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Original Article

Association of rs7754840 G/C polymorphisms in CDKAL1 with type 2 diabetes: a meta-analysis of 70141 subjects

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Abstract: The reported association of the CDKAL1 rs7754840 G/C gene polymorphism with T2DM susceptibility remains controversial. In this study, this association was further investigated using a meta-analysis of 33,149 patients and 36,992 controls from 32 independent studies. The random-effect models were used in order to evaluate the pooled odds ratios (ORs) and their 95% confidence intervals (CIs). A significant relationship between the CDKAL1 rs7754840 G/C gene polymorphism and T2DM was observed under allelic (OR: 1.37, 95% CI: 1.22, 1.55, P < 0.001), recessive (OR: 1.58, 95% CI: 1.20-2.08, P < 0.001), dominant (OR: 1.13, 95% CI: 1.21-1.33, P = 0.01), and homozygous (OR: 1.27, 95% CI: 1.21-1.33, P < 0.001), and heterozygous (OR: 0.83, 95% CI: 0.75-0.93, P < 0.001). Overall, the CDKAL1 rs7754840 G/C gene polymorphism was found to be significantly associated with an increased T2DM risk; the C allele of the CDKAL1 rs7754840 G/C gene polymorphism may confer susceptibility to T2DM.

Keywords: CDKAL1, polymorphism, type 2 diabetes mellitus

Introduction

Type 2 diabetes mellitus (T2DM) is a complex multifactorial metabolic disease characterized by hyperglycemia, with a varying degree of insulin resistance, impaired insulin secretion and increased hepatic glucose production [1]. Using data from the International Diabetes Federation (IDF) it is speculated that the number of patients with diabetes mellitus will continually increase, reaching up to 552 million by 2030, of which 90-95% will be due to T2DM [2]. In China, it is estimated that the number of patients with diabetes will increase from 20.8 million in 2000 to 42.3 million in 2030 [3]. The large increase coincides with a higher prevalence of obesity and reduced levels of physical activity.

T2DM is the most common form of diabetes and has been shown to be caused by the interplay of multiple genes as well as environmental factors [4]. The well-established heritability of T2DM has resulted in intense efforts in determining genetic risk factors for this disease. Currently, 91 loci have been reported to be closely associated with T2DM susceptibility [5-16], however, the most commonly reported variants found within these loci account for only a small proportion of the heritability of T2DM and the functional role of the majority of these variants remains unclear. At least 16 candidate loci have been unequivocally associated with T2DM. One of the most reproducible risk genes for diabetes identified across different ethnic populations is Cyclin dependent kinase 5 (CDK), which regulates protein subunit 1 homolog 1 (CDKAL1) [17]. The CDK gene spans approximately 37 kb on chromosome 6p22.3 and encodes for 579 amino acids. CDKAL1 has been shown to have enzymatic activity and catalyzes the ms2t6A modification in tRNALys (UUU) in mammalian cells [18]. The functional loss of CDKAL1 affects the accuracy of protein translation, causing the synthesis of abnormal insulin which triggers endoplasmic reticulum stress in β cells.

In 2007, using the results obtained from the GWA studies of the Diabetes Genetic Initiative

Table 1. Characteristics of the included studies regarding the association of CDKAL1 rs7754840 G/C gene polymorphism and T2DM

Author	Year	Study design	Subgroup	Source of controls	NOS Score	T2DM			Control			Case/control
						GG	GC	CC	GG	GC	CC	
Scott [20]	2007	Case-control	Caucasian	PB	7	867	1094	344	957	1078	304	2305/2339
Saxena [21][a]	2007	Case-control	Caucasian	PB	8	1237	1231	307	1616	1496	346	2775/3458
Saxena [21][b]	2007	Case-control	Caucasian	PB	8	542	520	124	534	515	125	1186/1174
Saxena [21][c]	2007	Case-control	Caucasian	PB	8	409	445	120	443	436	108	974/987
Zeggini [25][a]	2007	Case-control	Caucasian	PB	6	399	1439	1304	345	1523	1690	3142/3558
Zeggini [25][b]	2007	Case-control	Caucasian	PB	6	118	414	368	96	426	399	900/921
Zeggini [25][c]	2007	Case-control	Caucasian	PB	6	41	169	197	66	290	322	407/678
Zeggini [25][d]	2007	Case-control	Caucasian	PB	6	87	247	179	54	205	199	513/458
Herder [26]	2008	Case-control	Caucasian	PB	5	177	200	56	746	611	126	433/1483
Horikawa [27]	2008	Case-control	Asian	HB	5	543	881	446	538	781	262	1861/1581
Lee [28]	2008	Case-control	Asian	HB	6	221	402	262	170	260	70	885/500
Lewis [29]	2008	Case-control	African	PB	6	155	499	400	161	453	319	933/1054
Liu [30]	2008	Case-control	Asian	PB	6	574	862	402	720	923	314	1838/1957
Ng [31][a]	2008	Case-control	Asian	PB	5	498	722	261	631	703	196	1481/1530
Ng [31][b]	2008	Case-control	Asian	PB	5	176	380	205	182	314	136	761/632
Ng [31][c]	2008	Case-control	Asian	PB	5	177	398	224	429	755	332	799/1516
Sanghera [32]	2008	Case-control	Asian	PB	6	281	196	46	203	134	31	523/368
Wu [33]	2008	Case-control	Asian	PB	6	106	212	106	316	921	671	424/1908
van Hoek [34]	2008	Case-control	Caucasian	PB	6	1533	958	149	1592	960	144	2640/2696
Kirchhoff [35]	2008	Case-control	Caucasian	HB	7	13	17	6	397	370	87	36/854
Hu [36]	2009	Case-control	Asian	PB	6	358	911	580	302	864	619	1849/1785
Rong [37]	2009	Case-control	Asian	PB	7	750	495	132	959	660	116	1377/1735
Tabara [38]	2009	Case-control	Asian	PB	7	149	225	117	137	203	57	491/397
Takeuchi [39][a]	2009	Case-control	Asian	PB	6	96	180	86	181	238	78	362/497
Takeuchi [39][b]	2009	Case-contro	Asian	PB	6	279	504	228	425	546	175	1011/1146
Ren [40]	2009	Case-control	Asian	PB	5	116	182	102	113	132	55	264/300
Chidambaram [41]	2010	Case-control	Asian	PB	8	408	279	45	420	229	25	732/674
Cruz [42]	2010	Case-control	Mexican	PB	6	243	224	52	267	230	50	519/547
Bao [43]	2012	Case-control	Asian	PB	6	239	354	167	184	194	54	761/433
Nemr [44]	2012	Case-control	Arabs	PB	7	279	247	104	421	295	76	630/792
Mansoori [45]	2015	Case-control	Arabs	PB	6	19	38	83	12	74	54	140/140
Song [46]	2015	Case-control	Asian	PB	6	15	25	11	30	18	3	51/51

T2DM: type 2 diabetes mellitus; Case: the total number of T2DM cases; control size: the total number of control group; PB: population-based; HB: hospital-based; NOS: Newcastle-Ottawa quality assessment scale.

(DGI) [19], Finland-United States Investigation of Non-Insulin-Dependent Diabetes Mellitus Genetics (FUSION) [20], Wellcome Trust Case Control Consortium (WTCCC), and the United Kingdom Type 2 Diabetes Genetics Consortium (UKT2D) [21] the rs7754840 G/C polymorphism in the CDKAL gene was reported for the first time to be strongly associated with T2DM.

Despite the multiple published studies on the relationship between the CDKAL1 gene rs7754840 G/C polymorphism and T2DM, the results remain controversial. Replicate studies reproducibly evaluated the association in multiple European and Asian populations. In the present study, a meta-analysis including European, Asian, African, Arab and Mexican population studies was performed in an effort to strengthen the association between T2DM and the rs7754840 SNP within the CDKAL1 gene.

Materials and methods

Publication search and inclusion criteria

A systematic search of electronic databases including Pub Med, Embase, Web of Science, China National Knowledge Infrastructure, and China Biological Medicine Database was done

Table 2. Summary of the meta-analysis of the association of the CDKAL1 gene rs7754840 G>C polymorphism and type 2 diabetes mellitus

Genetic model	Pooled OR (95% CI)	Z value	*P* value	Study number	T2DM size	Control size	*P* value for heterogeneity
Allelic genetic model	1.37 [1.22, 1.55]	5.24	< 0.00001	32	33149	36992	< 0.00001
Asia	1.31 [1.24, 1.39]	9.21	< 0.00001	17	15603	16872	< 0.00001
Caucasus	1.37 [1.03, 1.84]	2.14	0.03	11	15324	17060	< 0.00001
Africa	2.29 [2.03, 2.57]	13.83	< 0.00001	1	933	1581	NA
Mexico	1.07 [0.89, 1.29]	0.76	0.45	1	519	547	NA
Arabs	1.44 [1.24, 1.66]	4.91	0.76	2	770	932	0.99
Recessive genetic model	1.58 [1.20, 2.08]	3.27	< 0.00001	32	33149	36992	< 0.00001
Asia	2.18 [1.45, 3.27]	3.74	< 0.00001	17	15603	16872	< 0.00001
Caucasus	0.99 [0.66, 1.47]	0.07	0.94	11	15324	17060	< 0.00001
Africa	1.46 [1.17, 1.82]	3.30	0.001	1	933	1581	NA
Mexico	1.12 [0.74, 1.69]	0.54	0.59	1	519	547	NA
Arabs	2.08 [1.51, 2.86]	4.47	< 0.00001	2	770	932	NA
Dominant genetic model	1.13 [1.03, 1.23]	2.52	0.36	32	33149	36992	0.01
Asia	1.21 [1.04, 1.41]	2.51	0.01	17	15603	16872	< 0.00001
Caucasus	1.01 [0.90, 1.14]	0.16	0.88	11	15324	17060	< 0.00001
Africa	1.21 [0.95, 1.54]	1.55	0.12	1	933	1581	NA
Mexico	1.08 [0.85, 1.38]	0.65	0.52	1	519	547	NA
Arabs	1.00 [0.43, 2.32]	2.84	1.00	2	770	932	0.03
Homozygous genetic model	1.27 [1.21, 1.33]	3.64	0.93	32	33149	36992	< 0.00001
Asia	1.37 [1.16, 1.63]	2.84	0.004	17	15603	16872	< 0.00001
Caucasus	1.40 [1.11, 1.77]	1.85	0.06	11	15324	17060	< 0.00001
Africa	1.34 [0.98, 1.82]	1.95	0.05	1	933	1581	NA
Mexico	1.30 [1.00, 1.70]	0.61	0.54	1	519	547	NA
Arabs	1.14 [0.75, 1.75]	3.94	0.23	2	770	932	0.99
Heterozygous genetic model	0.83 [0.75, 0.93]	3.43	0.01	32	33149	36992	0.0006
Asia	0.78 [0.66, 0.90]	3.23	0.001	17	15603	16872	< 0.00001
Caucasus	1.01 [0.90, 1.13]	0.17	0.87	11	15324	17060	0.007
Africa	0.88 [0.72, 1.07]	1.31	0.19	1	933	1581	NA
Mexico	0.94 [0.61, 1.44]	0.30	0.76	1	519	547	NA
Arabs	0.47 [0.26, 0.84]	4.65	0.01	2	770	932	0.06

T2DM: type 2 diabetes mellitus; OR: odds ratio; CI: confidence interval; T2DM size: the total number of T2DM cases; control size: the total number of the control group; Allelic genetic model: C allele distribution frequency; recessive genetic model: CC versus GC + GG; Dominant genetic model: GG versus GC + CC; Homozygous genetic model: CC versus GG. Heterozygous genetic mode: GC versus AA.

in order to find potential studies. The following terms were used: 'CDKAL1', 'rs7754840', 'T2DM' and 'polymorphism', with the date of publication ranging from 2007 to March 18, 2015.

Potential studies were only included if they met the following criteria: (1) They included an evaluation of the CDKAL1 rs7754840 G/C gene polymorphism and T2DM; (2) The studies should be case-control or cohort studies published in official journals; (3) A diagnosis of T2DM was made using the World Health Organization and American Diabetes Association fasting plasma criteria, which requires that the fasting plasma glucose levels of patients to be no less than 7.0 mmol/l, or that the 2 hrs plasma glucose level be no less than 11.1 mmol/l; and (4) The studies should be consistent with the HWE.

Data extraction

The data were extracted following a standard protocol. The meta-analysis was done by two

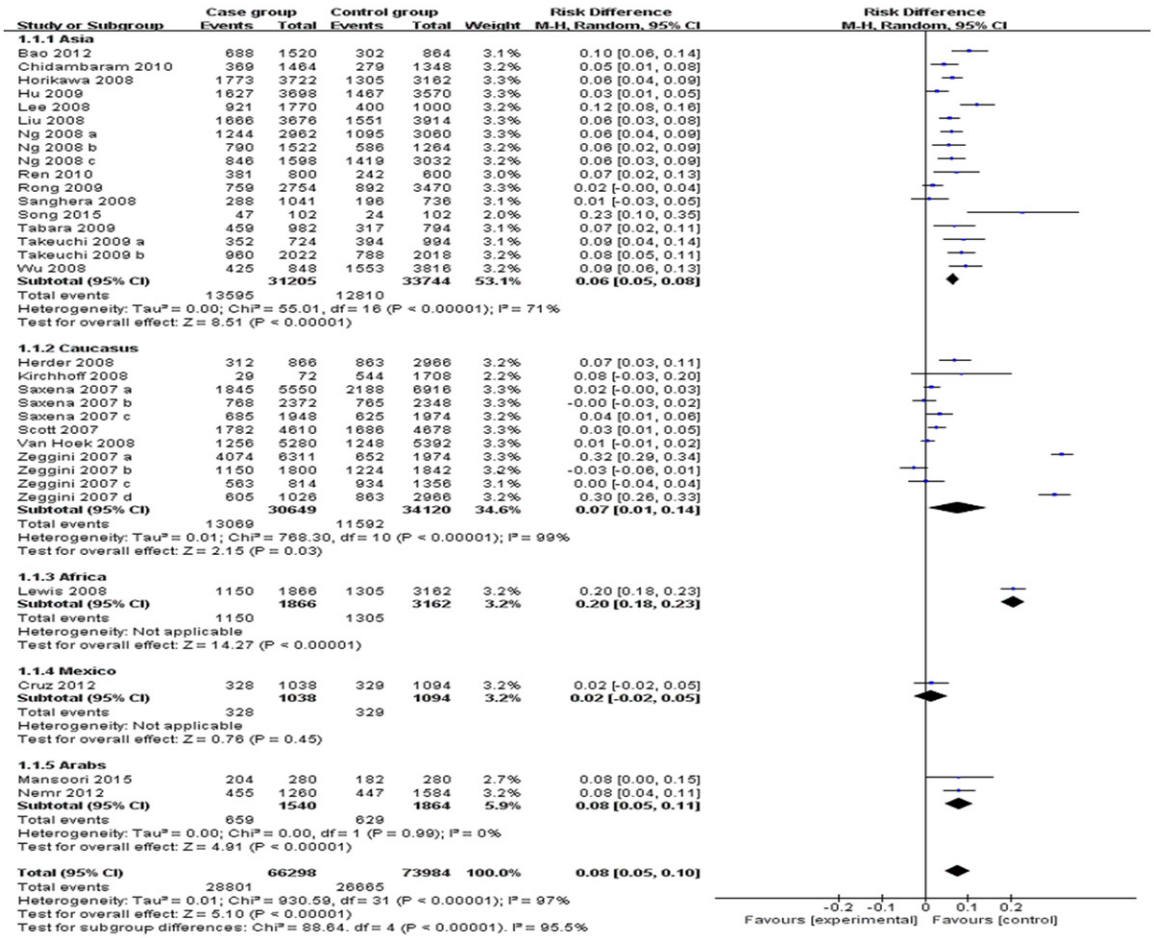

Figure 1. Forest plot of the T2DM associated gene rs7754840 G/C polymorphism under the allelic genetic model (distribution of C allelic frequency of CDKAL1 rs7754840 gene).

researchers, two of which independently searched for studies, while the third served as the arbitrator in case disagreements that occurred between the two researchers. The current meta-analysis did not accept studies that were not in accordance with the inclusion criteria, published repeatedly, or supplied insufficient data. If similar data were used in different studies, the data were only included once in this analysis. The following information was collected from each study: the first author's name, publication year, region, number of genotypes, genotyping, study design and the total number of T2DM and control groups.

Statistical analyses

In the present meta-analysis, four genetic models, including the allelic (G allele distribution frequency), recessive (CC vs. GG + GC), dominant (GG + GC vs. CC), homozygous (CC vs. GG), and the heterozygous (GC vs. GG) genetic models were used. The association of the CDKAL1 rs7754840 G/C gene polymorphism and T2DM was compared using the odd ratio (ORs) and their corresponding 95% confidence intervals (CIs). The heterogeneity between the individual studies was calculated using Chi-square-based Q-tests and the significance level was set at $P < 0.05$ level [22]. If heterogeneity existed, the random-effect model (DerSimonian and Laird method) [23] would be used in order to pooled the OR among the studies. Otherwise, the fixed-effect model was adopted (the Mantel-Haenszel method) [24]. A Z-test was used to determine the pooled OR, with the significance set at $P < 0.05$ level.

HWE was evaluated using Fisher's exact test with the significance set at $P < 0.05$ level. Potential publication bias was estimated using a funnel plot. A sensitivity analysis was per-

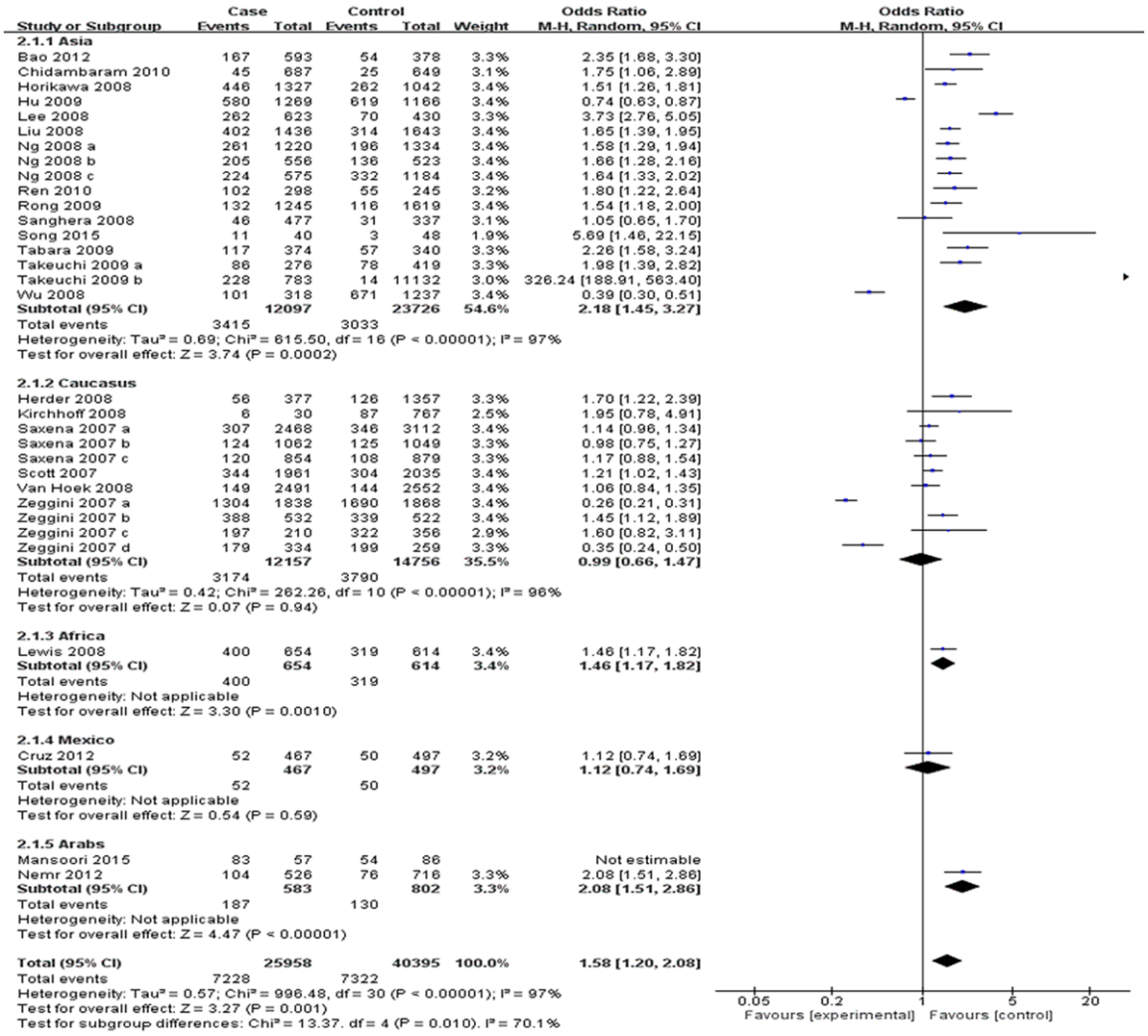

Figure 2. Forest plot of the T2DM associated gene rs7754840 G/C polymorphism under a recessive genetic model (CC vs. GC + GG).

formed to identify potential outliers. The statistical analyses were performed with Review Manager 5.3 software.

Results

Studies and populations

Three hundred eighty four studies were identified in the literature search. Twenty nine publications were obtained though the retrieval process and among these, twenty four papers that included thirty two studies met the inclusion criteria. Typically, one paper included one study, however, a few publications included multiple studies; such as the paper published by Zegginia et al, which included 4 individual studies. Among the five papers that were excluded, one paper had been published repeatedly, two papers were unrelated to the CDKAL1 gene rs7754840 G/C polymorphism or T2DM, and two papers were excluded for deviating from Hardy-Weinberg equilibrium (HWE). All information was extracted from 33,149 T2DM cases and 36,992 controls (**Table 1**) [21, 22, 25-46]. These populations included Asians, Caucasians, Africans, Mexicans and Arabs. The Caucasian subgroup is comprised of 11 studies, the Asian subgroup is comprised of 17 studies, both the African and the Mexican subgroups are comprised of only 1 study, and the Arab subgroup is comprised of 2 studies.

Pooled analyses

In the whole population, a significant relationship between the CDKAL1 rs7754840 G/C

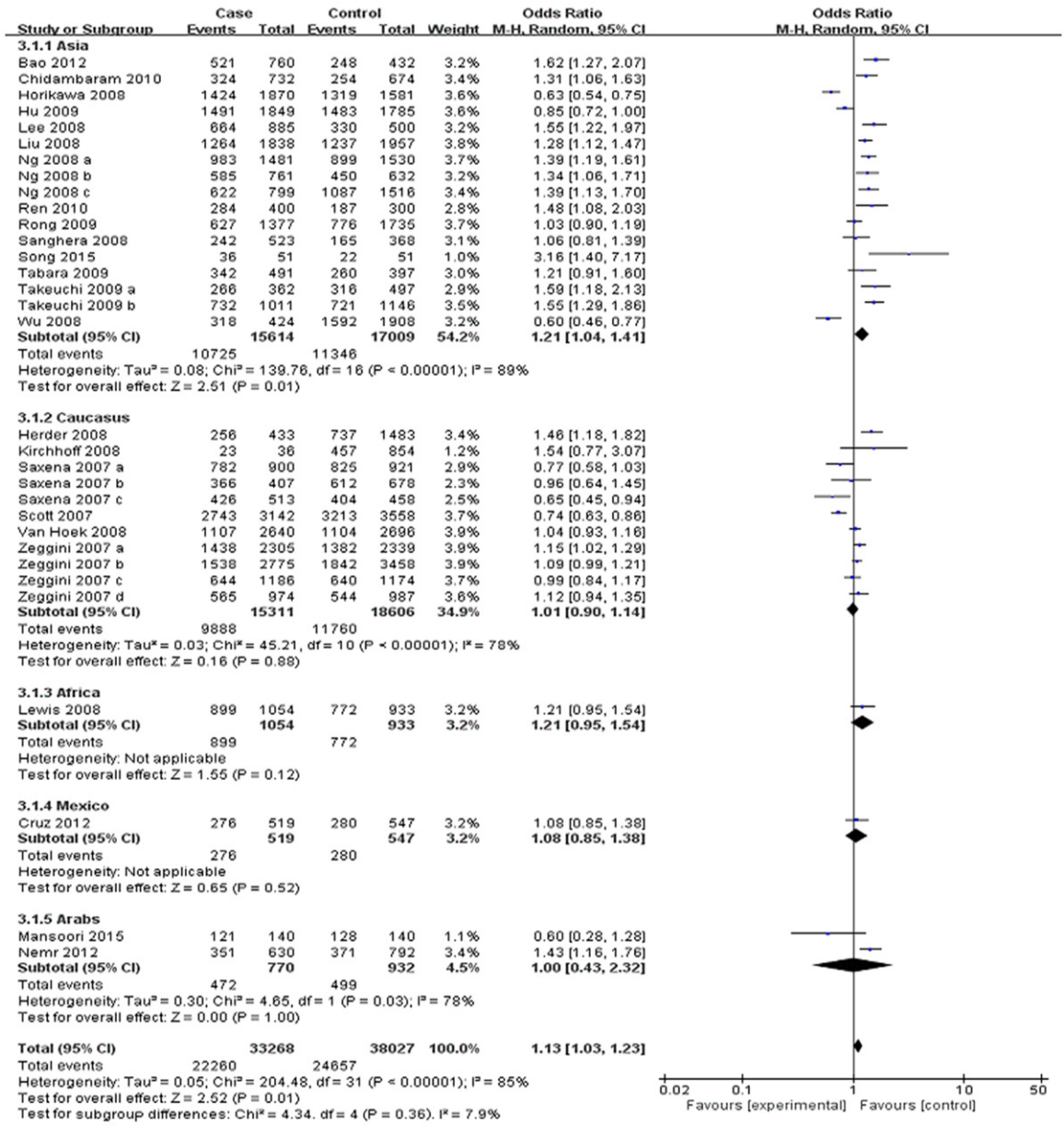

Figure 3. Forest plot of the T2DM associated gene rs7754840 G/C polymorphism under a dominant genetic model (GC + CC vs. GG).

gene polymorphism and T2DM was observed under the allelic (OR: 1.37, 95% CI: 1.22-1.55, P < 0.001), recessive (OR: 1.58, 95% CI: 1.20-2.08, P < 0.001), dominant (OR: 1.13, 95% CI: 1.21-1.33, P = 0.01), homozygous (OR: 1.27, 95% CI: 1.21-1.33, P < 0.001), or the heterozygous genetic model (OR: 0.83, 95% CI: 0.75-0.93, P < 0.001). In the subgroup analysis, a significant association was found in the Asian population under the allelic (OR: 1.31, 95% CI: 1.24-1.39, P < 0.001), recessive (OR: 2.18, 95% CI: 1.45-3.27, P < 0.001), dominant (OR: 1.21, 95% CI: 1.04-1.41, P = 0.01), homozygous (OR: 1.37, 95% CI: 1.16-1.63, P = 0.004) or the heterozygous genetic model (OR: 0.78, 95% CI: 0.66-0.90, P < 0.001) (**Table 2**; **Figures 1-5**).

In the subgroup analysis, there was a significant association between them in Caucasian population under allelic under allelic (OR: 1.37, 95% CI: 1.03-1.84, P = 0.03). No significant association was found under recessive (OR: 0.99, 95% CI: 0.66-1.47, P = 0.94), dominant

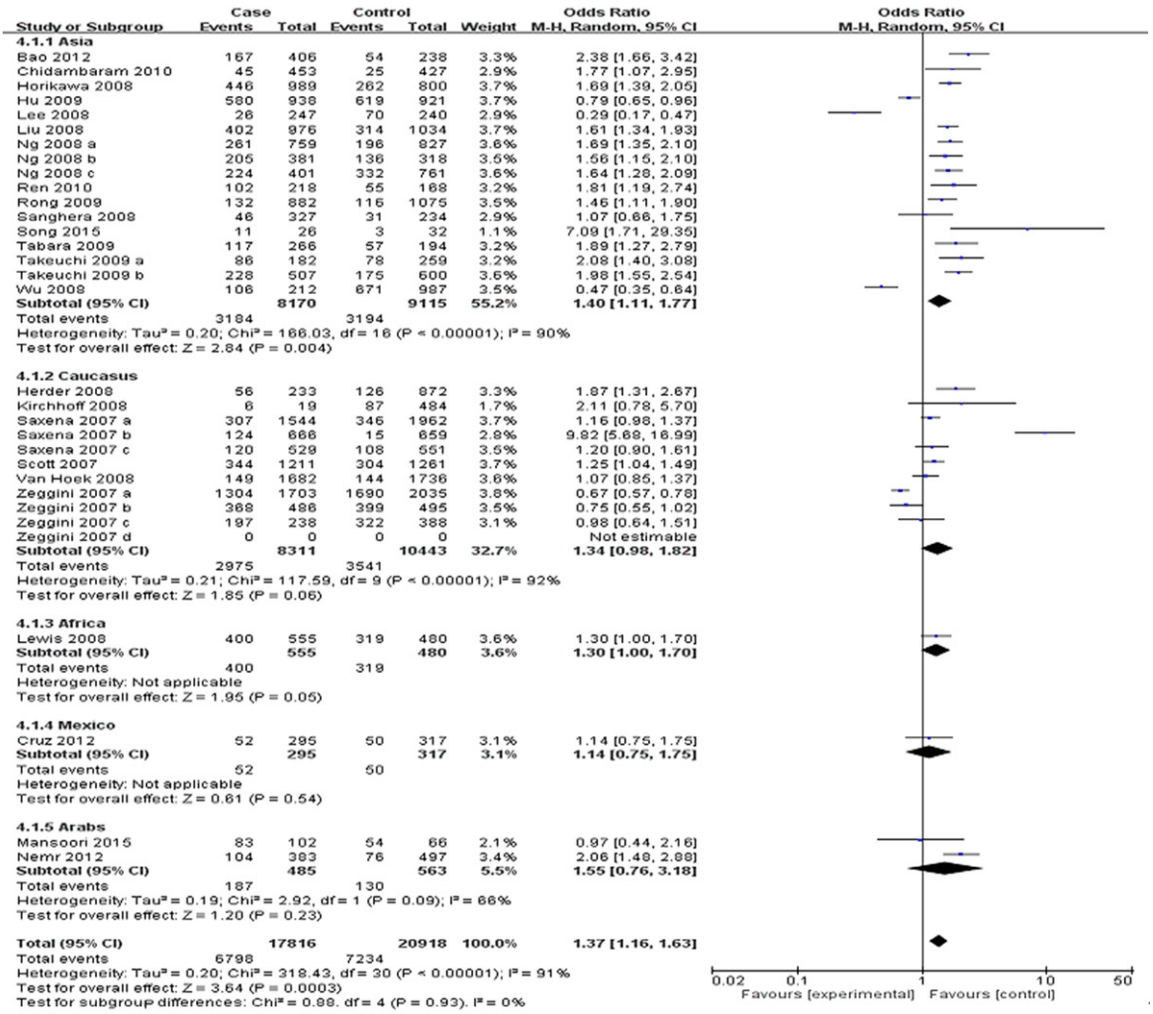

Figure 4. Forest plot of the T2DM associated gene rs7754840 G/C polymorphism under a Homozygous genetic model (CC vs. GG).

(OR: 1.01, 95% CI: 0.90-1.14, P = 0.88), homozygous (OR: 1.40, 95% CI: 1.11-1.77, P = 0.06), or the heterozygous genetic model (OR: 1.01, 95% CI: 0.90-1.13, P = 0.87). In the African subgroup, a significant association between the CDKAL1 rs7754840 G/C gene polymorphism and T2DM was identified under the allelic (OR: 2.29, 95% CI: 2.03-2.57, P < 0.001), recessive (OR: 1.46, 95% CI: 1.17-1.82, P < 0.001). No significant association was found under dominant (OR: 1.21, 95% CI: 0.95-1.54, P = 0.12), homozygous (OR: 1.30, 95% CI: 1.00-1.70, P = 0.05), or the heterozygous genetic model (OR: 0.88, 95% CI: 0.72-1.07, P = 0.19). In the Mexican subgroup. No significant association between the CDKAL1 rs7754840 G/C gene polymorphism and T2DM in the Mexican subgroup was identified under the allelic (OR: 1.07, 95% CI: 0.89-1.29, P = 0.45), recessive (OR: 1.12, 95% CI: 0.74-1.69, P = 0.59), dominant (OR: 1.08, 95% CI: 0.85-1.38, P = 0.52), homozygous (OR: 1.14, 95% CI: 0.75-1.75, P = 0.54), or the heterozygous genetic model (OR: 0.94, 95% CI: 0.61-1.44, P = 0.76). In the Arab subgroup, there was a significant association between the CDKAL1 rs7754840 G/C gene polymorphism and T2DM was identified under the allelic (OR: 1.44, 95% CI: 1.24-1.66, P < 0.001), dominant (OR: 1.34, 95% CI: 1.09-1.64, P = 0.005), recessive (OR: 2.08, 95% CI: 1.51-2.86, P < 0.001), homozygous (OR: 1.84, 95% CI: 1.36-2.50, P < 0.001), and the heterozygous genetic model (OR: 0.51, 95% CI: 0.38-0.68, P < 0.001).

Significant heterogeneity was observed in every subgroup for each genetic model (P < 0.05). In order to identify the source of this observed

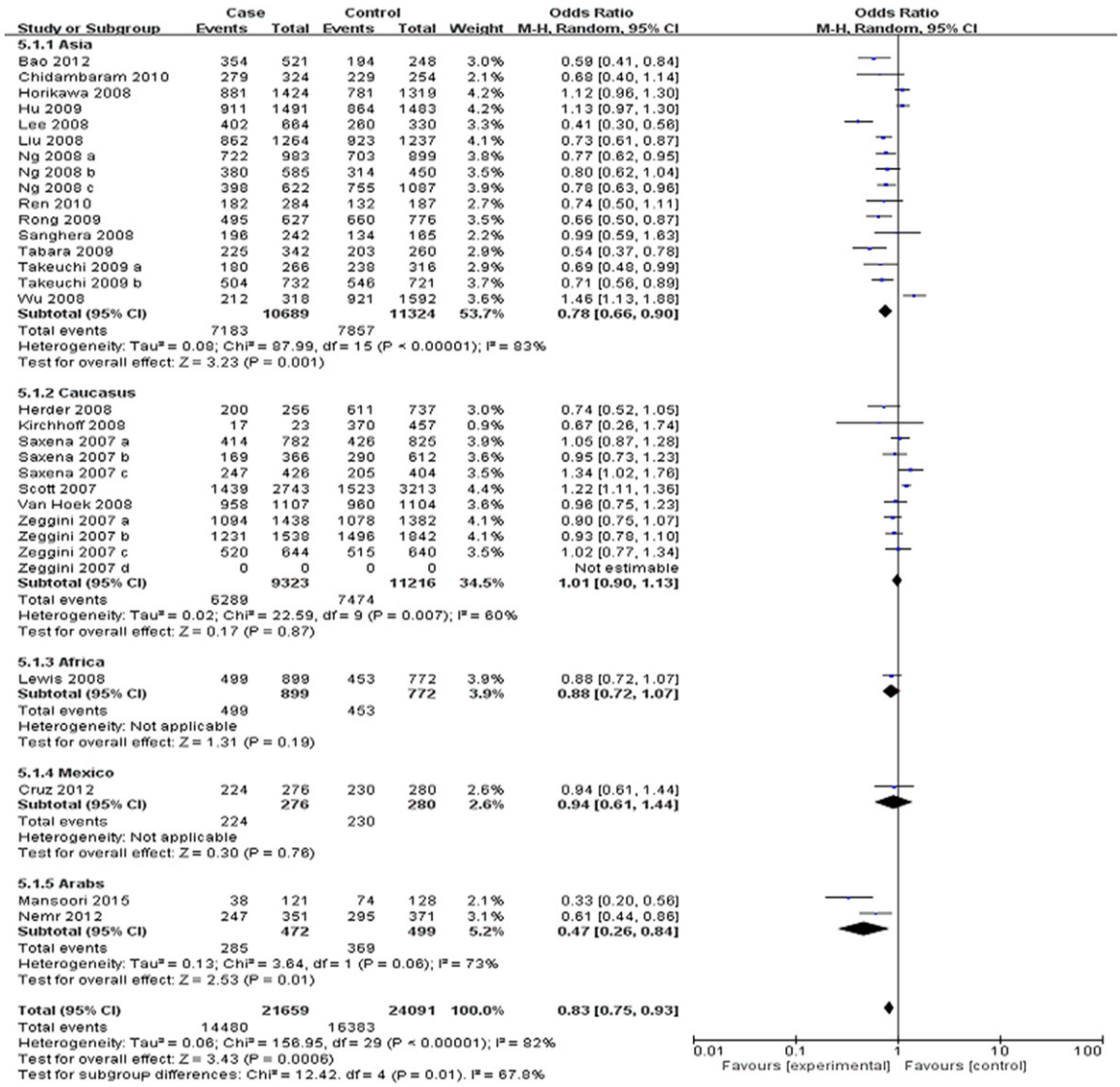

Figure 5. Forest plot of the T2DM associated gene rs7754840 G/C polymorphism under a heterozygous genetic model (GC vs. GG).

heterogeneity, a subsequent meta-regression was performed using the Asian population data. Under the allelic, recessive, and the homozygous genetic models, the CC genotype number in the T2DM group was verified to be the main confounding factor behind the source of the heterogeneity ($P < 0.05$).

Diagnostics bias

Funnel plots were performed in order to determine if there was a publication bias in the literature. Funnel plots were performed under the allelic genetic model (shown in **Figure 6**). Visual inspection of the funnel plots indicated an asymmetry. The asymmetry of the funnel plot may be due to an insufficient number of case (which may lead to a small-study effect) and significant statistical heterogeneity in the current meta-analysis.

Discussion

The association between the CDKAL1 rs7754840 SNP and T2DM has been investigated using different populations; however, the results of these studies are in disagreement. In this meta-analysis involving 33,149 T2DM patients and 36,992 controls from 21 independent studies, the relationship of the CDKAL1

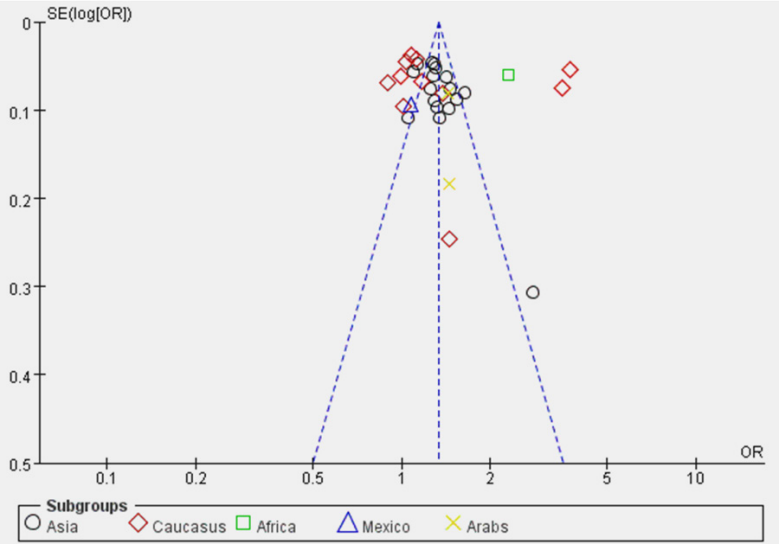

Figure 6. Funnel plots for the CDKAL1 gene G/C polymorphism and T2DM risk in the allelic genetic model.

gene rs7754840 G/C polymorphism with T2DM was investigated. Overall, our data indicated that a significant association exists between the CDKAL1 gene rs7754840 A/G polymorphism and T2DM under the allelic (OR: 1.37), recessive (OR: 1.58), dominant (OR: 1.13), homozygous (OR: 1.27), and the heterozygous genetic models (OR: 0.83).

Considering the possibility that different ethnic backgrounds may influence the results, a subgroup analysis stratified by the different ethnic backgrounds was also performed in the current meta-analysis. A significant association was shown to exist in the Asian and Arab subgroups ($P < 0.05$), while no significant association was detected in the Caucasian, African and Mexican subgroups ($P > 0.05$). In conclusion, the C allele of the CDKAL1 gene rs7754840 G/C polymorphism may increase susceptibility to developing T2DM, except in the Caucasian, African and Mexican populations. The results for the population as a whole and the Asian, Arab subgroups were genome-wide significant under most of the genetic models. In the Caucasian subgroup, the results reached genome-wide significance under the allelic genetic models. The negative results found for both the African and Mexican populations were perhaps not only associated with ethnic differences, but could also be a result of small sample sizes; only one research study with 933 T2DM subjects and one with 519 T2DM subjects were included for the African and Mexican subgroups. In comparison to the 6,798 and 6,535 research subjects used in the analysis for the Asian and Caucasian studies, the sample size for the Mexican and African studies was relatively small. Therefore, the results should be further verified using more studies with larger sample sizes for the African and Mexican subgroups.

Cyclin-dependent kinase 5 (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, especially in high glucose environments [47]. Ubeda et al suggested that CDKAL1 plays a role in the inhibition of CDK5 activity in pancreatic β cell expression, which prevents a decrease in insulin gene expression resulting from glucotoxicity [48]. As mutations accumulate in the CDKAL1 gene, the inhibition of CDK5 activity would decrease and β cell function, being the secretion of insulin, would be compromised. It has been reported that in relation to β cell function, the CDKAL1 gene has been significantly associated with insulin resistance, however, not the lack of insulin secretion. The rs7754840 C allele located in the CDKAL1 gene is a single nucleotide polymorphism associated with a genetic susceptibility towards type 2 diabetes. The mutation has two alleles, G and C; where G is the wild-type allele and C is the mutant. When the G→C mutation occurs, the β cells become degenerated and insulin secretion is inhibited; thus the CDKAL1 gene rs7754840 G/C mutation most likely leads to an increased risk of type 2 diabetes [49, 50].

In 2013, Peng et al [51] performed a meta-analysis regarding the relationship between the CDKAL1 rs7754840 G/C gene polymorphism and T2DM. They concluded that the CDKAL1 rs7754840 C allele increased the risk of T2DM. Despite the similarity between these results and the results performed in this study, the current meta-analysis was far superior in comparison. The previous study was published in 2012,

whereas the current meta-analysis included literature published from 2010 up to the present. Additionally, only basic data extraction was done and there was no use of any genetic models in Peng's work, whereas the present meta-analysis utilized five different genetic models, including the allelic, recessive, dominant, homozygous, and the heterozygous genetic models. Thus, the conclusions drawn from this study are more objective and scientifically validated than theirs.

As a result, in the current meta-analysis, the CDKAL1 gene rs7754840 G/C polymorphism was found to be significantly associated with T2DM susceptibility, particularly in the Asian and Arab populations. People with the G allele in the CDKAL1 gene rs7754840 G/C polymorphism may be predisposed to developing T2DM. This conclusion may lead to the formulation of new methods for T2DM therapies. Taking the limitations discussed above into consideration, more large-scale studies focusing on the association of the CDKAL1 gene rs7754840 G/C polymorphism and T2DM should be done to further validate the conclusion.

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Disclosure of conflict of interest

None.

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