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ORIGINAL ARTICLE

Variations in/nearby genes coding for *JAZF1*, *TSPAN8/LGR5* and *HHEX-IDE* and risk of type 2 diabetes in Han Chinese

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Several genetic loci (*JAZF1, CDC123/CAMK1D, TSPAN8/LGR5, ADAMTS9*, *VEGFA* and *HHEX-IDE*) were identified to be significantly related to the risk of type 2 diabetes and quantitative metabolic traits in European populations. Here, we aimed to evaluate the impacts of these novel loci on type 2 diabetes risk in a population-based case–control study of Han Chinese (1912 cases and 2041 controls). We genotyped 13 single-nucleotide polymorphisms (SNPs) in/near these genes and examined the differences in allele/genotype frequency between cases and controls. We found that both *IDE* rs11187007 and *HHEX* rs1111875 were associated with type 2 diabetes risk (for both variants: odds ratio (OR)=1.15, 95% confidence interval (CI) 1.04–1.28, P=0.009). In a meta-analysis where we pooled our data with the three previous studies conducted in East Asians, we found that the variants of *JAZF1* rs864745 (1.09 (1.03–1.16); $P=3.49\times10^{-3}$) and *TSPAN8/LGR5* rs7961581 (1.11 (1.05–1.17); $P=1.89\times10^{-4}$) were significantly associated with type 2 diabetes risk. In addition, the meta-analysis (7207 cases and 8260 controls) also showed that *HHEX* rs1111875 did have effects on type 2 diabetes in Chinese population (OR=1.15(1.10–1.21); $P=1.93\times10^{-8}$). This large population-based study and meta-analysis further confirmed the modest effects of the *JAZF1, TSPAN8/LGR5* and *HHEX-IDE* loci on type 2 diabetes in Chinese and other East Asians.
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Keywords: association study; Han Chinese population; HHEX; type 2 diabetes

INTRODUCTION

Type 2 diabetes is a prevalent chronic disease caused by the complex interplay of multiple genetic variants and environmental factors. In the past two decades, a total of 18 loci have been confirmed as type 2 diabetes risk loci with modest effect sizes in populations of European descent.[1,2] Although most of these same loci have been confirmed to be associated with type 2 diabetes in Chinese,[3–6] differences in allele frequency, genetic background, lifestyle and environmental exposures may lead to inconsistent results or different effect size of some genetic variants on type 2 diabetes risk between Chinese and European (for example, *TCF7L2, HHEX-IDE, JAZF1, CDC123/CAMK1D, TSPAN8/LGR5*).[3,6]

The association between the five loci (*JAZF1, CDC123/CAMK1D, TSPAN8/LGR5, VEGFA* and *ADAMTS9*) and type 2 diabetes were first identified by Zeggini *et al.*[7] with meta-analysis of three genome-wide association studies. Subsequently, several replication studies indicated that most of the novel type 2 diabetes genes (*JAZF1, TSPAN8/LGR5, CDC123/CAMK1D* and so on) appeared to affect various specific aspects of β-cell function.[8–10] However, no significant association was detected for single-nucleotide polymorphisms (SNPs) from *JAZF1, TSPAN8-LGR5, THADA, ADAMTS9, NOTCH2* in the previous Han Chinese study.[3] Replication studies in other Asian populations just identified marginal significance of type 2 diabetes risk associated with some of these novel loci.[11–13] We thought that the possible reasons for no or marginal significance were the limited sample size of these Asian population studies. To identify the effects of these genes on type 2 diabetes, we conducted a meta-analysis by pooling our data with those reported in the previous studies of East Asians.

HHEX-IDE locus was located at 10q region, which has previously been linked to fasting glucose, HbA1c levels and type 2 diabetes.[14] Both *HHEX* and *IDE* genes have strong biological claims for a role in type 2 diabetes pathogenesis. However, all significant variants of this

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locus identified by genome-wide association studies of different ethnic groups were all located in 3′ region of *HHEX* gene,[15–18] therefore, some studies suggested that *HHEX* was the most likely causal candidate gene for type 2 diabetes in chromosome 10q23–q25[19] and paid much attention to the *HHEX* gene. Here, eight common tag-SNPs, which covered both *HHEX* and *IDE* genes, were genotyped to analyze their effects on type 2 diabetes. Moreover, we also conducted a meta-analysis only in Chinese population to examine rs1111875 type 2 diabetes risk for the inconsistent results of previous studies.

MATERIALS AND METHODS

Participants

A total of 3953 individuals, Han Chinese, were enrolled in the current analysis from Shanghai, China.[20] An interview was conducted by trained physicians or public health workers from the Pudong and Baoshan Centers for Disease Control and Prevention. The study individuals need to meet the following two criteria: (1) they were stable residents in the areas and (2) they were free from severe psychological disorders, physical disabilities and diagnosed with cancer, tuberculosis, AIDS and other communicable diseases within 6 months. Written informed consent was obtained from all the participants.

A total of 1912 type 2 diabetes patients (785 men, 1127 women; age 63.9 ± 9.5 years) were defined in accordance with World Health Organization criteria (fasting plasma glucose (FPG) $\geqslant 7.0\,\mathrm{mmol\,l^{-1}}$ and/or 2-hour plasma glucose $\geqslant 11.1\,\mathrm{mmol\,l^{-1}}$). Moreover, more than 50% of type 2 diabetes patients were diagnosed at the age of 45–65 years and have 5–15 years duration of disease. In all, 2041 controls (635 men, 1406 women; age 58.1 ± 9.4 years),[4,20,21] with a FPG concentration $<6.1\,\mathrm{mmol\,l^{-1}}$, were enrolled from the same geographical area with cases. The overall age and sex distribution of controls were matched with that of case group.

Height, weight, hip and waist circumference, and blood pressure were measured by trained medical professionals using a standardized protocol. Body mass index (BMI) was calculated as weight (kg) per (height (m))^2. Total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, HbA1c and FPG were measured enzymatically according to standard methods using Roche modular P800 autoanalyzer (Roche, Mannheim, Germany) with reagents (Roche Diagnostics CmbH). Data are showed as medians (25–75% range) or means ± s.d. (Supplementary Table 1). High molecular weight genomic DNA was prepared from venous blood using the QuickGene 610L Automatic DNA/RNA Extraction System (Fujifilm, Tokyo, Japan).

SNPs selection

A total of 13 SNPs were genotyped, providing at least one representative SNP for each of the seven genes previously reported to be of some genome-wide significance in Europeans. These included five SNPs (rs864745 in *JAZF1*, rs7961581 in *TSPAN8/LGR5*, rs12779790 in *CDC123/CAMK1D*, rs4607103 in *ADAMTS9* and rs9472138 in *VEGFA*) with minor allele frequency >5% (7). For the HHEX-*IDE* locus, only representative SNPs with $r^2<0.80$ based on HapMap Han Chinese were selected for genotyping, and eight variants (rs1111875, rs2275729, rs5015480, rs7923837, rs1887922, rs2209772, rs1999763 and rs11187007) which had positive association with type 2 diabetes or diabetes-related traits in previous studies were selected.[15–18,22–26]

Genotyping

All 13 variants were genotyped using TaqMan genotyping assay on an ABI7900 system (Applied Biosystems, Foster City, CA, USA). Genotyping success rates were above 95% except rs12779790 and all mismatch rates were below 1% in duplicate samples.

Statistical analysis

We first evaluated the Hardy–Weinberg equilibrium for specific allele-genotype frequencies between cases and controls. We then calculated linkage disequilibrium (LD) coefficients (D′ and r^2) in the control group.[27] The association of all SNPs with type 2 diabetes was then examined by logistic regression adjusting for sex, age and loge-transformed BMI. We conducted a meta-analysis using comprehensive Meta Analysis software (Version 2.0, BIOSTAT, and Englewood, NJ, USA). Cochran's *Q*-test was performed to assess heterogeneity across different studies. For quantitative traits in relation to genotypes, a general linear statistical methodology was used, applying additive, dominant and recessive models while adjusting for the effect of age and sex (BMI, waist-to-hip ratio), or age, sex and loge-transformed BMI (all other traits). The statistical analyses were performed by using the SPSS program (SPSS, Chicago, IL, USA). A *P*-value of <0.05 was considered significant.

RESULTS

The genotype distributions of each SNP selected for the present study (see Methods) in the case and control groups were shown in Table 1. All 13 SNPs genotyped were in Hardy–Weinberg equilibrium among controls (Table 1). We further compared frequencies of the reported risk allele in the Chinese populations with those in the Japanese, Indian and European populations (Table 2 and Supplementary Table 2). The allele frequencies for most of the SNPs examined in the present study were considerably different from the populations of Indian and European descent, but close to the Japanese population.

As shown in Table 1, rs7961581 in *TSPAN8/LGR5* showed allelic difference between case and control groups (odds ratio (OR)=1.13, 95% confidence interval (CI) 1.01–1.26, P=0.031). After adjusting with age, gender and loge-transformed BMI, rs864745 and rs7961581 tend to have the same direction of the association with type 2 diabetes (P=0.085 and 0.055, respectively), as previously reported in European genome-wide association studies.[7] However, we could not observe any association between other SNP loci (rs12779790, rs4607103, rs9472138) and type 2 diabetes (nominal $P>0.05$). Similarly, subsequent meta-analyses (including six populations of >10 000 individuals)[3,11,13] only revealed that rs864745 (OR=1.09, 95% CI 1.03–1.16, $P=3.49\times10^{-3}$) and rs7961581 (OR=1.11, 95% CI 1.05–1.17, $P=1.89\times10^{-4}$) were significantly associated with type 2 diabetes risk in East Asian populations (Table 3).

For the *HHEX-IDE* locus, the LD coefficients (D′ and r^2) (Supplementary Table 3) suggested low pair-wise LD among most of the eight SNPs. However, rs11187007 in *IDE* and rs1111875 in *HHEX*, although which were about 250 kb apart from each other, were in a high LD (D′=0.90, r^2=0.77). Meanwhile, both rs11187007 and rs1111875 were identified to be associated with type 2 diabetes risk after further adjustment for age, gender and BMI (for both variants: OR=1.15, 95% CI 1.04–1.28, P=0.009 in an additive model; Table 1). In addition, meta-analysis of six populations, total individuals of 15 467 Chinese (7207 cases and 8260 controls)[3,5,6,28] confirmed the association of the *HHEX* rs1111875 with type 2 diabetes (OR=1.15, 95% CI 1.10–1.21, $P=1.93\times10^{-8}$) (Table 3).

In analysis of quantitative traits, rs7923837, rs2275729, rs1111875 and rs11187007 appeared to affect plasma triglyceride levels in our Chinese participants, whereas rs7923837 showed effects on FPG. However, none of these associations still reach conventional statistical significance after adjusting for multiple comparisons (Supplementary Table 4).

DISCUSSION

In the present study, we identified a variant (rs11187007) in the *IDE* gene with increased risk of type 2 diabetes and confirmed the effects of *HHEX-IDE* locus on type 2 diabetes in Chinese population. Our meta-analysis pooling data emanated from East Asians indicated that the *JAZF1* and *TSPAN8* loci may confer modest susceptibility to type 2 diabetes risk, as identified in the European decent populations.

Table 1 Association of candidate SNPs with type 2 diabetes in case and control individuals

					Allele data			*Genotype distribution* n *(%)*				
SNP	*Nearest genes*	*Chromosome*	*Alleles*	*Groups*	*MAF*	P	*Multiple testing*	*C/C*[a]	*C/R*[a]	*R/R*[a]	*OR (95% CI)*[b]	P[c]
rs864745	*JAZF1*	7	C<T[d]	Case	21.3			81	631	1148		
				Control	23.1	0.063	0.819	118	659	1161	1.11 (0.99–1.24)	0.086
rs12779790	*CDC123/CAMK1D*	10	G<A[d]	Case	17.4			60	482	1188		
				Control	17.1	0.709	1.00	46	489	1168	1.07 (0.93–1.22)	0.35
rs7961581	*TSPAN8/LGR5*	12	C<T[d]	Case	22.9			91	678	1111		
				Control	20.8	0.031	0.403	98	628	1251	1.12 (1.00–1.25)	0.055
rs4607103	*ADAMTS9*	3	T<C[d]	Case	36.3			250	836	755		
				Control	36.3	0.993	1.00	256	865	776	0.99 (0.90–1.10)	0.9
rs9472138	*VEGFA*	6	T<C[d]	Case	11.2			36	354	1504		
				Control	11.6	0.644	1.00	22	421	1565	1.02 (0.88–1.18)	0.846
rs2275729	*HHEX*	10	G<T[d]	Case	6.2			8	218	1656		
				Control	5.3	0.069	0.897	7	198	1810	1.19 (0.98–1.46)	0.085
rs1111875	*HHEX*	10	C<T[d]	Case	29.6			160	778	914		
				Control	26.8	0.006	0.078	151	766	1076	1.15 (1.04–1.28)	0.009
rs5015480	*HHEX*	10	C<T[d]	Case	18.5			70	531	1208		
				Control	16.8	0.049	0.637	47	557	1332	1.12 (1.00–1.25)	0.059
rs7923837	*HHEX*	10	G<A[d]	Case	22.4			103	636	1138		
				Control	20.9	0.104	1.00	72	688	1230	1.13 (1.00–1.29)	0.049
rs11187007	*IDE*	10	A<G[d]	Case	28.9			146	807	947		
				Control	26.1	0.004	0.052	137	777	1103	1.15 (1.04–1.28)	0.009
rs1887922	*IDE*	10	C<T[d]	Case	8.2			15	273	1570		
				Control	7.6	0.415	1.00	16	262	1644	1.07 (0.90–1.28)	0.43
rs1999763	*IDE*	10	A<G[d]	Case	11.5			24	381	1461		
				Control	11	0.469	1.00	26	377	1552	1.04 (0.89–1.21)	0.635
rs2209972	*IDE*	10	C<T[d]	Case	21.7			88	635	1142		
				Control	22	0.817	1.00	103	640	1183	0.99 (0.88–1.11)	0.822

Abbreviations: CI, confidence interval; MAF, minor allele frequency; OR, odds ratio; SNP, single-nucleotide polymorphism.
[a]C/C, homozygous for minor allele; C/R, heterozygous; R/R, homozygous for major allele.
[b]OR for original risk alleles reported in European populations.
[c]ORs and *P*-values were adjusted for age, gender and loge-transformed BMI under the additive model.
[d]Risk allele in the European populations.

Table 2 Comparison of risk-allele frequencies in the Chinese populations with those in other ethnic populations in previous studies

SNPs	*Risk allele*[a]	*Nearest genes*	*Chinese*	*Japanese*[b]	*Indians*[c]	*Europeans*[d]
rs864745	T	*JAZF1*	76.9	78.4	67.5	50.1
rs7961581	C	*TSPAN8/LGR5*	20.8	20.5	35.2	26.9
rs12779790	G	*CDC123/CAMK1D*	17.1	14.7	12.6	18.3
rs4607103	C	*ADAMTS9*	63.7	61	49.9	76.1
rs9472138	T	*VEGFA*	11.6	10	NA	28.2

Abbreviations: NA, not available; SNP, single-nucleotide polymorphism.
[a]Risk allele in the European populations.
[b]Risk-allele frequencies previously reported by Omori *et al.*[11]
[c]Risk-allele frequencies previously reported by Sanghera *et al.*[12]
[d]Risk-allele frequencies across the DGI/FUSION/UK stage 2 studies, previously reported by Zeggini *et al.*[7]

Although Florez *et al.*[29] previously conducted a well-designed large-scale study and reported that genetic variants in the human *IDE* gene did not contribute to susceptibility of type 2 diabetes, available evidence does support that *IDE* has strong functional roles in type 2 diabetes' pathogenesis. The *IDE* gene encodes a metallopeptidase, which can degrade insulin, initiate cellular insulin processing and terminate its action. Homozygous mice with *IDE* gene deletion resulted in hyperinsulinemia and glucose intolerance, which are classical hallmarks in type 2 diabetes development.[30] Here, we found a novel association of rs11187007 with type 2 diabetes and triglycerides, in line with the findings that variants and haplotypes in *IDE* were associated with FPG, HbA1c and type 2 diabetes.[22,23,30,31]

On the other hand, the association study and meta-analysis further confirmed the effect of *HHEX* rs1111875 on type 2 diabetes in Chinese population, consistent with previous genome-wide association studies and replication studies in other ethnic populations.[15–19,25,26,32–34] The *HHEX* gene encodes a transcription factor that is also involved in the Wnt signaling pathway and that has been shown to be essential for pancreas development. van Vliet-Ostaptchouk *et al.*[19] suggested that *HHEX* was the most likely causal candidate in chromosome 10q. However, in our study, both *IDE* rs11187007 and *HHEX* rs1111875 were detected to be associated with type 2 diabetes. It also shows that a 270-kb LD block covers the whole *HHEX-IDE* locus in the HapMap date of Chinese subjects. Moreover, the SNPs do not reside within the coding or putative regulatory regions of any gene. Therefore, it is difficult to explain which gene may be the susceptibility gene. Given the consistency of the association between the *HHEX-IDE* locus and type 2 diabetes risk observed in multiple populations, it does seem warranted to conduct deep sequencing of this region to identify potential causal variants in these two genes that may directly affect type 2 diabetes risk.

The *JAZF1* gene encodes a transcriptional repressor of *NR2C2* (nuclear receptor subfamily 2, group C, ember 2). Nr2c2−/− knock

Table 3 Meta-analysis of the association of candidate SNP loci with type 2 diabetes

		Type 2 diabetes[b]			*Normal controls*[b]				*Meta-analysis*		
SNPs	*Studies (ethnic)*[a]	*C/C*	*C/R*	*R/R*	*C/C*	*C/R*	*R/R*	P (Q)[c]	*OR*[c]	*95% CI*	P[d]
rs864745 (T>C),	Replication 1 (Japanese)	64	522	1009	52	320	612		1.07	(0.94–1.23)	
JAZF1 chromosome 7	Replication 2 (Japanese)	49	411	793	42	262	532		1.02	(0.88–1.19)	
	Replication 3 (Japanese)	19	136	310	49	321	557		1.27	(1.04–1.55)	
	Replication 4 (Japanese)	NA	NA	NA	NA	NA	NA		1.08	(0.95–1.22)	
	All Japanese							0.394	1.09	(1.01–1.17)	0.023
	Replication 6 (Chinese)	81	631	1148	118	659	1161		1.11	(0.99–1.23)	
	All (Japanese + Chinese)							0.549	1.09	(1.03–1.16)	3.49×10^{-3}
rs7961581 (T>C),	Replication 1 (Japanese)	81	540	966	49	317	606		1.05	(0.91–1.20)	
TSPAN8/LGR5 chromosome 12	Replication 2 (Japanese)	63	418	777	36	252	553		1.16	(0.99–1.35)	
	Replication 3 (Japanese)	23	167	273	40	306	581		1.14	(0.94–1.37)	
	Replication 4 (Japanese)	NA	NA	NA	NA	NA	NA		1.12	(0.99–1.27)	
	All Japanese							0.786	1.11	(1.03–1.19)	5.54×10^{-3}
	Replication 5 (Chinese)	NA	NA	NA	NA	NA	NA		1.08	(0.97–1.21)	
	Replication 6 (Chinese)	91	678	1111	98	628	1251		1.13	(1.01–1.26)	
	All (Japanese + Chinese)							0.933	1.11	(1.05–1.17)	1.89×10^{-4}
rs12779790 (A>G),	Replication 1 (Japanese)	48	457	1101	25	244	718		1.19	(1.02–1.39)	
CDC123/CAMK1D chromosome 10	Replication 2 (Japanese)	30	343	855	15	202	566		1.13	(0.95–1.35)	
	Replication 3 (Japanese)	8	122	348	25	216	683		1.00	(0.80–1.25)	
	Replication 4 (Japanese)	NA	NA	NA	NA	NA	NA		0.98	(0.85–1.13)	
	All Japanese							0.271	1.07	(0.99–1.17)	0.094
	Replication 6 (Chinese)	60	482	1188	46	489	1168		1.02	(0.90–1.16)	
	All (Japanese + Chinese)							0.367	1.06	(0.99–1.13)	0.109
rs4607103 (C>T),	Replication 1 (Japanese)	238	739	612	151	492	346		0.92	(0.82–1.04)	
ADAMTS9 chromosome 3	Replication 2 (Japanese)	165	622	469	116	402	317		1.00	(0.88–1.13)	
	Replication 3 (Japanese)	73	236	169	159	406	368		1.05	(0.90–1.23)	
	Replication 4 (Japanese)	NA	NA	NA	NA	NA	NA		1.09	(0.99–1.21)	
	All Japanese							0.186	1.02	(0.96–1.08)	0.618
	Replication 5 (Chinese)	NA	NA	NA	NA	NA	NA		1.03	(0.93–1.14)	
	Replication 6 (Chinese)	250	836	755	256	865	776		1.00	(0.91–1.10)	
	All (Japanese + Chinese)							0.461	1.01	(0.97–1.06)	0.522
rs9472138 (C>T),	Replication 1 (Japanese)	29	325	1259	7	173	808		1.28	(1.08–1.54)	
VEGFA chromosome 6	Replication 2 (Japanese)	22	234	1009	6	154	678		1.12	(0.92–1.37)	
	Replication 3 (Japanese)	5	69	407	8	181	744		0.76	(0.58–1.00)	
	All Japanese							0.007	1.05	(0.79–1.39)	0.743
	Replication 6 (Chinese)	36	354	1504	22	421	1565		0.97	(0.84–1.11)	
	All (Japanese + Chinese)							0.008	1.03	(0.85–1.25)	0.767
rs1111875 (T>C),	Ng *et al*. (Hongkong)[28]	NA	NA	NA	NA	NA	NA		1.09	(0.98–1.21)	
HHEX chromosome 10	Wu *et al*. (Beijing)[6]	NA	NA	NA	NA	NA	NA		1.00	(0.81–1.25)	
	Wu *et al*. (Shanghai)[6]	NA	NA	NA	NA	NA	NA		1.64	(1.25–2.15)	
	Hu *et al*. (Shanghai)[3]	NA	NA	NA	NA	NA	NA		1.20	(1.09–1.33)	
	Tan *et al*. (Singapore)[5]	NA	NA	NA	NA	NA	NA		1.15	(1.03–1.29)	
	Present (Shanghai)	914	778	160	1076	766	151		1.15	(1.04–1.28)	
	All (Chinese)							0.080	1.15	(1.10–1.21)	1.93×10^{-8}

Abbreviations: CI, confidence interval; NA, not available; OR, odds ratio; SNP, single-nucleotide polymorphism.
[a]Data of replication 1, 2 and 3 in Japanese come from the study by Omori *et al*.[11] Data of replication 4 in Japanese come from the study by Takeuchi *et al*.[13] Data of replication 5 in Chinese come from the study by Hu *et al*.[3] Data of replication 6 in Chinese come from the present study.
[b]C/C, homozygous for minor allele; C/R, heterozygous; R/R, homozygous for major allele.
[c]*P*-value of Cochran's *Q*-test for assessing heterogeneity among different groups. OR for original risk alleles reported by Zeggini *et al*.[7]
[d]*P*-value of the meta-analysis under the fixed model except rs9472138 (because of *P*-value of Cochran's *Q*-test <0.05).

out in mice retards growth and displays phenotypes of low serum concentrations of IGF1, hypoglycemia and reduced gluconeogenesis via PEPCK inactivation.[7,35] Zeggini *et al*.[7] have previously reported a strong association between rs864745 (in intron 1 of the *JAZF1* gene) and type 2 diabetes risk in Europeans (OR=1.10, $P=5.0\times10^{-14}$). In the study by Grarup *et al*.,[9] it has been estimated that carriers of the T allele of *JAZF1* rs864745 had a 2.6% (0.9–4.3%; $P=0.003$) decreased insulin release, as assessed by the BIGTT acute insulin response index. In this article, the association studies and meta-analysis further confirmed the association between *JAZF1* rs864745 and type 2

diabetes in Chinese population. In addition, compared with the Europeans, the frequency of this risk variant in Chinese appeared to be much higher (T allele, 0.77 vs 0.50).

We also observed significant association between *TSPAN8/LGR* rs7961581 and type 2 diabetes with a modest OR (OR=1.11, 95% CI 1.05–1.17) in East Asian populations, similar to that in European descents. In the study by Grarup *et al.*,[9] it was also reported that rs7961581 in *TSPAN8* was associated with various OGTT-based surrogate measures of insulin release, suggesting a role of *TSPAN8* in pancreatic β-cell function. In our meta-analysis, this variant also showed significant association with type 2 diabetes in Japanese population (OR=1.11, 95% CI 1.03–1.19, $P=5.54\times10^{-3}$). Therefore, rs7961581, which resides ~110 kb upstream of *TSPAN8* (tetraspanin 8), is associated with type 2 diabetes across the boundary of race.

In the current study, polymorphisms (rs12779790, rs4607103 and rs9472138) showed any significant relations neither with type 2 diabetes risk nor with quantitative metabolic traits. Aside from the fact that genetic background may differ between Chinese and Europeans, differences in statistical power across studies may also explain such inconsistent observations, especially when the SNP-type 2 diabetes relation was modest. For example, we had a power of ~99% to detect an OR of 1.15 for rs11187007 (given minor allele frequency=0.30 and ~4000 samples), but power declined to 79% for detecting an OR of 1.10.

In summary, in this large case–control study of type 2 diabetes among Han Chinese, the IDE rs11187007 and HHEX rs1111875 variants are significantly associated with increased type 2 diabetes risk. Our meta-analysis further confirmed the modest effects of the *JAZF1, TSPAN8* and *HHEX-IDE* loci on type 2 diabetes risk in Chinese and other East Asians.

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