**CLPTM1L** gene rs402710 (C > T) and rs401681 (C > T) polymorphisms associate with decreased cancer risk: a meta-analysis

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**ABSTRACT**

Cleft lip and palate transmembrane 1-like (CLPTM1L) gene rs402710 (C > T) and rs401681 (C > T) polymorphisms have been widely studied for their potential relation to cancer risk, but studies have produced conflicting results. To systematically evaluate the association between these two polymorphisms and overall cancer risk, we conducted a comprehensive meta-analysis on all relevant articles found in the PubMed and EMBASE databases published prior to May 1, 2017. There were 26 articles with 28 studies, including 30,770 cases and 34,089 controls, for the rs402710 polymorphism and 38 articles with 48 studies, including 67,849 cases and 328,226 controls, for the rs401681 polymorphism. The pooled results indicated that both rs402710 and rs401681 polymorphisms are significantly associated with decreased overall cancer risk. In our stratification analysis, a significant association of the rs402710 polymorphism with lung and bladder cancers was identified among Asian and Caucasian populations in both hospital-based and population-based studies. The rs401681 polymorphism was significantly associated with a decreased risk of lung cancer, bladder cancer, and basal cell carcinoma in Asians and in hospital-based studies. **CLPTM1L** gene rs402710 and rs401681 polymorphisms thus have a protective association with various types of cancer, especially lung cancer among Asians.

**INTRODUCTION**

The number of people who will develop and die from cancer is expected to climb rapidly around the world [1]. In 2016, a total of 1,685,210 cases of cancer were newly diagnosed and 595,690 people died from cancer in the United States [2]. Meanwhile, approximately 4,292,000 new cancer cases and 2,814,000 cancer deaths were projected in China in 2015 [3]. It is imperative to deal with the rising cancer burden by taking full advantage of the knowledge embedded in cancer statistics, causes, and mechanisms and apply it to cancer prevention and screening [4]. Genetic-environmental interaction has been considered an essential factor in carcinogenesis [5]. Meanwhile, the roles of multiple genetic changes in influencing the evolution of cancer have been investigated over the years [6].

Recently, a number of investigations have been conducted to study the potential influence of **Telomerase reverse transcriptase** (**TERT**) and **cleft lip and palate transmembrane 1-like** (**CLPTM1L**) gene variation on cancer susceptibility. The **TERT** gene encodes the rate-limiting catalytic subunit of the telomerase enzyme that is vital to the maintenance of telomere DNA length, chromosomal stability, and cellular immortality [7]. **CLPTM1L**, encodes a protein linked to cisplatin resistance and associated with the susceptibility to cleft lip palate. **CLPTM1L** was found to be overexpressed in cisplatin-resistant ovarian cancer cells and to promote apoptosis in cisplatin-sensitive cells.
TERT–CLPTM1L genetic variants, including single nucleotide polymorphisms, have been reported by several genome-wide association studies (GWAS) to associate with the risk of multiple cancer types [9–11]. Among these polymorphisms, rs402710 (C > T) and rs401681 (C > T) have been widely studied for their potential effect on the susceptibility to cancer. Jiang et al. found that rs401681 polymorphism was associated with a decreased risk of lung cancer [12], but other studies found no association was found between rs401681 polymorphism and lung cancer risk [13, 14]. For the rs402710 polymorphism, Ito et al. observed remarkable effects on susceptibility in lung cancer [15], but the results were not repeated in other similar studies [16, 17]. We conducted a comprehensive meta-analysis of all relevant articles to provide a systematic and cumulative assessment of the association of CLPTM1L rs402710 and rs401681 polymorphisms and overall cancer risk.

RESULTS

Study characteristics

As shown in Figure 1, 176 publications were initially identified from PubMed and EMBASE electronic databases that met our inclusion and exclusion criteria. After title and abstract screening, 61 records were excluded. The remaining 115 full text articles were further assessed and 67 were further excluded for the following reasons: 1) 12 were meta-analyses; 2) 43 were irrelevant; and 3) 12 had insufficient information to calculate odds ratios (ORs) and 95% confidence intervals (95% CIs). Additionally, 3 relevant studies were also retrieved manually from the pool. In the end, 51 eligible articles were included in the final meta-analysis.

The genotypic distribution of rs402710 and rs401681 polymorphisms in the controls in almost all of the studies followed Hardy-Weinberg equilibrium (HWE); four did not (Table 1) [11, 17–19]. Since the genotypic distribution of other polymorphisms was in agreement with HWE in these four studies, the investigators decided to include them in the final analysis. Together, there were 26 articles with 28 studies including 30,770 cases and 34,089 controls for the rs402710 polymorphism [13, 15–39] and 38 articles with 48 studies including 67,849 cases and 328,226 controls for the rs401681 polymorphism (Table 1) [9–12, 14, 16–18, 21, 23–25, 28, 29, 32, 34, 35, 37, 38, 40–58]. For the rs402710 polymorphism, 19 studies focused on lung cancer, 2 on bladder cancer, and the rest on other individual types of cancer. There were 21 studies conducted on Asian populations, 5 on Caucasians, and 2 on Africans. 15 were hospital-based, and 12 were population-based. One was nested. As to the rs401681 polymorphism, 20 studies focused on lung cancer, 5 on bladder cancer and pancreatic cancer, 4 on melanoma, 3 on basal cell carcinoma, 2 on esophageal cancer and squamous cell carcinoma, and 7 on other individual cancer types, which we grouped as “the others” for our analyses. 24 were conducted on Asians, 21 on Caucasians, 2 on Africans, and only one on mixed ethnicity. There were 19 studies with a hospital-based design, 21 with a population-based design, and 8 with a nested design.

Meta-analysis results of the rs402710 polymorphism

As shown in Table 2 and Figure 2, there was evidence of a significant association between the rs402710 polymorphism and overall cancer risk under all of the five genetic models [homozygous (TT vs. CC): OR = 0.77, 95% CI = 0.70–0.84; heterozygous (CT vs. CC): OR = 0.89, 95% CI = 0.86–0.92; recessive (TT vs. CT+CC): OR = 0.81, 95% CI = 0.74–0.88; and dominant (CT+TT vs. CC): OR = 0.87, 95% CI = 0.83–0.91; as well as allele comparison model (T vs. C): OR = 0.88, 95% CI = 0.84–0.92]. In the stratification analysis by cancer type, a statistically significant association was identified with lung cancer [homozygous (TT vs. CC): OR = 0.73, 95% CI = 0.67–0.79; heterozygous (CT vs. CC): OR = 0.88, 95% CI = 0.85–0.91; recessive (TT vs. CT+CC): OR = 0.77, 95% CI = 0.71–0.84; and dominant (CT+TT vs. CC): OR = 0.85, 95% CI = 0.82–0.88]; as well as allele comparison model (T vs. C): OR = 0.85, 95% CI = 0.81–0.89] and bladder cancer [dominant (CT+TT vs. CC): OR = 0.83, 95% CI = 0.70–0.99; and allele comparison model (T vs. C): OR = 0.85, 95% CI = 0.75–0.98]. In the subgroup analysis by ethnicity and control source, there was a statistically significant association found in the studies of Asians and Caucasians in the hospital-based and population-based studies under all genetic models.

Meta-analysis results of rs401681 polymorphism

As shown in Table 2 and Figure 3, similar to the rs402710 polymorphism, a significant association between the rs401681 polymorphism and overall cancer risk was also observed [homozygous (TT vs. CC): OR = 0.87, 95% CI = 0.76–0.98; recessive (TT vs. CT+CC): OR = 0.90, 95% CI = 0.81–0.99; and allele comparison model (T vs. C): OR = 0.93, 95% CI = 0.89–0.97]. In the stratification analysis by cancer type, a decreased association was identified with lung cancer [homozygous (TT vs. CC): OR = 0.73, 95% CI = 0.66–0.81; heterozygous (CT vs. CC): OR = 0.86, 95% CI = 0.81–0.92; recessive (TT vs. CT+CC): OR = 0.78, 95% CI = 0.70–0.88; and dominant (CT+TT vs. CC): OR = 0.84, 95% CI = 0.80–0.88]; as well as allele comparison model (T vs. C): OR = 0.86, 95% CI = 0.84–0.89; bladder cancer and basal cell carcinoma. On the contrary, there was an increased risk for melanoma [homozygous (TT vs. CC): OR = 1.47, 95% CI = 1.23–1.75; heterozygous (CT vs. CC): OR = 1.24, 95% CI = 1.09–1.41; recessive (TT vs. CT+CC): OR = 1.29, 95% CI = 1.09–1.53; and dominant (CT+TT vs. CC): OR = 1.16, 95% CI = 0.97–1.39].
| Surname    | Year | Country | Ethnicity | Cancer type | Control source | Genotyping method | Cases/Controls | HWE  |
|------------|------|---------|-----------|-------------|----------------|------------------|----------------|------|
| rs402710 polymorphism | | | | | | | | |
| Zhou       | 2016 | China   | Asian     | ESCC        | HB             | MassArray        | 588            | 600  | 0.762 |
| Zhang      | 2016 | China   | Asian     | NPC         | HB             | MassArray        | 855            | 1036 | 0.512 |
| Jin        | 2016 | China   | Asian     | Lung cancer | HB             | MassArray        | 552            | 717  | 0.007 |
| Ge         | 2016 | China   | Asian     | Thyroid carcinoma | HB     | MassArray   | 500            | 500  | 0.675 |
| Liu        | 2015 | China   | Asian     | Lung cancer | PB             | MassArray        | 288            | 318  | 0.997 |
| Zhao       | 2014 | China   | Asian     | Lung cancer | HB             | Taqman           | 951            | 954  | 0.502 |
| Xun        | 2014 | China   | Asian     | Lung cancer | HB             | MassArray        | 227            | 300  | 0.795 |
| Liang      | 2014 | China   | Asian     | Lung cancer | HB             | MassArray        | 308            | 309  | 0.670 |
| Zhao       | 2013 | China   | Asian     | Lung cancer | PB             | SNPScan          | 784            | 782  | /    |
| Lu         | 2013 | China   | Asian     | Lung cancer | HB             | Taqman           | 604            | 1062 | 0.971 |
| Zheng      | 2012 | USA     | African   | Breast cancer | HB         | Illumina       | 1509           | 1383 | /    |
| Zhao       | 2012 | China   | Asian     | Cervical cancer | HB   | MassArray | 452            | 486  | 0.308 |
| Wang       | 2012 | China   | Asian     | Prostate cancer | HB         | PCR–RFLP       | 1425           | 3011 | 0.356 |
| Ren        | 2012 | China   | Asian     | Lung cancer | HB             | Taqman           | 716            | 716  | 0.912 |
| Ito        | 2012 | Japan   | Asian     | Lung cancer | HB             | Taqman           | 1425           | 3011 | 0.356 |
| Chen       | 2012 | China   | Asian     | Lung cancer | PB             | Taqman           | 1425           | 3011 | 0.356 |
| Bae        | 2012 | Korea   | Asian     | Lung cancer | PB             | Taqman           | 1425           | 3011 | 0.356 |
| Pande      | 2011 | USA     | Caucasian | Lung cancer | HB             | Illumina        | 1681           | 1235 | /    |
| Jaworowska | 2011 | Poland  | Caucasian | Lung cancer | HB             | Taqman           | 848            | 845  | 0.696 |
| Gago-Dominguez 1 | 2011 | USA     | African   | Bladder cancer | PB   | Taqman      | 471            | 528  | 0.109 |
| Gago-Dominguez 2 | 2011 | USA     | African   | Bladder cancer | PB   | Taqman      | 503            | 527  | 0.223 |
| Yoon       | 2010 | Korea   | Asian     | Lung cancer | PB             | Taqman           | 1425           | 3011 | 0.356 |
| Truong 1   | 2010 | France  | Caucasian | Lung cancer | PB             | Taqman           | 8860           | 9198 | 0.961 |
| Truong 2   | 2010 | France  | Caucasian | Lung cancer | PB             | Taqman           | 1680           | 2117 | 0.828 |
| Liu        | 2010 | USA     | Caucasian | Lung cancer | PB             | Taqman           | 1680           | 2117 | 0.828 |
| Hsiung     | 2010 | China   | Asian     | Lung cancer | Nested         | Illumina        | 2659           | 2844 | 0.001 |
| Zienolddiny | 2009 | Norway  | Caucasian | Lung cancer | PB             | Taqman           | 356            | 432  | 0.787 |
| rs401681 polymorphism | | | | | | | | |
| Zhang      | 2016 | China   | Asian     | NPC         | HB             | MassArray        | 1852           | 2008 | 0.832 |
| Jin        | 2016 | China   | Asian     | Lung cancer | HB             | MassArray        | 554            | 695  | 0.411 |
| Liu        | 2015 | China   | Asian     | Lung cancer | PB             | MassArray        | 292            | 319  | 0.696 |
| Gibbons    | 2015 | USA     | Caucasian | Melanoma    | PB             | MassArray        | 1187           | 2409 | 0.512 |
| Campa      | 2015 | Germany | Caucasian | Pancreatic cancer | PB   | Illumina   | 1857           | 4048 | 0.482 |
| Zhang      | 2014 | China   | Asian     | Lung cancer | HB             | Taqman           | 366            | 364  | 0.097 |
| Zhang      | 2014 | China   | Asian     | Bladder cancer | HB         | PCR–LDR       | 367            | 420  | 0.683 |
| Yin        | 2014 | China   | Asian     | Esophageal cancer | HB         | PCR–LDR     | 604            | 664  | 0.365 |
| Xun        | 2014 | China   | Asian     | Lung cancer | HB             | MassArray        | 956            | 722  | 0.263 |
| Su         | 2014 | China   | Asian     | HCC         | HB             | Taqman           | 956            | 722  | 0.263 |
| Llorca-Cardenosa | 2014 | Spain   | Caucasian | Melanoma    | HB             | Taqman           | 956            | 722  | 0.263 |
| Liu        | 2014 | China   | Asian     | Pancreatic cancer | PB   | Taqman      | 766            | 821  | 0.263 |
| Liang      | 2014 | China   | Asian     | Lung cancer | HB             | MassArray        | 309            | 308  | 0.631 |
| Wang       | 2013 | China   | Asian     | Lung cancer | HB             | HRM              | 492            | 486  | 0.076 |
CC): OR = 1.31, 95% CI = 1.16–1.47; as well as allele comparison model (T vs. C): OR = 1.19, 95% CI = 1.14–1.24] and pancreatic cancer [homozygous (TT vs. CC): OR = 1.41, 95% CI = 1.24–1.60; heterozygous (CT vs. CC): OR = 1.17, 95% CI = 1.06–1.29; recessive (TT vs. CT+CC): OR = 1.27, 95% CI = 1.12–1.45; and dominant (CT+TT vs. CC): OR = 1.24, 95% CI = 1.13–1.36; as well as allele comparison model (T vs. C): OR = 1.19, 95% CI = 1.14–1.24]. When the analysis was stratified by ethnicity, there was a statistically significant association among Asians, but not in Caucasians or Africans. When the analysis was stratified by control source, there was a statistically significant association in the hospital-based studies, but not in population-based studies.

Heterogeneity and sensitivity analyses

Substantial heterogeneities were observed among all studies of the rs402710 polymorphism and cancer risk (homozygous: \( p = 0.006 \); recessive: \( p = 0.021 \);
| Variables | No. of individuals | rs402710 polymorphism | rs401681 polymorphism |
|-----------|--------------------|-----------------------|-----------------------|
|           |                    | OR (95% CI)           | OR (95% CI)           |
|           | Homozygous (TT vs. CC) | Phet (%) F (%) | Phet (%) F (%) |
|           | Heterozygous (CT vs. CC) | Phet (%) F (%) | Phet (%) F (%) |
|           | Recessive (TT vs. CT+CC) | Phet (%) F (%) | Phet (%) F (%) |
|           | Dominant (CT+TT vs. CC) | Phet (%) F (%) | Phet (%) F (%) |
|           | Allele T vs. C | Phet (%) F (%) | Phet (%) F (%) |

### rs402710 Polymorphism

| Variable | OR (95% CI) | Phet (%) | F (%) |
|----------|-------------|----------|-------|
| All      | 0.77 (0.70–0.84) | 0.006 | 46.8 |
| Asian    | 0.78 (0.69–0.88) | 0.002 | 53.6 |
| African  | 0.87 (0.56–1.36) | / | / |
| Caucasian| 0.73 (0.66–0.80) | 0.634 | 0.0 |
| Lung     | 0.73 (0.67–0.79) | 0.205 | 21.8 |
| Bladder  | 0.75 (0.55–1.01) | 0.347 | 0.0 |
| Others   | 0.98 (0.74–1.30) | 0.009 | 67.7 |
| HB       | 0.81 (0.69–0.95) | 0.002 | 60.1 |
| PB       | 0.73 (0.67–0.80) | 0.404 | 3.7 |
| Mixed    | 0.74 (0.61–0.89) | / | / |

### rs401681 Polymorphism

| Variable | OR (95% CI) | Phet (%) | F (%) |
|----------|-------------|----------|-------|
| All      | 0.87 (0.76–0.98) | < 0.001 | 79.2 |
| Asian    | 0.76 (0.66–0.87) | < 0.001 | 58.9 |
| Caucasian| 1.11 (0.90–1.37) | < 0.001 | 86.3 |
| African  | 0.71 (0.49–1.03) | / | / |
| Lung     | 0.73 (0.66–0.81) | 0.220 | 22.4 |
| Melanoma | 1.47 (1.23–1.75) | 0.291 | 19.0 |
| Pancreatic| 1.41 (1.24–1.60) | 0.576 | 0.0 |
| Bladder  | 0.70 (0.56–0.87) | 0.491 | 0.0 |
| Esophageal| 0.82 (0.64–1.05) | 0.395 | 0.0 |
| SCC      | 0.82 (0.53–1.26) | / | / |
| BCC      | 0.87 (0.60–1.32) | / | / |
| Others   | 0.86 (0.57–1.30) | 0.007 | 79.6 |
| HB       | 0.78 (0.66–0.94) | < 0.001 | 63.6 |
| PH       | 0.94 (0.79–1.12) | < 0.001 | 84.3 |

and dominant: p = 0.032; as well as allele comparison model: p < 0.001, except for the heterozygous model (p = 0.121). As to the rs401681 polymorphism, we also observed considerable heterogeneities (homozygous: p < 0.001; heterozygous: p < 0.001; recessive: p < 0.001; and dominant: p < 0.001; as well as allele comparison model: p < 0.001). So, the random-effects model was applied to generate crude ORs and 95% CIs. In addition, the leave-one-out sensitivity analysis indicated that no single study altered the corresponding pooled ORs and 95% CIs.
Publication bias

The shape of our funnel plot did not reveal any evidence of obvious asymmetry for the rs402710 polymorphism (homozygous: \( p = 0.738 \); heterozygous: \( p = 0.291 \); recessive: \( p = 0.954 \); and dominant: \( p = 0.318 \); as well as allele comparison model: \( p = 0.946 \)) and rs401681 polymorphism (homozygous: \( p = 0.264 \); heterozygous: \( p = 0.451 \); recessive: \( p = 0.114 \); and dominant: \( p = 0.564 \); as well as allele comparison model: \( p = 0.967 \)).

DISCUSSION

The \( CLPTM1L \) gene encodes the CLPTM1-like protein which is highly expressed in cisplatin-resistant ovarian tumor cell lines and is associated with cisplatin-induced apoptosis [8]. This gene has also been demonstrated to be overexpressed in many other cancers [58–61]. Blockade of CLPTM1-like protein has been shown to inhibit K-Ras-induced lung tumorigenesis [61]. \( CLPTM1L \), near the \( TERT \) gene, is located at chromosome 5p15.33 which is widely identified as a susceptibility region associated with several types of cancer [62]. Some common genetic variants of \( TERT-CLPTM1L \) are hypothesized to have an important role in initiation and development of many cancers, including lung, bladder, pancreatic, thyroid, and breast cancer.

To the best of our knowledge, the meta-analysis in this study is the largest to study the associations between \( CLPTM1L \) rs402710 (C>T) and rs401681 (C>T) polymorphisms and overall cancer risk. In this meta-analysis, based on the database of publications in respect of the rs402710 polymorphism and the rs401681 polymorphism, among which there are 26 articles with 28 studies including 30,770 cases and 34,089 controls for rs402710 polymorphism and 38 articles with 48 studies including 67,849 cases and 328,226 controls for rs401681 polymorphism respectively, we observed both rs402710 and rs401681 polymorphisms were significantly associated with a decreased overall cancer risk. In the stratification analysis, as to the rs402710 polymorphism, a statistically significant association was also identified for lung and bladder cancer. Likewise, the rs401681 polymorphism was significantly associated with a decreased risk for lung cancer, bladder cancer and basal cell carcinoma. Interestingly, an increased risk of melanoma and pancreatic cancer was found for the rs401681 polymorphism.

Up until now, there had been only one meta-analysis (in 2013) focusing on rs402710 and rs401681...
polymorphisms and overall cancer risk [62]; which only enrolled seven studies with 4,667 cancer patients and 4,990 controls for the rs402710 polymorphism and eight studies with 6,867 cancer patients and 7,746 controls for the rs401681 polymorphism. The said study found that rs402710 (A>G) and rs401681 (A>G) polymorphisms were associated with an increased cancer risk. In other words, rs402710 (C>T) and rs401681 (C>T) polymorphisms were significantly associated with a decreased overall cancer risk. In the stratification analysis by cancer type, Li et al. [62] included a few studies and did further stratification analysis only for lung and bladder cancer. Such associations were also observed with lung cancer from the meta-analyses before 2014 [63–65]. Since then, at least 8 studies for the rs402710 polymorphism and 13 studies for the rs401681 polymorphism have been published investigating the association with overall cancer risk, most of which focused on lung cancer. As the largest study with the strongest statistical power so far, the current meta-analysis also observed an association between the rs401681 polymorphism and an increased risk for melanoma and pancreatic cancer, which had been found in other meta-analyses [66, 67]. This observation suggested that the rs401681 polymorphism could play different roles in different types of cancer.

Several limitations in our meta-analysis should be acknowledged. First, we only included the studies published in English, which may have missed publications in other languages. Second, in the stratification analysis by cancer type and ethnicity, the sample sizes are relatively small and may be insufficient, which may have diminished the statistical power. Third, due to the lack of raw information such as age, sex, body mass index, smoking habits, and alcohol consumption, this meta-analysis was...
conducted on the basis of unadjusted estimates. Therefore, larger and well-designed studies with different types of cancer and multiple ethnic with sufficient raw information are warranted to validate the findings of this study.

In conclusion, the meta-analysis in this study demonstrated that CLPTM1L gene rs402710 and rs401681 polymorphisms were associated with a decreased risk of various types of cancer, especially for lung cancer among Asians.

MATERIALS AND METHODS

Search strategy

PubMed and EMBASE electronic databases were screened for publications investigating the association between CLPTM1L polymorphisms and overall cancer risk published prior to May 1, 2017. The following search terms were used: “CLPTM1L”, “5p15”, “polymorphism”,

Figure 3: Forest plot of the association between CLPTM1L rs401681 polymorphism and overall cancer risk under the allele contrast model.
“variant”, “cancer”, “tumor” and “carcinoma”. Additional relevant studies were also retrieved manually from all the relevant publications, including the eligible original publications and reviews. Only the latest or the largest study would be included in the final meta-analysis.

Inclusion and exclusion criteria

All studies included in the current meta-analysis met the following criteria: (1) evaluating the association between CLPTM1L rs402710 and rs401681 polymorphisms and the risk of all types of cancer; (2) case-control or cohort studies; (3) published in English; (4) including sufficient data for genotype frequencies; and (5) providing sufficient data to calculate ORs and 95% CIs. Exclusion criteria include: (1) insufficient raw data; (2) meta-analyses, reviews and comments; (3) duplicates of previous publications; and (4) case-only studies. Studies that were departure from HWE in controls were also excluded, unless further evidence indicated that another polymorphism was in agreement with HWE.

Data extraction

Two investigators extracted the following information from all the eligible studies independently: surname of the first author, publication year, country of origin, ethnicity, cancer type, control source, genotyping method, number of cases and controls, and genotype frequencies of cases and controls. Different ethnicities were stratified into Asian, African, and Caucasian. The source of controls was categorized as hospital-based and population-based studies. Any disagreements were discussed and resolved until the consensus was reached.

Statistical analysis

The strength of association between the CLPTM1L rs402710 and rs401681 polymorphisms and the risk of all types of cancer were assessed by the calculation of crude ORs and 95% CIs. Stratification analyses were further performed according to ethnicity, cancer type and control source. The pooled ORs and 95% CIs were estimated for rs402710 polymorphism under the homozygous (TT vs. CC), heterozygous (CT vs. CC), recessive (TT vs. CT+CC), and dominant (CT+TT vs. CC), as well as allele comparison model (T vs. C) and so was rs401681 polymorphism under the homozygous (TT vs. CC), heterozygous (CT vs. CC), recessive (TT vs. CT+CC), and dominant (CT+TT vs. CC), as well as allele comparison model (T vs. C).

The Chi square-based Q-test was applied to evaluate between-study heterogeneity. If the studies were found to have no heterogeneity (p > 0.10), the fixed-effects model (the Mantel-Haensz method) was used [68]. Otherwise, the random-effects model (the DerSimonian and Laird method) was adopted [69]. Furthermore, heterogeneity was also identified with the I² test [70]. The higher values suggest the greater degree of heterogeneity. Thus the publication bias was quantified by Begg’s funnel plot and Egger’s linear regression test [71].

All the statistical analyses were conducted using STATA software (version 12.0, STATA Corporation, College Station, TX) and were two-sided, with P values less than 0.05 as statistically significant.

CONFLICTS OF INTEREST

The authors have declared that no competing interests exist.

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