Association of uncoupling protein-2-866G/A and Ala55Val polymorphisms with susceptibility to type 2 diabetes mellitus

A meta-analysis of case-control studies

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Abstract

Background: Recently, the relationships between uncoupling protein-2 (UCP2)-866G/A (rs659366) and Ala55Val (rs660339) polymorphisms and the risk of type 2 diabetes mellitus (T2DM) have been explored considerably, but the results are greatly inconsistent. This meta-analysis was performed to further identify the association of UCP2 rs659366 and rs660339 with the risk of T2DM.

Methods: Eligible studies were searched from PubMed, Embase, Cochrane Library, VIP database, Chinese National Knowledge Infrastructure, and Chinese WanFang database until March 8, 2020. The odds ratios with corresponding 95% confidence intervals (CIs), and P-values were used to assess the strength of the association.

Results: A total of 26 studies were included in this study. UCP2 rs659366 was associated with the risk of T2DM in allele model (OR: 1.112, 95%CI: 1.009–1.224, P=0.032), dominant model (OR: 1.189, 95%CI: 1.035–1.366, P=0.014), and heterozygous model (OR: 1.177, 95%CI: 1.032–1.342, P=0.015). A significantly increased risk of T2DM was detected in Asians by UCP2 rs659366 allele (OR: 1.132, 95%CI: 1.016–1.262, P=0.025), dominant (OR: 1.218, 95%CI: 1.046–1.418, P=0.011), homozygous (OR: 1.254, 95%CI: 1.022–1.540, P=0.031) or heterozygous (OR: 1.198, 95%CI: 1.047–1.371, P=0.009) models. There was no significant correlation between UCP2 rs660339 and the risk of T2DM (P>0.05).

Conclusions: The UCP2 rs659366 is significantly associated with the risk of T2DM, especially in Asian population, while no evidence is found between the UCP2 rs660339 and the susceptibility to T2DM.

Abbreviations: ATP = adenosine triphosphate, CIs = confidence intervals, NOS = Newcastle-Ottawa scale, PCR-RFLP = polymerase chain reaction-restriction fragment length polymorphism, rs659366 = -866G/A, rs660339 = Ala55Val, T2DM = type 2 diabetes mellitus, UCP2 = uncoupling protein-2.

Keywords: -866G/A, Ala55Val, type 2 diabetes mellitus, uncoupling protein-2

1. Introduction

Type 2 diabetes mellitus (T2DM) is a serious public health hazard characterized by inadequate secretion and utilization of insulin, with increasing morbidity and mortality worldwide.1 As a multifactorial disease, the susceptibility of T2DM is affected by the combination of various genetic and environmental factors.2 It is believed that the environmental factors only affect the presence of T2DM genetic background, while genetic factors are considered to play a crucial role in the pathogenesis and chronic
complications of T2DM.\[^{2}\]\ Therefore, genetically susceptible subjects who are exposed to the environmental risk factors are easier to develop the T2DM.

As a family member of the mitochondrial anion transporter proteins, uncoupling protein-2 (UCP2) is broadly expressed in tissues and cell types.\[^{3,4}\] UCP2 mediates proton leakage across the inner membrane by uncoupling the substrate oxidation from the adenosine triphosphate (ATP) synthesis, causing the decrease of ATP production by the mitochondrial respiratory chain.\[^{5}\] Therefore, the glucose-stimulated insulin secretion which is regulated by the ATP/ADP ratio may be suppressed by the UCP2 activity.\[^{6,7}\] This mechanism is closely associated with the pathogenesis and chronic complications of T2DM. The UCP2 promoter -866G/A (rs659366) polymorphism, which serves as a binding site for insulin promoter factor 1 and the pancreatic transcription factor parried box-containing 6, is found to have the association with increased UCP2 mRNA levels, decreased insulin secretion and higher T2DM risk.\[^{8-10}\]\ In addition, the Ala55Val (CT; rs660339) polymorphism in exon 4 has also been confirmed to be associated with a reduced uncoupling degree and energy expenditure, as well as an increased risk of obesity and diabetes.\[^{11,12}\]\

Recently, the relationships between UCP2 -866G/A (rs659366) and Ala55Val (rs660339) polymorphisms and T2DM risk have been explored in various studies. However, the results of these studies are greatly inconsistent. A few studies demonstrated that UCP2 rs659366 and rs660339 polymorphisms were correlated with T2DM risk,\[^{13,14}\]\ while some other studies failed to discover the association.\[^{15-17}\]\ The identification of the relationship between UCP2 and T2DM susceptibility will help the diagnosis, prevention, and treatment of T2DM. Hence, we conducted this meta-analysis by systematically reviewing the current evidence to clarify the relationship between UCP2 rs659366 and rs660339 polymorphisms and risk of T2DM.

2. Methods

2.1. Search strategy

Articles were retrieved from PubMed, Embase, Cochrane Library, VIP database, Chinese National Knowledge Infrastructure, and Chinese WanFang database until March 8th, 2020. Key words and subject terms used for search included ‘Type 2 Diabetes’ OR ‘Type 2 diabetes mellitus’ OR ‘T2DM’ AND ‘Uncoupling protein 2’ OR ‘UCP2’ AND ‘mutation’ OR ‘variant’ OR ‘polymorphism’ OR ‘single nucleotide polymorphism’.

2.2. Inclusion and exclusion criteria

All involved articles were screened by the following inclusion criteria:

(1) case-control studies investigating the association of UCP2 rs659366 and rs660339 polymorphisms with T2DM;
(2) clear definition of T2DM;
(3) cases of diabetes ≥ 50;
(4) sufficient data on the genotype distribution;
(5) articles published in peer-reviewed journals;
(6) language in English or Chinese;
(7) evidence of Hardy-Weinberg equilibrium (HWE) >0.05.

Exclusion criteria were as follows:

(1) reviews, letters, meetings;
(2) duplicated reports;
(3) outcomes not relevant to rs659366 or rs660339;
(4) studies using genome wide association study to detect the genotyping.

2.3. Methodological quality appraisal

Two researchers independently assessed the methodological quality of the included studies using the Newcastle-Ottawa scale (NOS).\[^{18}\] The NOS evaluates quality of observational study based on 3 aspects: selection, comparability and ascertainment of exposure and outcomes. Three aspects assign a maximum score of 4, 2, and 3, respectively, and the assessment score for each study ranges from 0 to 9. Studies with a NOS score of 7 or more were regarded as high-quality study. Any disagreements were settled by the consensus.

2.4. Data extraction

The following data were extracted from each independent study: first author, year of publication, country, ethnicity, sample size, source of control, genotyping method, single nucleotide polymorphism type, HWE, and NOS score. All data were extracted from the included studies, and we did not contact the authors for additional data.

2.5. Statistical analysis

To investigate the relationships of UCP2 rs659366 and rs660339 polymorphisms with T2DM risk, we conducted the meta-analyses using a series of genetic models, including allele model (A vs G for rs659366 and T vs C for rs660339), homozygous model (AA vs GG for rs659366 and TT vs CC for rs660339), dominant model (AG/AA vs GG for rs659366 and TC/TT vs CC for rs660339), recessive model (AA vs GG/AG for rs659366 and TT vs CC/TC for rs660339), and heterozygous model (AG vs GG for rs659366 and CT vs TT for rs660339). Besides, subgroup analyses were carried out according to ethnicity, source of control, genotyping method, and quality of articles.

The strength of correlation between UCP2 variants and T2DM was measured by odds ratios and the corresponding 95% confidence intervals (CIs). Between-study heterogeneity was evaluated by the \( \chi^2 \)-based Q-test and \( I^2 \) statistics. \( P \) value of Q-test <.10 and \( I^2 \) >50% indicated evidence of heterogeneity, and then a random-effect model was used to count the summary risk estimate; otherwise, the fixed-effect model was performed. Harbord test was used to estimate the potential publication bias. All above statistical analyses were performed using Stata 14.0 (Stata Corporation, College Station, TX), and \( P \) values were 2-sided with a statistical significance level of 0.05, except for tests of heterogeneity where a level of 0.10 was used.

3. Results

3.1. Characteristics of included studies

A total of 322 relevant articles were recognized from electronic databases. 110 duplicate articles were excluded, 152 articles were removed by screening titles and abstracts, and further 34 articles were excluded based on appraising the full text. Finally, 26 case-control studies meeting all inclusion criteria were included in this
The flow diagram was shown in the Figure 1.

Among the included studies, 19 studies were performed in Asian population, and 7 in Caucasian population. Polymerase chain reaction–restriction fragment length polymorphism (PCR-RFLP) was adopted for genotyping of UCP2 rs659366 and rs660339 in most studies. The detailed characteristics and quality assessment of all included studies were listed in the Table 1.

3.2. Correlation between UCP2 rs659366 polymorphism and risk of T2DM

20 studies including 6895 T2DM cases and 4999 controls were pooled to estimate the relationship of UCP2 rs659366 polymorphism with T2DM risk. Significant correlations were discovered in allele model (OR: 1.112, 95%CI: 1.009–1.224, P = .032), dominant model (OR: 1.189, 95%CI: 1.035–1.366, P = .014), and heterozygous model (OR: 1.177, 95%CI: 1.032–1.342, P = .015), while no evidence of association was found in recessive model (OR: 1.086, 95%CI: 0.945–1.248, P = .246) and homozygous model (OR: 1.207, 95%CI: 0.997–1.461, P = .054). (Table 2, Fig. 2).

Due to the significant heterogeneity in the genetic models among included studies, subgroup analyses were performed to identify the source of heterogeneity based on the ethnicity, source of control, genotyping method and quality assessment. For ethnicity, a significantly increased risk of T2DM was detected in Asians by allele (OR: 1.132, 95%CI: 1.016–1.262, P = .025), dominant (OR: 1.218, 95%CI: 1.046–1.418, P = .011), homozygous (OR: 1.254, 95%CI: 1.022–1.540, P = .031), or heterozygous (OR: 1.198, 95%CI: 1.047–1.371, P = .009) models, while no statistical significance was found in the recessive model (OR: 1.105, 95%CI: 0.963–1.268, P = .154). Regarding the source of control, significant differences were presented between T2DM risk and UCP2 rs659366 allele (OR: 1.212, 95%CI: 1.104–1.330, P < .001), dominant (OR: 1.342, 95%CI: 1.151–1.565, P < .001), recessive (OR: 1.215, 95%CI: 1.077–1.371, P = .002), homozygous (OR: 1.424, 95%CI: 1.204–1.684, P < .001), or heterozygous (OR: 1.308, 95%CI: 1.114–1.535, P = .001) models in hospital-based studies. For genotyping methods, the risk of T2DM was found to be associated with
Table 1
Basic characteristics of the studies included in this meta-analysis.

| First author, year | Country | Ethnicity | Case/Control | Source of control | Genotyping method | SNP type | HWE | NOS score |
|-------------------|---------|-----------|--------------|------------------|------------------|----------|------|-----------|
| Gorani 2019       | India   | Asian     | 318/312      | Hospital-based   | PCR-RFLP         | rs659366 | 0.490 | 7         |
| Su 2019           | China   | Asian     | 397/409      | Population-based | Mass ARRAY system| rs659369 | 0.751 | 7         |
| Shen 2019         | China   | Asian     | 479/470      | Hospital-based   | DNA sequencing   | rs659366, rs660399 | 0.160/0.117 | 6 |
| Sun 2013          | China   | Asian     | 471/78       | Hospital-based   | PCR-RFLP         | rs659366 | 0.630 | 5         |
| Qin 2013          | China   | Asian     | 352/363      | Hospital-based   | PCR-RFLP         | rs659366, rs660399 | 0.487/0.222 | 6 |
| Souza 2013        | Brazil  | Caucasian | 981/534      | Hospital-based   | TaqMan           | rs659366, rs660399 | 0.932/0.536 | 6 |
| Hu 2010           | China   | Asian     | 104/114      | Unknown          | PCR+DHPLC        | rs660339 | 0.460 | 5         |
| Hedari 2010       | Iran    | Asian     | 75/75        | Population-based | PCR-RFLP         | rs659366 | 0.125 | 7         |
| Crispim 2010      | Brazil  | Caucasian | 240/258      | Unknown          | TaqMan           | rs659366, rs660399 | 0.997/0.613 | 6 |
| Beilfushees 2010  | Italy   | Caucasian | 107/341      | Population-based | Pyrosequencing/TaqMan | rs659366 | 0.192 | 7         |
| Wang 2009         | China   | Asian     | 470/217      | Population-based | PCR-RFLP         | rs659366 | 0.634 | 6         |
| She 2009          | China   | Asian     | 370/166      | Hospital-based   | PCR-RFLP         | rs659366 | 0.076 | 7         |
| Li 2008           | China   | Asian     | 192/101      | Population-based | PCR-RFLP         | rs659366 | 0.395 | 6         |
| Shen 2008         | China   | Asian     | 229/196      | Population-based | PCR-RFLP         | rs659366 | 0.894 | 5         |
| Gu 2007           | China   | Asian     | 278/162      | Population-based | PCR-RFLP         | rs659366 | 0.671 | 8         |
| Yu 2006           | China   | Asian     | 122/55       | Population-based | PCR-RFLP         | rs659366 | 0.893 | 7         |
| Pinelli 2006      | Italy   | Caucasian | 342/305      | Population-based | ASAT-PCR         | rs660339 | 0.315 | 6         |
| Bullota 2005      | Italy   | Caucasian | 746/327      | Population-based | Unknown          |          |      |           |
| Xu 2004           | China   | Asian     | 173/177      | Population-based | PCR-RFLP         | rs660339 | 0.633 | 7         |
| Satsahara 2004    | Japan   | Asian     | 413/172      | Population-based | PCR-RFLP         | rs659366 | 0.446 | 4         |
| Ji 2003           | Japan   | Asian     | 342/134      | Population-based | PCR-RFLP         | rs659366 | 0.689 | 3         |
| D'Adamo 2004      | Italy   | Caucasian | 483/565      | Hospital-based   | TaqMan           | rs659366, rs660399 | 0.069 | 3         |
| Cho 2003          | Korea   | Asian     | 504/133      | Population-based | PCR-RFLP         | rs659366 | 0.097 | 4         |
| Krempfer 2002     | Austria | Caucasian | 201/291      | Hospital-based   | PCR-RFLP         | rs659366 | 0.132 | 6         |
| Zheng 2000        | China   | Asian     | 166/193      | Population-based | PCR-RFLP         | rs660339 | 0.121 | 4         |
| Kubota 1998       | Japan   | Asian     | 210/218      | Unknown          | PCR-RFLP         | rs660339 | 0.107 | 3         |

DHPLC = denaturing high-performance liquid chromatography, HWE = Hardy-Weinberg equilibrium, PCR = polymerase chain reaction, RFLP = restriction fragment length polymorphism, RT-PCR = Real-time reverse transcription-polymerase chain reaction.

3.3. Correlation between UCP2 rs660399 polymorphism and risk of T2DM

There were 9 studies on the correlation between UCP2 rs660339 and the risk of T2DM,\[15,19,20,22,23,25,37,39,40\] including 3042 T2DM cases and 2388 controls. Pooled analysis exhibited that no significant difference was presented between rs660339 and the risk of T2DM (all P > .05). Details were shown in the Table 3 and Figure 3.

Table 2
Stratified meta-analyses of the correlation between UCP2 rs659366 polymorphism and risk of T2DM.

| Characteristics | No. of studies | Sample size (case/control) | A vs. G (allele model) | AG+AA vs. GG (dominant model) | AA vs. GG (recessive model) | AA vs. GG (homologous model) | AG vs. GG (heterologous model) |
|-----------------|----------------|-----------------------------|------------------------|-------------------------------|----------------------------|-------------------------------|-------------------------------|
| Ethnicity       | 13             | 4088/2479                   | 0.112 (0.109–1.224)    | 0.118 (0.105–1.166)          | 0.114 (0.108–1.166)        | 0.126 (0.119–1.326)          |
| Caucasian       | 7              | 2897/2520                   | 0.132 (0.126–1.262)    | 0.128 (0.124–1.418)          | 0.130 (0.124–1.458)        | 0.135 (0.128–1.508)          |
| Hospital-based  | 14             | 4732/3779                   | 0.121 (0.114–1.330)    | 0.125 (0.118–1.442)          | 0.127 (0.120–1.452)        | 0.130 (0.122–1.462)          |
| Population-based| 5              | 1911/1068                   | 0.132 (0.124–1.262)    | 0.132 (0.126–1.424)          | 0.134 (0.126–1.478)        | 0.136 (0.128–1.518)          |
| Unknown         | 1              | 342/734                     | 0.132 (0.126–1.262)    | 0.132 (0.126–1.424)          | 0.134 (0.126–1.478)        | 0.136 (0.128–1.518)          |
| Genotyping method | 7             | 3150/2677                   | 0.104 (0.087–1.218)    | 0.107 (0.083–1.337)          | 0.111 (0.094–1.294)        | 0.114 (0.097–1.342)          |
| Quality         | 13             | 3835/2322                   | 0.116 (0.103–1.308)    | 0.127 (0.107–1.512)          | 0.128 (0.106–1.458)        | 0.129 (0.106–1.497)          |

CI = confidence interval, OR = odds ratio, PCR-RFLP = polymerase chain reaction-restriction fragment length polymorphism, T2DM = type 2 diabetes mellitus, UCP2 = uncoupling protein-2.
3.4. Publication bias

Harbord test showed no publication bias in allele ($t = 1.42$, $P = .172$), dominant ($t = 1.89$, $P = .075$), recessive ($t = 0.48$, $P = .638$), homozygous ($t = 1.98$, $P = .342$) and heterozygous models ($t = 2.08$, $P = .032$) of UCP2 rs659366, as well as in allele ($t = 1.29$, $P = .240$), dominant ($t = 0.91$, $P = .392$), recessive ($t = 1.63$, $P = .347$), homozygous ($t = 1.49$, $P = .180$) and heterozygous models ($t = 0.69$, $P = .511$) of UCP2 rs660339. Details were shown in the Table 4, Figs. 4 and 5.

4. Discussion

As an inner mitochondrial membrane transporter protein, UCP2 enables oxidative phosphorylation of ADP uncoupled to ATP. This may influence the specific function of tissues, such as thermogenesis, regulation of glucose and free fatty acid metabolism. The high expression of UCP2 in the pancreatic β-cells regulates the insulin negatively, resulting in the dysfunction and development of T2DM.\[40,41\] Considering the importance of UCP2 in the T2DM pathogenesis, the relationship

**Table 3**

Stratified meta-analyses of the correlation between UCP2 rs660339 polymorphism and risk of T2DM.

| Characteristics       | No. of studies | Sample size (case/control) | T vs. C (allele model) | CT+CC vs. TT (dominant model) | CC vs. TT (recessive model) | CC vs. TT (homozygous model) | CT vs. TT (heterozygous model) |
|-----------------------|----------------|---------------------------|------------------------|-------------------------------|----------------------------|-------------------------------|-------------------------------|
| Total                 | 9              | 3042/2388                 | 1.066 (0.887–1.282)    | 1.056 (0.827–1.349)          | 1.132 (0.851–1.506)       | 1.160 (0.803–1.676)         | 1.026 (0.825–1.276)           |
| Ethnicity             |                |                           |                        |                               |                           |                               |                               |
| Asian                 | 7              | 2016/1678                 | 1.034 (0.825–1.296)    | 0.994 (0.760–1.300)          | 1.126 (0.767–1.653)       | 1.107 (0.695–1.762)         | 0.965 (0.776–1.219)           |
| Caucasian             | 2              | 1026/712                  | 1.186 (0.777–1.808)    | 1.291 (0.612–2.725)          | 1.148 (0.682–1.494)       | 1.369 (0.655–2.863)         | 1.236 (0.592–2.668)           |
| Source of control     |                |                           |                        |                               |                           |                               |                               |
| Hospital-based        | 2              | 1671/1330                 | 1.078 (0.912–1.272)    | 1.083 (0.844–1.388)          | 1.145 (0.840–1.560)       | 1.176 (0.829–1.668)         | 1.054 (0.811–1.370)           |
| Population-based      | 4              | 553/591                   | 1.182 (0.788–1.751)    | 1.217 (0.743–1.998)          | 1.206 (0.717–2.309)       | 1.431 (0.655–3.127)         | 1.155 (0.770–1.732)           |
| Unknown               | 3              | 819/467                   | 0.920 (0.775–1.091)    | 0.892 (0.654–1.110)          | 0.963 (0.665–1.389)       | 0.863 (0.607–1.330)         | 0.844 (0.561–1.271)           |
| Genotyping method     |                |                           |                        |                               |                           |                               |                               |
| Others                | 5              | 1989/1655                 | 1.001 (0.799–1.254)    | 0.995 (0.734–1.306)          | 0.995 (0.734–1.306)       | 1.005 (0.656–1.542)         | 0.980 (0.765–1.359)           |
| PCR-RFLP              | 4              | 1033/723                  | 1.164 (0.827–1.637)    | 1.120 (0.723–1.737)          | 1.197 (0.769–2.537)       | 1.422 (0.691–2.865)         | 1.035 (0.698–1.536)           |
| Quality               |                |                           |                        |                               |                           |                               |                               |
| High                  | 6              | 2162/1842                 | 1.115 (0.856–1.452)    | 1.127 (0.809–1.570)          | 1.191 (0.798–1.776)       | 1.273 (0.749–2.162)         | 1.084 (0.825–1.425)           |
| Low                   | 3              | 880/546                   | 0.975 (0.831–1.144)    | 0.920 (0.682–1.241)          | 1.046 (0.714–1.532)       | 0.986 (0.695–1.343)         | 0.904 (0.600–1.362)           |

CI = confidence interval, OR = odds ratio, PCR-RFLP = polymerase chain reaction-restriction fragment length polymorphisms, T2DM = type 2 diabetes mellitus, UCP2 = uncoupling protein-2.
between UCP2 polymorphisms and T2DM susceptibility has been studied in the current study. A total of 26 studies were finally included. Results showed that the risk of T2DM was associated with the allele model, dominant model, and heterozygous model of UCP2 rs659366, especially in Asians. However, we did not find the significant correlation between UCP2 rs660339 and the risk of T2DM.

The polymorphism in the promoter region of UCP2 is reported to elevate the expression of UCP2, resulting in decreased insulin secretion and early onset of T2DM. UCP2 rs659366, situated in the core promoter of the region with putative binding sites for 2 β-cell transcription factors, is associated with differential expression of UCP2 and increased levels of oxidative stress markers. Compared with G allele, the A allele in the UCP2 rs659366 is related to higher UCP2 mRNA expression levels.

Enormous studies showed that the A allele in the UCP2 rs659366 had the association with insulin resistance and T2DM risk. In our meta-analysis, the risk of T2DM was found to be associated with the allele model, dominant model, and heterozygous model of UCP2 rs659366 in Asian population, but not Caucasian population, supported by the result of a previous meta-analysis that UCP2 rs659366 polymorphism in European ancestry was irrelevant to T2DM risk. This ethnic discrepancy in susceptibility to T2DM might be attributed to the genetic variation. In addition, our study also found significance differences between the risk of T2DM and UCP2 rs659366 allele, dominant, homozygous or heterozygous models in the hospital-based studies and PCR-RFLP assay.

UCP2 rs660339 is located in exon 4 in the UCP2 gene where the base change can cause the changes in coding amino acids from alanine to valine. Previous studies showed that the TT of rs660339 could increase the risk of overweight, suggesting rs660339 might contribute to facilitating the development of prediabetes or T2DM via overweight. Vimaleswaran et al. found that UCP2 rs660339 was associated with a significantly lowered risk of T2DM in Asian Indians. Nevertheless, no association between UCP2 rs660339 and incidence T2DM was found in the Atherosclerosis Risk in Communities Study cohort. Our results further confirmed no association of UCP2 rs660339 with susceptibility to T2DM either in Asian population or Caucasian population, which may be explained by the fact that the UCP2 gene was probably a genetic risk factor for diabetes, while UCP2 rs660339 polymorphism may not be a key variant.

Although our meta-analysis included the latest publications and conducted a series of subgroup analyses to provide a comprehensive evaluation for the relationship between UCP2 variants and T2DM risk, several potential limitations remained to be taken into consideration. First, the results of our study were based on the unadjusted estimates. The adjusted estimates might be more precise in evaluating the real relationship. Second, T2DM was a complex multifactorial disease produced by the

![Figure 3. Forest plots for the correlation between UCP2 rs660339 polymorphism and risk of T2DM (A. allele model; B. dominant model; C. recessive model; D. homozygous model; E. heterozygous model).](image-url)

| SNP               | t    | p    |
|-------------------|------|------|
| rs659366          |      |      |
| A vs G (allele model) | 1.42 | .172 |
| AG+AA vs GG (dominant model) | 1.89 | .075 |
| AA vs GG+AG (recessive model) | 0.48 | .638 |
| AA vs GG (homozygous model) | 1.98 | .342 |
| AG vs GG (heterozygous model) | 2.08 | .052 |
| rs660339          |      |      |
| T vs C (allele model) | 1.29 | .240 |
| CT+CC vs TT (dominant model) | 0.91 | .392 |
| CC vs TT+CT (recessive model) | 1.63 | .147 |
| CC vs TT (homozygous model) | 1.49 | .180 |
| CT vs TT (heterozygous model) | 0.69 | .511 |

SNP = single nucleotide polymorphism, UCP2 = uncoupling protein-2.
synthesized effect of genetic and environmental risk factors. The effects of gene-gene and gene-environmental interactions were not assessed on account of lacking original data. Additionally, the accuracy of our results might be affected due to exclusion of studies with genome wide association study to detect the genotyping. In the future, further well-designed studies, especially those on gene-gene and gene-environmental interactions, will be undertaken to verify our results.

Figure 4. Begg funnel plot of publication bias for UCP2 rs659366 (A. allele model; B. dominant model; C. recessive model; D. homozygous model; E. homozygous model).

Figure 5. Begg funnel plot of publication bias for UCP2 rs660339 (A. allele model; B. dominant model; C. recessive model; D. homozygous model; E. homozygous model).
5. Conclusions
The UCP2 rs663366 was significantly associated with the risk of T2DM, especially in Asian population, while no evidence was found between the UCP2 rs660339 and the susceptibility to T2DM.

Author contributions
LX and LBZ conceived and designed the study. LX wrote the manuscript and collected the data. SYC participated in data analysis and literature review. LBZ critically reviewed and edited the manuscript. All authors read and approved the final manuscript.

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