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CDKAL1 and type 2 diabetes: a global meta-analysis

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ABSTRACT. *CDKAL1* (cyckin-dependent kinase 5 regulatory subunit-associated protein 1-like 1) has been shown to be associated with type 2 diabetes in various ethnic groups; however, contradictory results have been reported. We performed a comprehensive meta-analysis of 21 studies for rs7756992, 17 studies for rs7754840 and 10 studies for rs10946398 variants of the *CDKAL1* gene to evaluate the effect of *CDKAL1* on genetic susceptibility for type 2 diabetes. We found a significant association of rs7756992, rs7754840 and rs10946398 in *CDKAL1* with type 2 diabetes (odds ratio (OR) = 1.15, 95% confidence interval (CI) = 1.07-1.23, P < 0.0001; OR = 1.14, 95%CI = 1.06-1.24, P = 0.001, and OR = 1.12, 95%CI = 1.07-1.18, P < 0.0001, respectively). We conclude that there are significant associations between *CDKAL1* polymorphisms and type 2 diabetes, but these associations vary in different ethnic populations.

Key words: *CDKAL1*; Meta-analysis; Single nucleotide polymorphism; Type 2 diabetes

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is characterized by hyperglycemia that can occur through mechanisms such as impaired insulin secretion, insulin resistance in peripheral tissues and increased glucose output by the liver (Anonymous, 2008). Most individuals with type 2 diabetes suffer serious complications from chronic hyperglycemia, involved in nephropathy, neuropathy, retinopathy, and accelerated development of cardiovascular disease (Grant et al., 2006). The rapid increase in prevalence of type 2 diabetes has been a major public health challenge worldwide, including China. The total number of people with diabetes in China is expected to increase from 20.8 million in 2000 to 42.3 million in 2030 (Boutayeb and Boutayeb, 2005). The new diagnosis of type 2 diabetes subjects in developing countries with a mass of populations such as China and India has increased rapidly (Wang et al., 1998; Ramachandran et al., 1997, 2001). Incidence rates are diverse in females and males in Europe, Africa, North America, Latin America, and East Asia, and there is little consensus amongst articles on the subject (Tong et al., 2009).

The *CDKAL1* (cyclin-dependent kinase 5 (CDK5) regulatory subunit-associated protein 1-like 1) gene spans 697,948 bp on chromosome 6p22.3 and encodes a 65-kD protein. Its protein product shares protein domain similarity with cyclin-dependent kinase 5 (cdk5) regulatory subunit-associated protein 1 (CDK5RAP1), a neuronal protein that specifically inhibits activation of CDK5 (Lew et al., 1994). CDK5 is a small serine/threonine protein kinase recognized as an essential molecule in the brain and has several extra-neuronal effects (Rosales and Lee, 2006). CDK5 has been shown to blunt insulin secretion in response to glucose and to play a permissive role in the decrease of insulin gene expression that results from glucotoxicity, as well as in the pathophysiology of β-cell dysfunction and predisposition to type 2 diabetes (Ubeda et al., 2006). Thus, one can speculate that reduced expression of *CDKAL1* would result in enhanced activity of CDK5 in β cells, which would lead to decreased insulin secretion. In agreement with this speculation, this locus was significantly associated with small decreases in insulin response to a glucose load (Steinthorsdottir et al., 2007; Saxena et al., 2007; Pascoe et al., 2007; Palmer et al., 2008; Stancáková et al., 2008).

CDKAL1 was recently identified as a susceptibility gene for type 2 diabetes through five subsequent genome wide association studies (GWAS) in white Europeans and Asian (Steinthorsdottir et al., 2007; Saxena et al., 2007; Scott et al., 2007; Zeggini et al., 2007; Takeuchi et al., 2009). Replication studies reported significant associations between type 2 diabetes and rs10946398, rs7754840 and rs7756992 in the Han Chinese population (Liu et al., 2008), and rs10946398 and rs7754840 in the African American population (Lewis et al., 2008). However, the only trend found for association in the Morrocan population was for rs7754840 and rs10946398 (Cauchi et al., 2008a). Significant associations between rs7756992 and type 2 diabetes in Han Chinese individuals from Hong Kong (Steinthorsdottir et al., 2007), French individuals first set (Cauchi et al., 2008a) and Japanese (Horikoshi et al., 2007; Omori et al., 2008) were observed. *CDKAL1* rs7754840 and rs7756992 were significantly associated with type 2 diabetes in the Israeli Ashkenazi population (Cauchi et al., 2008a) and Japanese population (Horikawa et al., 2008; Tabara et al., 2009). *CDKAL1* rs7754840 was significantly associated with type 2 diabetes in the Korean population (Lee et al., 2008), Finnish men (Stancáková et al., 2008), but not in Asian Indian Sikhs (Sanghera et al., 2008). No association was found between *CDKAL1* variants and type 2 diabetes in the Austrian population (Cauchi et al., 2008a), Norwegian population-based sample (Hertel et al., 2008) or Pima Indians (Rong et al., 2009).

Most replication studies on the association between *CDKAL1* variants and type 2 diabetes focused on rs7754840 and rs7756992 or both and contradictory results were reported. Given the amount of accumulated data, it is important and urgent to perform a quantitative synthesis of this evidence. We, therefore, undertook a large meta-analysis of studies of the association between rs7754840, rs7756992 and rs10946398 in *CDKAL1* and type 2 diabetes.

METHODS

Search strategy and data collection

A PubMed search up to August 2009, using "CDK5 regulatory subunit-associated protein 1-like 1" or "*CDKAL1*" or "*CDKAL1* gene polymorphism" and "diabetes" or "diabetes 2" or "type 2 diabetes" or "type 2 diabetes mellitus" or "T2D" or "T2DM" as key words, was performed. The references of all computer-identified publications were searched for additional studies. The PubMed option ''Related Articles'' was used to search for potentially relevant articles. Reference lists in retrieved articles were also screened. Searching was performed in duplicate by two independent reviewers (M.A.S.D. and M.W.). Without any language restriction, we only selected published manuscripts (including their online supporting materials). When eligible articles had insufficient information, we contacted authors by e-mail or mail for additional information. We performed a literature review on articles concerning *CDKAL1* polymorphism with type 2 diabetes. Only the studies with complete data on comparison of frequency of *CDKAL1* gene polymorphism between type 2 diabetes and control were selected. The articles with incomplete data were not included in our meta-analysis. The frequency of *CDKAL1* polymorphism reported from all detected articles was recorded and used as primary data for further analysis.

We found 45 published articles but only 14 with genotype frequency information were used in our meta-analysis (Table 1, Figure 1). The odds ratios (ORs) were calculated using 2 × 2 contingency tables for each study, based on rs7756992, rs7754840 and rs10946398 and prevalence of type 2 diabetes (present *vs* not present).

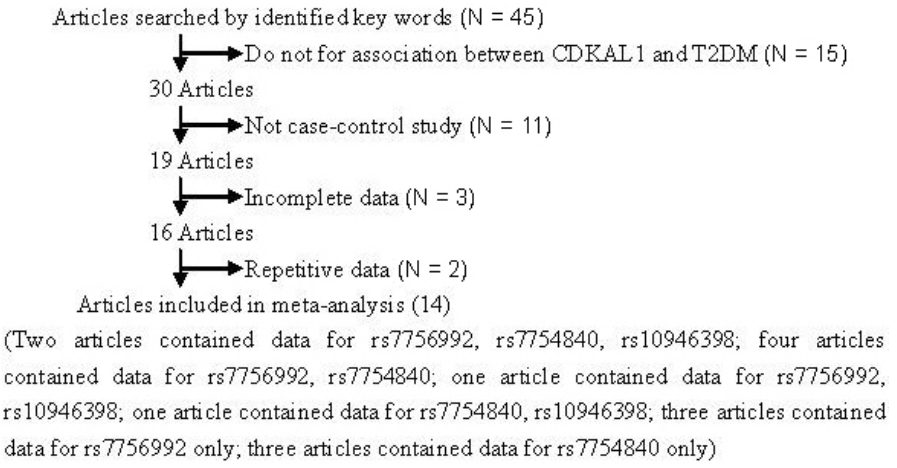

Figure 1. QUORUM statement flow chart.

Statistical analysis

Stata 10.0 software was used to estimate the heterogeneity between studies. Pooled ORs were computed by the fixed-effects method of Mantel-Haenszel (Peto's method) if no heterogeneity between studies exists. If there was significant heterogeneity between studies, then a random effects model of DerSimonian-Laird (D-L method) is appropriate for data combined. The conservative Egger's regression analysis was used to evaluate publication bias.

RESULTS

Table 1 summarized the characteristics of 14 published articles in our meta-analysis. Twenty-seven association studies of *CDKAL1* with type 2 diabetes included 73,024 subjects. Egger regression analysis indicated no publication bias for the SNPs rs7756992, rs7754840 and rs10946398, which indicated reliability of the pooled results (data not shown).

CDKAL1 rs7756992 and type 2 diabetes

Figure 2A presents the forest plot of risk allele OR of an individual study and meta-analysis for association between *CDKAL1* rs7756992 and type 2 diabetes in a total of 22,839 type 2 diabetes patients and 31,429 control subjects from the 21 studies. Nineteen studies showed a trend of elevated OR for the risk allele G. Two studies from Japan (Horikoshi et al., 2007; Horikawa et al., 2008) showed a trend in the opposite direction. Significant heterogeneity between studies was found ($P < 0.0001$, $I^2 = 83.6\%$). A random effect model was thus performed for meta-analysis and generated a combined allelic OR = 1.15 (95%CI = 1.07-1.23, $P < 0.0001$) for the risk allele G of rs7756992. After the exclusion of two Japanese studies (Horikoshi et al., 2007; Horikawa et al., 2008), a weak between-study heterogeneity was observed ($P = 0.079$, $I^2 = 33.3\%$). A random effect model generated a combined allelic OR = 1.2 (95%CI = 1.16-1.25, $P < 0.0001$) for the risk allele G of rs7756992.

In the stratified meta-analysis on the basis of ethnicity, 8 European studies including 8210 type 2 diabetes patients and 17,606 control subjects showed no heterogeneity between studies ($P = 0.37$, $I^2 = 7.7\%$). All studies showed a trend of elevated OR for the risk allele G. A fixed effect model generated a combined allelic OR = 1.22 (95%CI = 1.17-1.27, $P < 0.0001$) for the risk allele G of rs7756992 in the European population (data not shown). Ten Asian studies including 13,180 type 2 diabetes patients and 12,713 control subjects showed significant heterogeneity between studies ($P < 0.0001$, $I^2 = 91.1\%$). Eight studies showed a trend of elevated OR for the risk allele G. Two studies from Japan (Horikoshi et al., 2007; Horikawa et al., 2008) showed a trend in the opposite direction. A random effect model generated a combined allelic OR = 1.13 (95%CI = 1.00-1.27, $P = 0.05$) for the risk allele G of rs7756992 in the Asian population (data not shown). However, if the two Japanese studies (Horikoshi et al., 2007; Horikawa et al., 2008) were excluded, the between-study heterogeneity becomes moderate ($P = 0.057$, $I^2 = 49\%$). It is worth noting that the mean age of control groups is older than that of case groups in these two Japanese studies and also much older than that of control groups in others, whereas the mean age of control groups is younger than that of case groups in other studies. A random effect model generated a combined allelic OR = 1.22 (95%CI = 1.15-1.29, $P < 0.0001$) for the risk allele G of rs7756992 in the Asian population.

Table 1. Characteristics of case-control studies included in a meta-analysis of the association between *CDKAL1* rs7756992, rs7754840, rs10946398 and type 2 diabetes.

Reference	Population	Groups	Gender (M/F)	Age (years)	BMI (kg/m^2)	rs7756992 GG/AG/AA	rs7754840 CC/CG/GG	rs10946398 CC/AC/AA
Steinthorsdottir et al., 2007	1. Iceland	case	832/567	64.4 ± 12.8	29.8 ± 5.4	108/539/751	-	-
		control	2743/2532	58.3 ± 17.4	27.1 ± 4.9	277/1887/3107	-	-
	2. Denmark A	case	0/263	65.5 ± 7.0	28.3 ± 4.1	30/99/111	-	-
		control	0/579	64.4 ± 8.5	25.2 ± 3.7	50/255/292	-	-
	3. Denmark B	case	821/538	56.8 ± 10.5	29.7 ± 5.3	144/564/624	-	-
		control	2249/2576	46.4 ± 8.8	25.5 ± 4.1	394/1884/2503	-	-
	4. Philadelphia	case	288/159	64.3 ± 10.7	30.3 ± 5.8	40/174/216	-	-
		control	629/321	61.7 ± 12.2	28.1 ± 4.8	68/331/492	-	-
	5. Netherlands	case	169/199	71.2 ± 9.9	27.8 ± 4.2	30/138/186	-	-
		control	553/353	47.7 ± 12.7	-	63/359/475	-	-
	6. Hong Kong	case	588/869	49.8 ± 13.7	25.1 ± 4.1	400/681/351	-	-
		control	418/568	32.0 ± 14.3	21.8 ± 3.5	220/446/293	-	-
	7. West Africa	case	345/520	53.5 ± 10.6	26.6 ± 5.5	344/349/137	-	-
		control	471/635	42.4 ± 15.5	25.2 ± 5.9	397/499/160	-	-
Scott et al., 2007	8. Finnish	case	-	-	-	-	343/1096/866	-
		control	-	-	-	-	295/1096/948	-
Saxena et al., 2007	9. Polish	case	422/587	62 ± 10	29.6 ± 4.8	-	112/461/401	115/454/416
		control	422/587	59 ± 7	26.1 ± 3.6	-	89/474/424	92/464/426
	10. Sweden	case	1667/1163	59 ± 12	29.6 ± 5.5	-	314/1217/1244	313/1131/1254
		control	1340/2210	57 ± 6	25.1 ± 3.6	-	363/1462/1633	357/1438/1640
	11. American	case	644/582	63 ± 11	32.9 ± 6.9	-	136/496/554	137/499/566
		control	644/582	61 ± 10	27.4 ± 5.2	-	116/533/525	118/530/541
Horikoshi et al., 2007	12. Japanese	case	535/329	63.1 ± 9.5	24.3 ± 3.9	188/426/238	-	179/434/239
		control	386/478	69.5 ± 6.8	23.8 ± 3.7	216/450/191	-	158/423/280
Omori et al., 2008	13. Japanese	case	978/652	61.5 ± 11.6	23.7 ± 3.9	430/782/398	-	-
		control	638/426	45.5 ± 9.5	22.9 ± 3.0	238/508/293	-	-
Ng et al., 2008	14. Hong Kong/Korean	case	-	-	-	742/1054/486	-	-
		control	-	-	-	701/1338/698	-	-
Cauchi et al., 2008a	15. French A	case	2035/1260	62 ± 11	28.3 ± 3.7	330/1373/1436	399/1439/1304	393/1426/1300
		control	1521/2074	56 ± 10	24.9 ± 3.3	258/1394/1888	345/1523/1690	341/1513/1684
	16. French B	case	578/359	66 ± 10	31.1 ± 5.7	100/378/419	118/414/368	118/410/372
		control	428/572	50 ± 6	24.1 ± 3.5	78/389/469	96/426/399	96/432/413
	17. Austrian	case	298/206	57 ± 10	30.5 ± 6.4	43/174/233	41/169/197	46/180/216
		control	462/291	52 ± 6	26.8 ± 4.0	56/269/368	66/290/322	66/273/315
	18. Morrocan	case	159/362	58 ± 11	28.0 ± 4.8	57/225/238	67/219/232	67/220/231
		control	132/291	55 ± 12	27.2 ± 5.3	41/172/204	38/176/204	38/176/204
	19. Israeli Ashkenazi	case	279/298	63 ± 10	29.0 ± 5.0	69/236/208	87/247/179	72/205/150
		control	209/343	56 ± 26	26.0 ± 4.0	45/201/229	54/205/199	61/200/168
Horikawa et al., 2008	20. Japanese	case	1093/828	61.7 ± 9.9	23.7 ± 3.6	442/876/537	543/881/446	-
		control	708/914	70.0 ± 7.5	22.5 ± 3.1	438/818/330	538/781/262	-

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Table 1. Continued.

Reference	Population	Groups	Gender (M/F)	Age (years)	BMI (kg/m^2)	rs7756992 GG/AG/AA	rs7754840 CC/CG/GG	rs10946398 CC/AC/AA
Liu et al., 2008	21. Chinese	case	-	63.8 ± 9	25.3 ± 3.4	506/800/394	420/862/574	372/862/588
		control	-	58.1 ± 9	24.5 ± 3.2	457/956/471	314/923/720	293/903/707
Lee et al., 2008	22. Korean	case	439/469	58.2 ± 11.1	24.3 ± 3.2	-	262/402/221	-
		control	269/233	55.0 ± 9.4	22.1 ± 3.0	-	70/260/170	-
Sanghera et al., 2008	23. Asian Indian Sikhs	case	-	-	-	-	46/196/281	-
		control	-	-	-	-	31/134/203	-
Rong et al., 2009	24. Indian	case	-	-	-	178/547/610	132/495/750	-
		control	-	-	-	184/744/820	116/660/959	-
Tabara et al., 2009	25. Japanese	case	280/226	60 ± 11	24 ± 4	155/217/119	117/225/149	-
		control	214/188	59 ± 9	23 ± 3	78/217/102	57/203/137	-
Takeuchi et al., 2009	26. Japanese A	case	315/204	66.6 ± 9.8	24.5 ± 3.6	135/257/127	90/172/100	-
		control	264/239	64.7 ± 6.8	23.3 ± 3.1	116/231/155	83/228/186	-
	27. Japanese B	case	613/497	62.7 ± 11.7	23.3 ± 3.9	328/516/260	248/464/299	-
		control	542/472	71.1 ± 9.6	23.0 ± 3.1	194/498/312	152/484/373	-

CDKAL1 rs7754840 and type 2 diabetes

Figure 2B presents the forest plot of risk allele OR of the individual study and meta-analysis for association between *CDKAL1* rs7754840 and type 2 diabetes in a total of 21,095 type 2 diabetes patients and 22,038 control subjects from 17 studies. Fourteen studies showed a trend of elevated OR for the risk allele C. One study from Japan (Horikawa et al., 2008) showed a trend in the opposite direction. Two studies from Europe (Saxena et al., 2007; Cauchi et al., 2008a) showed no association. Significant heterogeneity between studies was found ($P < 0.0001$, $I^2 = 86.2\%$). A random effect model was thus performed for meta-analysis and generated a combined allelic OR = 1.14 (95%CI = 1.06-1.24, P = 0.001) for the risk allele C of rs7754840.

In the stratified meta-analysis by ethnicity, 7 European studies included 11,689 type 2 diabetes patients and 13,115 control subjects. Five studies showed a trend of elevated OR for the risk allele C. Two studies, USA European ancestry and Austrian (Saxena et al., 2007; Cauchi et al., 2008a), showed no significant association. Moderate heterogeneity between studies was found ($P = 0.049$, $I^2 = 52.6\%$). A random effect model was performed and generated a combined allelic OR = 1.1 (95%CI = 1.04-1.17, P = 0.001) for the risk allele C of rs7754840 in the European population (data not shown). Eight Asian studies included 8625 type 2 diabetes patients and 8044 control subjects. Seven studies showed a trend of elevated OR for the risk allele C. One study from Japan (Horikawa et al., 2008) showed a trend in the opposite direction. Significant heterogeneity between studies was found ($P < 0.0001$, $I^2 = 92.9\%$). A random effect model indicated no association between *CDKAL1* rs7754840 and type 2 diabetes (P = 0.076) in the Asian population. After the exclusion of the Japanese study (Horikawa et al., 2008), the between-study heterogeneity still remained ($P < 0.0001$, $I^2 = 80.4\%$). A random effect model generated a combined allelic OR = 1.25 (95%CI = 1.1-1.41, $P < 0.0001$) for the risk allele C of rs7754840 in the Asian population (data not shown).

CDKAL1 rs10946398 and type 2 diabetes

Figure 2C presents the forest plot of risk allele OR of the individual study and meta-analysis for association between *CDKAL1* rs10946398 and type 2 diabetes in a total of 12,965 type 2 diabetes patients and 14,350 control subjects from 10 studies. Eight studies showed a trend of elevated OR for the risk allele C. Two studies showed no association (Saxena et al., 2007; Cauchi et al., 2008a). Moderate heterogeneity between studies was found ($P = 0.045$, $I^2 = 47.9\%$). A random effect model was thus performed for meta-analysis and generated a combined allelic OR = 1.12 (95%CI = 1.07-1.18, $P < 0.0001$) for the risk allele C of rs10946398.

In the stratified meta-analysis on the basis of ethnicity, 6 European studies included 9346 type 2 diabetes patients and 10,739 control subjects. Significant heterogeneity between studies was found ($P = 0.024$, $I^2 = 61.2\%$). A random effect model generated a combined allelic OR = 1.09 (95%CI = 1.01-1.17, P = 0.021) for the risk allele C of rs10946398 in European population (data not shown). Two Asian studies included 2674 type 2 diabetes patients and 2764 control subjects. No heterogeneity was found between studies ($P = 0.47$, $I^2 = 0\%$). A fixed effect model generated a combined allelic OR = 1.2 (95%CI = 1.12-1.3, $P < 0.0001$) for the risk allele C of rs10946398 in the Asian population (data not shown).

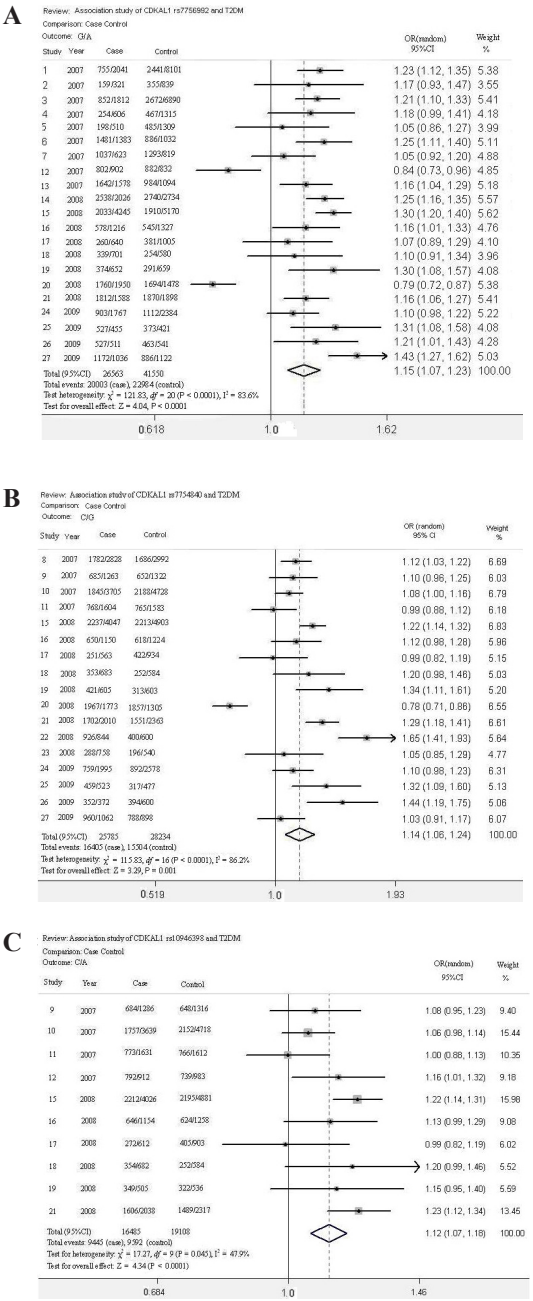

Figure 2. Forest plots of meta-analysis of the association of *CDKAL1* rs7756992 (A), rs7754840 (B) and rs10946398 (C) with type 2 diabetes mellitus (T2DM) in 21 case-control studies. Estimation of odds ratios (OR) and 95% confidence intervals (CI) in each study are displayed as closed square and horizontal line, respectively. The size of the black squares reflects the weight of the study in the meta-analysis. The diamond represents the combined OR, calculated using a random or fixed effect model, with its 95%CI.

DISCUSSION

Recent GWAS have identified several SNPs in intron 5 of *CDKAL1* associated with type 2 diabetes (Steinthorsdottir et al., 2007; Saxena et al., 2007; Scott et al., 2007; Zeggini et al., 2007; Takeuchi et al., 2009). The association between *CDKAL1* variants and type 2 diabetes has been widely studied. Most of the studies confirmed significant association; however, some studies failed to identify significant association, suggesting variability in the contribution of these variants to the risk of type 2 diabetes. To investigate this issue, we performed a comprehensive meta-analysis for the eligible studies.

The results of the global meta-analysis revealed that the SNPs rs7756992, rs7754840 and rs10946398 in *CDKAL1* were significantly associated with the susceptibility of type 2 diabetes (OR = 1.15, $P < 0.0001$; OR = 1.14, $P = 0.001$; OR = 1.12, $P < 0.0001$, respectively). Our stratified meta-analysis by ethnicity suggested a similar effect size for allele C of rs10946398 in both European and Asian populations (European: 1.09, $P = 0.021$ and Asian: 1.2, $P < 0.0001$). However, a different association was observed for the allele G of rs7756992 and the allele C of rs7754840 in European and Asian populations. Significant associations were observed for allele G of rs7756992 (OR = 1.22, $P < 0.0001$), and allele C of rs7754840 (OR = 1.1, $P = 0.001$) in the European population. However, only a borderline association for the SNPs rs7756992 and rs7754840 was found ($P = 0.05$ and $P = 0.076$) in the Asian population. But, if the two Japanese studies (Horikoshi et al., 2007; Horikawa et al., 2008) were excluded, the associations become significant ($P < 0.0001$ and $P < 0.0001$).

Our meta-analysis revealed significant between-study heterogeneity for SNPs rs7756992 ($P < 0.0001$, $I^2 = 83.6\%$), rs7754840 ($P < 0.0001$, $I^2 = 86.2\%$), and rs10946398 ($P = 0.045$, $I^2 = 47.9\%$). Between-study heterogeneity may be due to: 1) Difference in the sample content. Some are thousands in a large sample size, and some only a few hundred; 2) Difference in geographical regions and race of subjects; 3) Differences in sample selection (age, gender). For example, mean age of control groups is older than that of case groups in two Japanese studies (Horikoshi et al., 2007; Horikawa et al., 2008) and also much older than that of control groups in others; 4) Differences in diagnostic criteria for type 2 diabetes. Type 2 diabetes was diagnosed based on 1985 or 1999 World Health Organization criteria in some studies (Saxena et al., 2007; Horikawa et al., 2008), whereas other studies (Tabara et al., 2009) were based on 1998 American Diabetes Association criteria; 5) The sources of the control groups are slightly different: some from the general healthy population, some from the patients of the hospital over the same period, and some may be healthy donors. The different sources of control may affect the representativeness of the sample; 6) Hardy-Weinberg equilibrium is the principal law in population genetic studies. Generally, meeting Hardy-Weinberg equilibrium suggests that samples have representation. The genotypic distributions of these SNPs were in Hardy-Weinberg equilibrium in both type 2 diabetes patients and control groups in all selected studies for our meta-analysis. Sometimes Hardy-Weinberg equilibrium was met, but the genotype frequency was not always consistent to that of the local population. The complexity of type 2 diabetes or family history of cases may also affect the results. The factors that play a leading role across populations may be different.

Notably, *CDKAL1* rs7756992 showed stronger effect sizes in combined samples of Asians ancestry from Hong Kong and Korea than in Europeans (1.26 *vs* 1.14) (Ng et al., 2008). However, the result of our stratified meta-analysis by ethnicity indicated similar effect

sizes for Europeans and Asians (1.22). The SNPs rs7754840 was only 216-bp downstream from rs10946398. Although rs7754840 and rs10946398 are in complete linkage disequilibrium in the Hispanic American population ($r^2 = 1.0$) (Palmer et al., 2008), Japanese population (Horikoshi et al., 2007), Korean population (D' = 1, $r^2 = 1$) (Lee et al., 2008), and Pima Indian population (Rong et al., 2009), the rs7754840 variant was found in a region with extensive linkage disequilibrium differences between multiple groups from South-East Asia (Chinese, Malay and Indian) recruited for the Singapore Genome Variation Project (Teo et al., 2009).

CDKAL1 gene codes for the CDK5 regulatory subunit-associated protein 1-like 1. This protein may affect the activity of the CDK5 protein, which stimulates insulin production and may influence other processes in the insulin-producing β cells of the pancreas. In addition, excessive activity of CDK5 in the pancreas may lead to the degeneration of β cells. It is thought to play a role in the pathophysiology of β-cell dysfunction and predisposition to type 2 diabetes (Ubeda et al., 2006). *CDKAL1* expression in human pancreatic islets (Zeggini et al., 2007) supports the notion that *CDKAL1* and CDK5-mediated pathways in β cells are related. *CDKAL1* is related to impaired first-phase insulin release (Stancáková et al., 2008). Multiple studies have indicated that *CDKAL1* variants were associated with impaired insulin secretion in European ancestry subjects (Pascoe et al., 2007), Netherlands and Germany participants (Groenewoud et al., 2008; Kirchhoff et al., 2008), Hispanic American and African American subjects (Palmer et al., 2008), the Han Chinese population (Wu et al., 2008), French population (Cauchi et al., 2008b), Danish, Finnish, German, Italian, and Swedish populations (Stancáková et al., 2008), suggesting that *CDKAL1* is likely to increase the risk of type 2 diabetes by impairing insulin secretion.

To our knowledge, the present study is the first meta-analysis to evaluate the association of *CDKAL1* polymorphisms and type 2 diabetes. Our meta-analysis demonstrated significant associations of rs7756992, rs7754840 and rs10946398 in the *CDKAL1* gene with the susceptibility of type 2 diabetes. Furthermore, population differences of the association of *CDKAL1* with type 2 diabetes were found in different ethnic and environmental backgrounds.

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