CDKAL1 gene rs7756992 A/G polymorphism and type 2 diabetes mellitus: a meta-analysis of 62,567 subjects

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The Cyclin-dependent kinase 5 regulatory subunit-associated protein 1-like (CDKAL1) gene rs7756992 A/G polymorphism has been suggested to be associated with type 2 diabetes mellitus (T2DM), but the individual studies results are still controversial. To explore the association of CDKAL1 gene rs7756992 A/G polymorphism with T2DM, a meta-analysis involving 62,567 subjects from 21 separate studies was conducted. In the whole population, a significant association was found between CDKAL1 gene rs7756992 A/G polymorphism and T2DM under allelic (OR: 1.180, 95% CI: 1.130–1.230, P < 1.60 × 10⁻¹⁴), recessive (OR: 1.510, 95% CI: 1.380–1.660, P = 8.41 × 10⁻¹⁸), dominant (OR: 1.175, 95% CI: 1.109–1.246, P = 6.30 × 10⁻⁸), homozygous (OR: 1.400, 95% CI: 1.282–1.530, P = 8.02 × 10⁻¹⁴), and heterozygous genetic models (OR: 1.101, 95% CI: 1.040–1.166, P = 0.001). CDKAL1 gene rs7756992 A/G polymorphism was significantly associated with T2DM. The person with G allele of CDKAL1 gene rs7756992 A/G polymorphism might be predisposed to T2DM.

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disturbance syndrome led by the combined actions of genetic gene and environmental factors. The data from International Diabetes Federation showed that in 2011, there were approximately 366 million diabetes mellitus (DM) patients in the globe and it has been speculated that the DM patients quantity will continually increase and be up to 552 million by 2030, of which the type 2 DM (T2DM) accounts for 90–95%¹. The large scale investigations performed in the Chinese adults in June 2007 and May 2008 have shown that T2DM and impaired glucose tolerance (IGT) patients were about 92.4 million and 148 million respectively which are predominantly the young and middle-aged people and the number is in the first place of the world. Therefore, it is no time to delay to prevent T2DM².

The interaction of genetic and environmental factors is universally acknowledged as the primary underlying T2DM mechanism. It is now generally considered that T2DM is not a sole disorder, but a multi-gene disorder with extensive heredity heterogeneity which results from the insulin resistance and β cell dysfunction of pancreatic island. The T2DM risk in the first degree relatives of T2DM patients is 3.62 times that in the common population³, so the researchers of various countries make great efforts to explore the T2DM susceptible genes. Once the T2DM susceptible genes are sought out, it means that the T2DM prevention clues have been found. It is an effective measure to screen the T2DM susceptible population and prevent T2DM progress.

It has been reported that more than 50 genes are closely associated with T2DM by genome wide association study (GWAS) technology⁴⁵. *Cyclin-dependent kinase 5 regulatory subunit-associated protein 1-like (CDKAL1)* is one of the novel T2DM associated genes identified recently⁶. *CDKAL1* gene, located in 6p22.3, spans 37 kb which encodes 579 amino acids. *CDKAL1* gene encode tRNA decoration enzyme, namely methyl transfer enzyme which is responsible for the 2-methylthio-N6-threonylcarbamoyladenosine synthesis of the 37th base of tRNALys(UUU)⁷. Wei et al found the mitochondria adenosine triphosphate (ATP) generation obstacle and the first stage insulin secretion impairment in the *CDKAL1* gene knock-out mice⁸. In 2007, the GWAS study in Iceland population first reported that the *CDKAL1* gene rs7756992 A/G polymorphism was associated with T2DM risk which was repeatedly verified in Caucasian populations⁹.
Although many studies on the relationship between CDKAL1 gene rs7756992 A/G polymorphism and T2DM have been performed so far, the researches results were still controversial. In 2011, Chistiakov et al found that the allele G of rs7756992 with higher diabetes risk thereby replicating the predisposing role of CDKAL1 gene in etiology of T2DM in a Russian population (OR = 1.21, 95% CI: 1.04–1.42, P = 0.017)\(^9\). In 2013, Li W et al found the similar result in a Chinese population (OR: 1.68, 95% CI: 0.91–3.09, P = 0.009)\(^{10}\). In 2007, Horikoshi et al observed that in a Japanese population with CDKAL1 gene rs7756992 GG genotypes, the T2DM risk was significantly decreased (OR:0.78, 95% CI: 0.61–0.98, P = 0.017)\(^9\). In 2013, Li W et al found the similar result in a Chinese population (OR:1.79, 95% CI:1.28–2.50, P = 0.001)\(^{11}\). In 2010, Xu et al reported that allele G of rs7756992 with higher diabetes risk was not significantly associated with T2DM susceptibility in another Chinese population (OR: 1.68, 95% CI: 0.91–3.09, P = 0.10)\(^{12}\).

In the present study, a meta-analysis involving 26,120 T2DM patients and 36,447 controls from 21 separate studies was performed to estimate the relationship of CDKAL1 gene rs7756992 A/G polymorphism and T2DM.

**Results**

**Studies and populations.** Twenty-eight publications were obtained through the retrieval process, among which fourteen manuscripts including twenty one studies met the inclusion criteria. Among the fourteen discharged papers, four papers were of review character, and five papers were not involved with CDKAL1 gene rs7756992 A/G polymorphism or T2DM. Two studies deviating from the Hardy-Weinberg equilibrium (HWE) were rejected. All of information was extracted from above studies.

| Author          | Year | Country     | Subgroup     | sample size |
|-----------------|------|-------------|--------------|-------------|
| Steinhorsdottir | 2007 | Iceland     | Caucasian    | 1396/5271   |
| Steinhorsdottir | 2007 | Denmark     | Caucasian    | 1572/5378   |
| Steinhorsdottir | 2007 | US          | Caucasian    | 430/891     |
| Steinhorsdottir | 2007 | Netherlands | Caucasian    | 354/897     |
| Steinhorsdottir | 2007 | West Africa | African      | 830/1056    |
| Horikoshi       | 2007 | Japan       | Asian        | 852/857     |
| Omori           | 2008 | Japan       | Asian        | 1610/1039   |
| Cauchi          | 2008 | France      | Caucasian    | 492/961     |
| Cauchi          | 2008 | Austria     | Caucasian    | 450/693     |
| Cauchi          | 2008 | Morocco     | African      | 510/475     |
| Liu             | 2008 | Israel      | Asian        | 1700/1884   |
| Ng              | 2008 | China,Korea | Asian        | 2282/2737   |
| Horikawa        | 2008 | Japan       | Asian        | 1855/1856   |
| Rong            | 2009 | India       | Asian        | 1335/1748   |
| Takeuchi        | 2009 | Japan       | Asian        | 1104/1004   |
| Tabara          | 2009 | Japan       | Asian        | 491/397     |
| Xu M            | 2010 | China       | Asian        | 67/656      |
| Chistjakov      | 2011 | Russia      | Caucasian    | 765/766     |
| Lu F            | 2012 | China       | Asian        | 2903/3264   |
| Li W            | 2013 | China       | Asian        | 534/453     |

Abbreviations: T2DM: type 2 diabetes mellitus; BMI: body mass index; PR: polymerase chain reaction restriction fragment length polymorphism genotyping method and Case-control study design were adopted in the above studies.
under recessive genetic model, a significant association was found between them (OR: 1.420, 95% CI: 1.040–1.940, P = 0.03). (Table 2, Figure 1–5).

There was significant heterogeneity in the Asian subgroup under all of the genetic models (P < 0.05), while the heterogeneity did not exist under all of the genetic models in the Caucasian or African subgroup (P > 0.05). In order to explore the heterogeneity source, subsequent meta-regression was performed in the Asian population. Under the allelic, recessive, and homozygous genetic models, the GG genotype number of T2DM group (GG1) was verified to be the main confounding factor to explain the heterogeneity source (P < 0.05).

According to the GG genotype of T2DM group, the Asian population was separated into two subgroups. The studies with GG1 > 200 were grouped to subgroup 1 and the residual studies with GG1 < 200 belonged to subgroup 2. In the following subgroup analysis stratified by GG1, significant increased T2DM risk was only detected under the recessive genetic model (T2DM size: the total number of T2DM cases; control size: the total number of control group; Allelic genetic model: G allele distribution frequency; recessive genetic model: GG vs. AA; Dominant genetic model: AG + GG vs. AA; Homozygous genetic model: GG vs. AA; Heterozygous genetic model: AG vs. AA; Additive genetic model: total G allele vs. total A allele.

Bias diagnostics. The publication bias among the individual studies was evaluated by funnel plot and Egger’s test. There was no visual publication bias in the Begg’s funnel plot (Figure 6). There was no significant difference in the Egger’s test yet, which suggested that no publication bias was detected in the current meta-analysis by using recessive genetic model (T = –0.29, P = 0.777). As no duplicate publications were included in the meta-analysis and every included individual study was a case-control study, there was no sample overlap in the cases or controls. In addition, as the controls data in each individual study were originally collected by the authors themselves and not cited from other studies, the samples in each of the studies were entirely independent and could not cause the results to be biased.

Discussion

In the current meta-analysis, a significant association was detected in the whole population between CDKAL1 gene rs7756992 A/G polymorphism and T2DM under allelic (OR: 1.180), recessive (OR: 1.220), and homozygous (OR: 1.190) genetic models. In the subgroup analysis, there was a significant association in Caucasian and Asian subgroups (P < 0.05), while no significant association was detected in African subgroup (P > 0.05).

Table 2 | Summary of meta-analysis of association of CDKAL1 gene rs7756992 A/G gene polymorphism and type 2 diabetes mellitus (T2DM)

| Genetic model | Pooled OR (95% CI) | Z value | P value | Study number | T2DM size | control size | Pheterogeneity(25%) |
|---------------|--------------------|---------|---------|--------------|-----------|--------------|---------------------|
| Allelic genetic model | 1.180(1.130–1.230) | 7.68 | 1.60 x 10^{-14} | 21 | 26120 | 36447 | 0.0001* (61.3%) |
| Caucasian subgroup | 1.220(1.170–1.270) | 9.51 | 5.85 x 10^{-22} | 7 | 9005 | 18372 | 0.47% |
| Asian subgroup | 1.190(1.110–1.270) | 5.09 | 3.58 x 10^{-7} | 12 | 16765 | 16602 | <0.0001* (73.3%) |
| African subgroup | 1.070(0.960–1.190) | 1.20 | 0.23 | 2 | 1350 | 1473 | 0.70% |
| Recessive genetic model | 1.510(1.380–1.660) | 8.70 | 8.41 x 10^{-18} | 21 | 26120 | 36447 | <0.0001* (70.3%) |
| Caucasian subgroup | 1.470(1.340–1.610) | 8.15 | 4.22 x 10^{-16} | 7 | 9005 | 18372 | 0.88% |
| Asian subgroup | 1.570(1.360–1.800) | 6.26 | 3.85 x 10^{-16} | 12 | 16765 | 16602 | <0.0001* (81.9%) |
| African subgroup | 1.420(1.040–1.940) | 2.20 | 0.03 | 2 | 1350 | 1473 | 0.19% |
| Dominant genetic model | 1.175(1.109–1.246) | 5.41 | 6.30 x 10^{-8} | 21 | 26120 | 36447 | 0.001* (56.4%) |
| Caucasian subgroup | 1.239(1.176–1.305) | 8.02 | 7.85 x 10^{-15} | 7 | 9005 | 18372 | 0.439% |
| Asian subgroup | 1.173(1.068–1.289) | 3.33 | 6.86 x 10^{-4} | 12 | 16765 | 16602 | <0.0001* (67.2%) |
| African subgroup | 1.008(0.843–1.206) | 0.09 | 0.927 | 2 | 1350 | 1473 | 0.21% |
| Homozygous genetic model | 1.400(1.282–1.530) | 7.47 | 8.02 x 10^{-14} | 21 | 26120 | 36447 | <0.0001* (59.9%) |
| Caucasian subgroup | 1.530(1.391–1.684) | 8.72 | 5.81 x 10^{-18} | 7 | 9005 | 18372 | 0.767% |
| Asian subgroup | 1.404(1.237–1.594) | 5.25 | 1.52 x 10^{-7} | 12 | 16765 | 16602 | <0.0001* (70.9%) |
| African subgroup | 1.058(0.840–1.332) | 0.48 | 0.631 | 2 | 1350 | 1473 | 0.537% |
| Heterozygous genetic model | 1.101(1.040–1.166) | 3.31 | 0.001* | 21 | 26120 | 36447 | 0.007* (48.6%) |
| Caucasian subgroup | 1.185(1.122–1.252) | 6.04 | 1.54 x 10^{-9} | 7 | 9005 | 18372 | 0.574% |
| Asian subgroup | 1.078(0.990–1.174) | 1.74 | 0.083 | 12 | 16765 | 16602 | 0.012* (54.6%) |
| African subgroup | 0.954(0.788–1.154) | 0.49 | 0.626 | 2 | 1350 | 1473 | 0.103 (62.4%) |

*P < 0.05

Abbreviations: T2DM: type 2 diabetes mellitus; CI: confidence interval; OR: odds ratio; T2DM size: the total number of T2DM cases; control size: the total number of control group; Allelic genetic model: G allele distribution frequency; recessive genetic model: GG vs. AA; Dominant genetic model: AG + GG vs. AA; Homozygous genetic model: GG vs. AA; Heterozygous genetic model: AG vs. AA; Additive genetic model: total G allele vs. total A allele.
Figure 1 | Forest plot of T2DM associated with CDKAL1 gene rs7756992 A/G polymorphism under an allelic genetic model (distribution of G allelic frequency of CDKAL1 rs7756992 gene).

| Study or sub-category | T2DM group | Control group | OR (random) 95% CI | Weight | OR (random) 95% CI |
|-----------------------|------------|---------------|---------------------|--------|---------------------|
| 01 Caucasian          |            |               |                     |        |                     |
| Steinhoff1970a        | 785/1796   | 2443/10542    | 0.69                | 1.23   | (1.12, 1.35)        |
| Steinhoff1970b        | 1011/3144  | 3027/10756    | 0.65                | 1.21   | (1.11, 1.32)        |
| Steinhoff2001         | 264/980    | 467/1976      | 0.97                | 1.09   | (0.99, 1.11)        |
| Steinhoff2007         | 139/708    | 485/1794      | 0.97                | 1.08   | (0.86, 1.37)        |
| Causioh 2008a         | 661/1672   | 2425/6952     | 0.73                | 1.27   | (1.16, 1.38)        |
| Causioh 2006          | 246/960    | 398/1186      | 0.84                | 1.07   | (0.89, 1.29)        |
| Chatoo 2011           | 465/1330   | 425/1552      | 0.61                | 1.21   | (1.04, 1.42)        |
| Subtotal (95%)        | 3240       |               | 0.77                | 1.22   | (1.17, 1.27)        |

| 02 Asia               |            |               |                     |        |                     |
| Horioka 2007          | 602/1794   | 602/1714      | 0.66                | 0.93   | (0.73, 1.19)        |
| Caucho 2006           | 374/1026   | 298/960       | 0.71                | 1.00   | (0.89, 1.11)        |
| Horita 2006           | 1950/3710  | 1479/3172     | 0.69                | 1.00   | (1.15, 1.15)        |
| Liu Y 2006            | 1012/3460  | 1870/7069     | 0.67                | 1.00   | (0.99, 1.11)        |
| Ng 2008               | 258/1044   | 2740/5474     | 0.70                | 1.00   | (0.99, 1.11)        |
| Orosi 2006            | 1642/3260  | 994/2079      | 0.59                | 1.00   | (0.99, 1.11)        |
| Pooling 2008          | 902/2670   | 1152/2946     | 0.81                | 0.99   | (0.99, 1.12)        |
| Takara 2009           | 527/862    | 370/794       | 0.61                | 1.00   | (0.81, 1.20)        |
| Takara 2000           | 1699/3246  | 1745/3012     | 0.79                | 0.90   | (0.82, 1.00)        |
| Li et al 2011         | 72/134     | 666/1312      | 0.11                | 0.79   | (0.69, 0.91)        |
| Liu F 2012            | 3243/9066  | 3039/6259     | 0.70                | 0.96   | (0.89, 1.05)        |
| LUV 2013              | 580/1068   | 431/906       | 0.44                | 1.20   | (0.99, 1.46)        |
| Subtotal (95%)        | 3330       |               | 0.70                | 1.13   | (1.11, 1.21)        |

| Total events: 1914 (T2DM group), 1505 (Control group) |
| Test for heterogeneity: CH2 = 51.24, df = 11 (P = 0.0001), I2 = 73.3% |
| Test for overall effect: Z = 6.09 (P = 0.0001) |

Figure 2 | Forest plot of T2DM associated with CDKAL1 gene rs7756992 A/G polymorphism under a recessive genetic model (GG vs. AA + AG).

| Study or sub-category | T2DM group | Control group | OR (random) 95% CI | Weight | OR (random) 95% CI |
|-----------------------|------------|---------------|---------------------|--------|---------------------|
| 01 African            |            |               |                     |        |                     |
| Steinhoff1970a        | 1027/1420  | 1295/2112     | 0.43                | 1.05   | (0.92, 1.20)        |
| Caucho 2006           | 339/1049   | 254/834       | 0.53                | 1.00   | (0.91, 1.18)        |
| Subtotal (95%)        | 370        |               | 0.74                | 0.92   | (0.89, 1.15)        |

| Total events: 1720 (T2DM group), 1957 (Control group) |
| Test for heterogeneity: CH2 = 11.0 (P = 0.0009), I2 = 51.2% |
| Test for overall effect: Z = 1.20 (P = 0.23) |

| 02 Asia               |            |               |                     |        |                     |
| Horioka 2007          | 109/1296   | 2779/4994     | 0.56                | 1.30   | (1.23, 1.96)        |
| Caucho 2006           | 1784/3398  | 444/6954      | 0.55                | 1.24   | (1.19, 1.29)        |
| Horita 2006           | 49/390     | 68/823        | 0.70                | 1.27   | (0.94, 1.71)        |
| Steinhoff1970a        | 30/104     | 63/654        | 2.72                | 1.22   | (0.79, 1.92)        |
| Pooling 2008          | 440/405    | 3246/4410     | 0.68                | 1.23   | (1.06, 1.41)        |
| Takara 2001           | 43/409     | 56/627        | 2.03                | 1.23   | (1.06, 1.41)        |
| Takara 2000           | 622/862    | 732/1095      | 1.66                | 1.16   | (0.99, 1.39)        |
| Subtotal (95%)        | 8894       |               | 0.70                | 1.13   | (1.12, 1.23)        |

| Total events: 2073 (T2DM group), 2673 (Control group) |
| Test for heterogeneity: CH2 = 30.24 (P = 0.0001), I2 = 61.3% |
| Test for overall effect: Z = 7.68 (P = 0.0001) |

Figure 3 | Forest plot of T2DM associated with CDKAL1 gene rs7756992 A/G polymorphism under a dominant genetic model (GG vs. AA).
In conclusion, it was indicated that the G allele of CDKAL1 gene rs7756992 A/G polymorphism might increase the T2DM risk, except in the African population. Moreover, the results in the whole population and Caucasian subgroup were genome-wide significant under most of the genetic models (P < 8.0 × 10^-7). In Asian subgroup, the results reached the genome-wide significant threshold under allelic, recessive and homozygous genetic models. The negative results in the African population was perhaps not only associated with the different ethnicity, but also associated with the small sample size, because only two researches with 1350 T2DM subjects were included in this subgroup. In comparison to 9005 and 16,765 for the Caucasian and Asian studies respectively, the sample size for the African studies was too small. Hence, the conclusion needs to be further verified by more and more studies with larger sample size in the African subgroup in the future.

In consideration of the significant heterogeneity in the Asian populations, the meta-regression has been performed. The confounding factor GG1 was confirmed to be the main heterogeneity source under the allelic, recessive, and homozygous genetic models. AA0 was considered as the main heterogeneity source under the dominant and heterozygous genetic models. In the subgroup analysis stratified by the two confounding factors under the five genetic models, the larger the confounding factors number (the subgroup in GG1 > 200, AA0 < 300), the larger the heterogeneity (allelic: I^2 = 78.0%; recessive: I^2 = 86.9%; dominant: I^2 = 70.7%; homozygous: I^2 = 77.6%; and heterozygous: I^2 = 60.2%), the weaker the association between them (allelic: OR = 1.120; recessive: OR = 1.470; dominant: OR = 1.088; homozygous: OR = 1.272; heterozygous: OR = 1.010). It suggested that the larger sample size could reduce the heterogeneity between the individual studies and the research sample size needs to be further expanded in the future.

Cyclin-dependent kinase 5 (CDK5) is a serine/threonine protein kinase. The CDK5 is activated by producing CDK5/p35 compounds in the pancreatic tissue, thus the β cells are degenerated and the insulin secretion is inhibited, especially in the high glucose condition. In 2006, Ubeda et al found that in the high glucose internal environment, the CDK5 overactivity could decrease the insulin release rate and reduce the insulin production and restrain the insulin gene expression. They found that inhibition of CDK5 activity could protect pancreatic cells from glucotoxicity.

CDKAL1 is highly expressed in the human pancreas, skeletal muscle, and brain tissue and can specially inhibit CDK5 activity. In 2010, Ohara-Imaizumi et al found that CDKAL1 controls first-phase insulin exocytosis in β cells by facilitating ATP generation, K (ATP) channel responsiveness and the subsequent activity of Ca (2+ ) channels through pathways other than CDK5-mediated regulation. CDKAL1 gene rs7756992 A/G mutation probably leads to the inhibition effect loss on CDK5, thus the T2DM risk is increased. However, the exact underlying mechanism of CDKAL1 gene mutation changing the insulin secretion pattern are still unclear and need to be clarified in the further researches.

Figure 3 | Forest plot of T2DM associated with CDKAL1 gene rs7756992 A/G polymorphism under a dominant genetic model (AG + GG vs. AA).
Figure 4 | Forest plot of T2DM associated with CDKAL1 gene rs7756992 A/G polymorphism under a homozygous genetic model (GG vs. AA).

Figure 5 | Forest plot of T2DM associated with CDKAL1 gene rs7756992 A/G polymorphism under a heterozygous genetic model (AG vs. AA).
No similar meta-analysis on the association of T2DM with CDKAL1 gene rs7756992 A/G polymorphism has been found internationally so far. Some limitations still existed in the present meta-analysis. Large-scale researches on the association of T2DM with CDKAL1 gene rs7756992 A/G polymorphism are still inadequate. The serum CDKAL1 level was influenced not only by the CDKAL1 gene rs7756992 A/G polymorphism, but also by other gene polymorphisms and unscientific dietary habits. As the heredity model of T2DM is multiple gene inheritance which means that many micro-effect genes produce a general effect and leads to T2DM, other genes polymorphisms might be predisposed to T2DM risk.

Finally, CDKAL1 gene rs7756992 A/G polymorphism was significantly associated with T2DM susceptibility, particularly in the Caucasian and Asian population. The persons with the G allele of CDKAL1 gene rs7756992 A/G polymorphism might be predisposed to T2DM. This conclusion might guide us to formulate new T2DM therapy strategy. Taken account the above limitations, more studies on the association of CDKAL1 gene rs7756992 A/G polymorphism and T2DM are needed to be carried out to further clarify the conclusion in the future.

Methods

Publication search and inclusion criteria. The electronic databases including PubMed, Web of Science, Embase, China Biological Medicine Database, and China National Knowledge Infrastructure were searched by using the words as “CDKAL1”, “rs7756992”, “polymorphism” and “type 2 diabetes mellitus”. The last research was updated on October 15, 2013 with the publication years ranging from 2007 to 2013. The following major criteria should be met by the included studies. The CDKAL1 gene rs7756992 A/G polymorphism and T2DM were evaluated. T2DM was diagnosed by the American Diabetes Association fasting plasma criteria (2005). The fasting plasma glucose level was no less than 7.0 mmol/L or the 2 h plasma glucose of oral glucose tolerance test was no less than 11.1 mmol/L. Furthermore, no genetic relationship existed between the subjects in the individual studies. Only the data drawn from officially published manuscripts with case-control or cohort studies could be adopted. The HWE should be followed by genotype member of the control group in the individual studies.

Data extraction. The informed consent was obtained from all subjects. The studies data was extracted in the light of a standard protocol. Three researchers carried out the meta-analysis; two of whom searched out the studies duplicitously, and the third researcher acted as the arbitrator to resolve the conflict between the two researchers and come to an agreement. The current meta-analysis rejected the studies that did not follow the selection criteria, that were repeatedly published, or that provided insufficient data. If similar data was rooted in different manuscripts by the same authorship, the data was only once adopted. The following items including the first author’s name, publication year, region, continents, number of genotypes, matching criteria and total number of cases and controls should be shown in the extracted data.

Statistical analyses. Five genetic models as the allelic (G allele distribution frequency), recessive (GG vs. AA + AG), dominant (GG + AG vs. AA), homozygous (GG vs. AA), and heterozygous (AG vs. AA) genetic models were used in the present meta-analysis. The odds ratios (ORs) and their corresponding 95% confidence intervals (CIs) were used to compare the association of CDKAL1 gene rs7756992 A/G polymorphism and T2DM. The heterogeneity among the studies was calculated by Chi-square-based Q-tests with significance set at $P < 0.05$ level. If heterogeneity existed, the random-effect model (DerSimonian and Laird method) would be used. Or else, the fixed-effect model was adopted (the Mantel–Haenszel method). Z test was used to estimate the pooled OR with significance set at $P < 0.05$ level. The HWE was assessed by using Fisher’s exact test with significance set at $P = 0.05$ level. The potential publication bias was estimated by adopting the funnel plot. The funnel plot symmetry was evaluated by using Egger’s linear regression test on the natural logarithm scale of the OR and significance was set at $P < 0.001$ level. The statistical analyses were performed by Stata 12.0 software (StataCorp, College Station, TX, USA).

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Author contributions
Conceived and designed the experiments: Y.L. Performed the experiments: Y.L., L.W. Analyzed the data: Y.L., C.Z., Z.Y. Contributed reagents/materials/analysis tools: Y.L., J.X. Wrote the manuscript: Y.L., Y.Q. Reference collection and data management: Y.L., X.W. Statistical analyses and paper writing: Y.L., X.L. Study design: Y.L., A.C.

Additional information
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