99/289	1.04 (0.79-1.35)	.792	1.14 (0.43-3.03)	.788	1.03 (0.77-1.39)	.831	.953
ADAMTS9	rs4607103 (0.342)	C	CC/CT/TT	226/205/65 171/180/49	1.04 (0.86-1.27)	.664	1.12 (1.12-0.86)	.399	0.93 (0.62-1.38)	.703	.544
THADA	rs7578597 (0.006)	T	TT/TC/CC	485/7/0 394/4/0	0.71 (0.21-2.42)	.578	0.70 (0.20-2.42)	.577			
JAZF1	rs864745 (0.194)	T	TT/TC/CC	330/140/24 261/113/22	1.05 (0.83-1.33)	.673	1.04 (0.79-1.38)	.779	1.15 (0.64-2.09)	.641	.889
PANK1	rs11185790 (0.428)	G	GG/GA/AA	156/244/90 130/199/69	0.96 (0.80-1.16)	.694	0.96 (0.73-1.28)	.793	0.93 (0.66-1.32)	.690	.915
HK1	rs7072268 (0.303)	T	TT/TC/CC	249/209/40 185/165/43	1.15 (0.94-1.41)	.183	1.12 (0.86-1.47)	.386	1.41 (0.89-2.21)	.139	.304

Previously reported risk alleles are shown. Frequency differences in each genotype were assessed by the χ^2 test. MAF indicates minor allele frequency. Statistical significance is highlighted by bold text.

Table 2 – Cross-sectional analysis with T2DM-related plasma markers in a general population sample (n = 1969)

Gene	rs no.	Glucose (mg/dL)			Insulin (μU/mL)			HOMA-IR			HOMA-β		
		β	(SE)	P	β	(SE)	P	β	(SE)	P	β	(SE)	P
KCNQ1	rs2237892	−0.34	(0.55)	.535	−0.08	(0.14)	.571	−0.03	(0.04)	.515	0.86	(1.44)	.553
MTNR1B	rs1387153	−0.27	(0.55)	.627	−0.02	(0.14)	.886	−0.01	(0.04)	.785	0.67	(1.44)	.643
MTNR1B	rs10830963	−0.51	(0.55)	.350	−0.07	(0.13)	.588	−0.03	(0.04)	.484	0.62	(1.43)	.665
MTNR1B	rs1447352	−0.09	(0.57)	.881	−0.09	(0.14)	.501	−0.03	(0.04)	.538	−1.19	(1.47)	.419
WFS1	rs10010131	−0.02	(1.69)	.992	0.02	(0.42)	.955	−0.01	(0.12)	.958	−0.26	(4.40)	.953
TCF2	rs4430796	−0.18	(0.59)	.764	0.19	(0.14)	.194	0.05	(0.04)	.266	0.58	(1.53)	.705
TSPAN8	rs7961581	−0.56	(0.62)	.368	0.12	(0.15)	.442	0.03	(0.05)	.556	1.28	(1.62)	.430
CDC123	rs12779790	0.78	(0.76)	.303	−0.15	(0.19)	.418	−0.02	(0.06)	.717	−1.01	(1.98)	.610
ADAMTS9	rs4607103	−0.95	(0.56)	.089	0.03	(0.14)	.806	0.00	(0.04)	.949	1.02	(1.46)	.484
THADA	rs7578597	−0.25	(2.63)	.926	0.67	(0.64)	.296	0.18	(0.19)	.336	9.76	(6.84)	.154
JAZF1	rs864745	−0.42	(0.67)	.525	0.16	(0.16)	.321	0.04	(0.05)	.412	0.80	(1.73)	.644
PANK1	rs11185790	0.41	(0.54)	.451	−0.12	(0.13)	.360	−0.03	(0.04)	.473	−1.25	(1.41)	.375
HK1	rs7072268	−0.10	(0.60)	.861	−0.01	(0.14)	.920	0.00	(0.04)	.912	0.17	(1.56)	.915

Analyses were performed in subjects without antihyperglycemic treatment. Adjusted coefficients and standard errors were calculated using linear multiple regression analysis with adjustment for sex, age, and BMI. The HOMA-IR was calculated using the following equation: [fasting immunoreactive insulin (microunits per milliliter) × fasting glucose (milligrams per deciliter)]/405. The HOMA-β was calculated as follows: [fasting immunoreactive insulin (microunits per milliliter) × 360]/[fasting glucose (milligrams per deciliter) − 63].

T2DM susceptibility of all these SNPs except KCNQ1 elsewhere [8,24,25]. All statistical analyses were performed using a commercially available statistical software package (JMP version 8; SAS Institute, Cary, NC).

3. Results

3.1. Cross-sectional analysis of candidate SNPs

Table 1 shows the results of cross-sectional association analysis in the T2DM case-control subjects (Supplemental Table 1). Among 13 recently identified candidate SNPs, a significant association was observed only for the KCNQ1 rs2237892 polymorphism. Associations with T2DM-related plasma markers in the general population sample without antihyperglycemic treatment are summarized in Table 2. None of 13 SNPs, including KCNQ1, showed any significant correlation with plasma levels of glucose, insulin, HOMA-IR, or HOMA-β.

3.2. Cumulative effects of risk alleles

The cumulative effects of the T2DM SNPs on the plasma markers are shown in Table 3. The genotype risk score was calculated by adding the risk allele number of KCNQ1 and the following 7 SNPs that we previously confirmed to have T2DM susceptibility by meta-analyzing association studies in Japanese, namely, TCFL7L2, CDKAL1, HHEX, IGF2BP2, CDKN2AB, SLC30A8, and KCNJ11 [8]. Susceptibility of the other 2 SNPs in Japanese, namely, PPARG and GCKR, has also been confirmed in several studies, including our previous report [24-27]. Although each SNP had only a small effect on plasma glucose and insulin levels [8,24,25], the genotype risk score, calculated by adding the number of risk alleles of 10 validated SNPs, showed stepwise association with plasma glucose levels and HOMA-β after adjustment for possible covariates (Table 3). The genetic score was also associated with the frequency of T2DM in the case-control sample (Supplemental Figure 1), with the highest odds ratio in subjects having more than 12 risk alleles being 5.60 (95% confidence interval [CI], 3.19-11.2; $P = 3.1 * 10^{-8}$).

Table 3 – Genotype risk score and plasma markers in the general population sample (n = 1908)

No. of risk genotypes	n	Glucose (mg/dL)	Insulin (μU/mL)	HOMA-IR	HOMA-β
<6	168	94.5 ± 16.9	6.89 ± 4.93	1.68 ± 1.52	83.5 ± 52.8
7	243	94.5 ± 11.5	6.55 ± 4.91	1.56 ± 1.33	78.2 ± 51.5
8	338	96.3 ± 19.2	6.51 ± 4.76	1.60 ± 1.35	76.6 ± 53.6
9	368	96.6 ± 19.3	6.43 ± 4.38	1.58 ± 1.29	73.3 ± 46.3
10	324	97.1 ± 15.9	6.61 ± 4.58	1.64 ± 1.28	74.5 ± 46.9
11	250	99.4 ± 21.2	6.58 ± 5.18	1.66 ± 1.48	70.9 ± 48.6
12<	217	98.3 ± 17.0	6.77 ± 5.68	1.74 ± 1.79	72.2 ± 51.3
P (crude)		$4.8^* 10^{-5}$	.752	.580	.004
P (adjusted)		$1.2^* 10^{-6}$	.511	.083	.006

Values are mean ± standard deviation. Analyses were performed in subjects without antihyperglycemic treatment and genotyped for all SNPs. Statistical significance was assessed by simple linear regression analysis (crude model) and a multiple linear regression model adjusted for sex, age, and BMI. All dependent variables were log-transformed in the regression analysis. Genotype risk score was calculated by adding the risk allele number of the following 10 SNPs: KCNQ1 rs2237892, TCF7L2 rs12255372, CDKAL1 rs7754840, HHEX rs7923837, IGF2BP2 rs4402960, CDKN2AB rs10811661, SLC30A8 rs13266634, KCNJ11 rs5219, PPARG rs1801282, and GCKR rs780094.

Table 4 – Development of T2DM and accumulation of risk genotypes on follow-up for 9.4 years (n = 1824)

		Model 1		Model 2	
		Odds ratio (95% CI)	P	Odds ratio (95% CI)	P
Age (y)		1.02 (1.00-1.04)	.073	1.00 (0.99-1.03)	.416
Sex		1.58 (1.40-2.40)	.031	1.14 (0.72-1.79)	.567
BMI (kg/m^2)				1.17 (1.09-1.26)	<.001
Glucose (mg/dL)				1.05 (1.04-1.06)	<.001
No. of risk genotypes	≤7	Reference		Reference	
	8-10	2.22 (1.20-4.51)	.010	2.67 (1.35-5.86)	.008
	≥11	2.12 (1.05-4.54)	.035	2.48 (1.16-5.73)	.025

Adjusted odds ratio for T2DM was calculated using logistic regression analysis.

3.3. *9.4-year longitudinal analysis for the development of T2DM*

To clarify the prognostic significance of the T2DM SNPs in the development of diabetes, we retrospectively analyzed the association between genotype risk score and the development of T2DM with 9.4 years of follow-up (Table 4). Among the 1824 subjects who did not have T2DM at baseline, 95 cases of T2DM were newly diagnosed during the follow-up period. These subjects were slightly older (58 ± 9 vs 56 ± 10 years, $P = .091$) and more frequently male (50.5% vs 39.6%, $P = .035$). Mean risk score in these subjects was significantly higher than that in the 1729 subjects who remained nondiabetic (9.5 ± 1.8 vs 9.1 ± 2.0, $P = .042$). Although the initial mean BMI (24.7 ± 3.2 vs 23.0 ± 2.8, $P < .001$) and initial glucose (106 ± 18 vs 90 ± 13 $P < .001$) were also significantly higher in those subjects who developed T2DM, the genotype risk score remained an independent determinant of the development of T2DM even after adjustment for these parameters and possible confounding factors (Table 4). Per-allele odds ratio for the development of T2DM was 1.12 (95% CI, 1.00-1.25; $P = .049$).

4. Discussion

Here, we found that T2DM-susceptible genetic variants identified in a cross-sectional GWAS were significantly associated with the future development of T2DM in a Japanese general population sample. Predictive ability was independent of major clinical risk factors, including BMI and glucose levels. Genetic information may provide additional information that facilitates the differentiation of persons at risk for T2DM before the manifestation of clinical signals.

The cross-validity of these T2DM-susceptible variants has been reported by numerous studies in various populations. However, cross-sectional results do not always warrant predictive value. Confirmation of predictability requires independent data based on longitudinal genetic epidemiological studies, but little such data are presently available. Three recent articles based on Swedish and Finnish general populations [9], the Framingham study cohort [10], and the Nurses' Health Study [13] reported that the common genetic variants conferring susceptibility for diabetes predict the future development of T2DM independently of clinical risk factors. Because the etiology of T2DM in East Asians, who show lower basal insulin secretion and a marked decrease in insulin release in response to the development of glucose tolerance [28,29], appears to differ from that in whites or individuals of European origin, our results provide further evidence for the disease predictability of the common genetic variants that are likely associated with insulin secretion levels from β-cells [30].

Our subjects were slightly older (56 ± 10 years old) than those in previous studies of the predictive value of common susceptible variants, namely, the Framingham study (35 years) [10], DESIR (Data from an Epidemiological Study on the Insulin Resistance syndrome) prospective study (48 years) [12], Botnia study (45 years) [11], Malmö study (46 years) [9], and the Nurses' Health Study (44-56 years) [13]. Our present finding that mean age did not differ between subjects who did and did not develop T2DM during the follow-up period suggests that genotype risk score might also be a marker in middle-aged and elderly subjects. Similar to these previous results, however, we found that the genotype risk score based on 10 risk alleles has only a small effect in predicting the future development of T2DM. Per-allele odds ratio in our Japanese subjects was closely similar to that in subjects of European descent [9-13]. Meigs et al [10] reported that the combination of risk alleles showed modest discriminatory ability in the Framingham offspring cohort, particularly in subsamples of younger subjects. Lyssenko et al [9] also reported that the predictive ability of genetic risk factors was increased by increasing the duration of follow-up. These results suggest that genetic risk factor assessments are more meaningful during earlier life. The finding that our older subjects' assessments showed similar impact on the development of T2DM suggests that East Asians benefit more greatly from genetic assessment.

No significant association was observed between common individual susceptible variants and plasma glucose or insulin levels. Furthermore, we also previously reported a lack of association of initially identified susceptible variants with these plasma markers [8]. Although the effect of individual variants on the plasma markers appeared to be small, the accumulation of risk genotypes was significantly correlated with increased plasma glucose and decreased HOMA-β levels. Association with these plasma markers may be a factor in the disease predictability of the genotype risk score.

Several limitations of this study warrant mention. First, the present study is retrospective in design; and the period of T2DM onset in each subject was not precisely determined. Furthermore, changes in clinical parameters during the follow-up period could not be taken into consideration. Second, because our subjects consisted of middle-aged and

elderly persons, our findings cannot be simply extrapolated to adolescents. Extension of these findings to estimate the size of the genetic effect will require further studies with younger subjects. Third, our sample size, in particular the number of persons who developed T2DM during the follow-up period, was relatively small. Analysis using a larger population may elucidate details of genetic determination for the onset of T2DM.

In summary, we found that genotype risk score based on 10 common susceptible variants was significantly associated with the new onset of T2DM in Japanese. Although the discrimination model can be further improved, namely, via the addition of a greater number of common variants with lesser effects or of rarer variants with apparently greater impact on disease susceptibility, genotype information has the possibility of allowing the more accurate prediction of T2DM onset than variable pathophysiological markers.

Supplementary materials related to this article can be found online at doi:10.1016/j.metabol.2011.03.014.

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