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# The association of Cystathionine β Synthase (*CBS*) T833C polymorphism and the risk of stroke: A meta-analysis

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ABSTRACT

As results from published studies on the association of Cystathionine β Synthase (CBS) T833C genetic polymorphism with the risk of stroke are inconsistent, we performed a meta-analysis to summarize the possible association. Eligible studies published were searched for in PubMed, Elsevier Science Direct, Chinese National Knowledge Infrastructure (CNKI), Chinese Biomedical Literature Database (CBM), and the Chinese database, Wanfang. Crude odds ratios (ORs) with 95% confidence intervals (CIs) were assessed for the association using fixed- or random-effect model. We identified 10 case–control studies including 2247 cases and 1813 controls for the present meta-analysis. Significant associations between CBS T833C genetic polymorphism and risk of stroke were observed in most genetic models (OR = 1.57, 95% CI = 1.02–2.41, $p = 0.039$ for TC + CC vs. TT; OR = 1.79, 95% CI = 1.14–2.82, $p = 0.012$ for CC vs. TT; OR = 1.56, 95% CI = 1.01–2.40, $p = 0.044$ for TC vs. TT). Moreover, in the subgroup analysis based on ethnicity, significant associations were observed in most genetic models in Chinese but not in Caucasian. This meta-analysis provided evidence that CBS T833C genetic polymorphism was associated with increased risk of stroke, and the C allele probably acts as an important stroke risk factor.



## 1. Introduction

Stroke is a complex multifactorial and polygenic disease arising from a wide number of gene–gene and gene–environment interactions, comprising of a mix of clinically different risk profiles, incidence rates, management and outcomes. Stroke is the second leading cause of death globally, behind ischemic heart disease [1]. It is also the second cause of death and the leading cause of adult disability in China [2]. According to the World Health Organization (WHO), stroke accounted for 6.15 million deaths worldwide, equivalent to 10.8% of all deaths [1].

Hyperhomocysteinemia is an important risk factor in developing stroke, this is demonstrated by the results derived from several studies involving different ethnic groups [3–7]. Homocysteine level is influenced by genetic polymorphisms of several enzymes in the folate metabolism pathway such as 5,10-methylenetetrahydrofolate reductase (MTHFR), Cystathionine β Synthase (CBS), Methionine synthase (MTR); and environmental factors such as vitamin $B_{12}$, vitamin $B_6$, folate deficiency, estrogen ingestion, alcohol consumption, smoking, etc. [4].

Cystathionine beta synthase (CBS) is a cytosolic homotetramer composed of 63 kD subunits. As an important enzyme which affects homocysteine levels, CBS plays a crucial role in the trans-sulphuration pathway to convert homocysteine to cystathionine. The human CBS gene is located at 21q22.3 [8], which is reported to have several kinds of mutations. A transition mutation, T833C polymorphism, is characterized by a T to C transition at nucleotide position 833, causes an Ile to Thr amino acid substitution [9]. CBS T833C genetic polymorphism may affect the function of CBS. An association of this CBS variant with hyperhomocysteinemia was observed in different studies [3–7], thus its effects on the risk of stroke aroused the interest of researchers.

Several studies were performed to evaluate the effects of CBS T833C genetic polymorphism on the risk of stroke, but the results were of contradiction and inconclusive, partially due to the relatively small sample size of individual studies and sampling effects. Some studies have demonstrated that CBS T833C genetic polymorphism is a risk factor of stroke [10–14]. However, other studies did not confirm this correlation [15–19]. Therefore, the aims of the current meta-analysis were to identify the association of CBS T833C genetic polymorphism and the risk of stroke.

## 2. Materials and methods

### 2.1. Study selection

All studies that examined the association between CBS T833C genetic polymorphism and stroke were carefully selected. Data were collected from the following databases: PubMed, Elsevier Science Direct, Chinese National Knowledge Infrastructure (CNKI), Chinese Biomedical Literature Database (CBM), and the Chinese database, Wanfang.

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The key words were as follows: ("cystathionine beta synthase" OR "CBS"), ("stroke" OR "cerebrovascular disease" OR "cerebrovascular attack" OR "cerebral infarct" OR "intracranial hemorrhage"), ("Polymorphism" OR "Mutation" OR "Variation" OR "Genotype" OR "Gene"). In the CNKI, CBM, and Wanfang, corresponding Chinese characters of the keywords were used for searching. There was no restriction on language.

A study was included in the current meta-analysis if (1) it was published up to June 2011, (2) it was a case–control study, and (3) it was about CBS T833C polymorphism and risk of stroke. Studies reported the results on different subpopulations were treated as separate studies. When there were multiple publications from the same population, only the latest study was included.

An independent PubMed search by DR, an independent Elsevier Science Direct search by CDJ, and independent CNKI, CBM, and Wanfang searches by LSL were performed using the same criteria. The abstracts were carefully reviewed to determine if they met the eligibility criteria. References in the studies were also reviewed and hand-searched to obtain additional studies.

### 2.2. Data extraction

Two investigators (DR and LSL) extracted data independently and in duplicate with the standard protocol and the results were reviewed by a third investigator (CDJ). Disagreements were discussed and resolved with consensus. From each study, information such as the first author's last name, journal and year of publication, country of origin, genotypes and numbers of cases and controls, genotype and allele frequency information from genetic polymorphisms were extracted.

### 2.3. Statistical analysis

We firstly assessed Hardy–Weinberg equilibrium (HWE) in control groups of each study using goodness-of-fit test ($\chi^2$ of Fisher's exact test). The odds ratios (ORs) and their 95% confidence intervals (CI) were estimated and used to assess the strength of association between CBS T833C polymorphism and stroke risk. The pooled ORs were performed for dominant model (TC + CC vs. TT), recessive model (CC vs. TT + TC), and codominant model (homozygote comparison: CC vs. TT, heterozygote comparison: TC vs. TT and CC vs. TC), respectively. Stratified analysis was also performed by different country (Chinese and Caucasian).

Heterogeneity among studies was examined with $\chi^2$ test-based $Q$ statistic [20]. If there was no statistical heterogeneity among studies ($P>0.10$), the ORs and 95% CI were estimated by Mantel–Haenszel's method in a fixed-effect model [21]. Otherwise, the ORs were obtained by DerSimonian–Laird method in a random-effect model [22]. The effect of heterogeneity was also measured by: $I^2 = 100\% \times (Q - \mathrm{df})/Q$ [23].

The meta-analysis was performed by using Stata 10.0 software. In the case of heterogeneity between studies, indicated by a significant Q statistic ($p<0.10$), the result of the random-effects model was selected. Otherwise, the result of the fixed-effects model was selected. The pooled OR was performed by weighting individual ORs by the inverse of their variance, and the significance of the pooled OR was determined by the $z$ test.

### 2.4. Evaluation of publication bias

Publication bias was investigated with the funnel plot, in which the standard error of log(OR) of each study was plotted against its OR value. Funnel plot asymmetry was further assessed using Egger's linear regression test using Stata 10.0 software [24,25]. The $p$-value of Egger's linear regression test less than 0.05 was considered representative of statistically significant publication bias.

## 3. Results

### 3.1. Study characteristics

The detailed characteristics of the studies investigated the association of CBS T833C polymorphisms with stroke were shown in Table 1, the details for the study searching were shown in Fig. 1.

There were 1017 articles relevant to the search words (PubMed 37, Elsevier Science Direct 931, Wanfang 23, CKNI 4, CBM 18, handsearch 4), of which 948 articles were excluded and a total of 69 articles were identified through literature search and selection based on the inclusion criteria. Of these, 3 articles were review, 49 studies did not explore CBS T833C genetic polymorphisms, 1 article did not explore stroke, and 1 article was not a case–control study. During the extraction of data, 1 article were excluded owing to unavailable data [26], and 4 articles were excluded as they were duplicate reports. Thus, 10 studies were included in the current meta-analysis [10–19].

The results of Hardy–Weinberg equilibrium test for the distribution of the genotype in control population are shown in Table 1. The genotype distribution of the control groups of all the 10 studies included in the present meta-analysis are in Hardy–Weinberg equilibrium.

### 3.2. Association between CBS T833C genetic polymorphism and the risk for stroke

For the CBS T833C genetic polymorphism, the data available for this meta-analysis were obtained from 10 studies consisted of 2247 cases and 1813 controls. Associations of the CBS T833C polymorphism with stroke risk were estimated using dominant, recessive, and codominant genetic models in fixed or random effect model according to the heterogeneity test in Table 2.

In the overall analysis, significant associations were observed for dominant model (TC + CC vs. TT, OR = 1.57, 95% CI = 1.02–2.41,

**Table 1**
Main characteristics of the studies included in the meta-analysis*.

| ID | Study | Country | Sample size (frequency of C allele, %) | | OR (95% CI for C vs. T allele) | HWE of genotype of control |
|---|---|---|---|---|---|---|
| | | | Case | Control | | |
| 1 | Zhang et al. [17] | Chinese | 1122 (0.40) | 1123 (6.68) | 0.60 (0.26–1.37) | 1.000 |
| 2 | Nan et al. [18] | Chinese | 100 (28.50) | 100 (26.00) | 1.13 (0.73–1.76) | 0.570 |
| 3 | Liu et al. [10] | Chinese | 59 (33.05) | 29 (12.07) | 3.60 (1.50–8.66) | 0.215 |
| 4 | Liu et al. [11] | Chinese | 67 (34.33) | 39 (14.10) | 3.18 (1.53–6.61) | 0.331 |
| 5 | Liu et al. [12] | Chinese | 183 (27.32) | 54 (11.11) | 3.01 (1.58–5.72) | 0.593 |
| 6 | Linnebank et al. [14] | German | 225 (0.89) | 46 (2.17) | 0.40 (0.07–2.34) | 0.222 |
| 7 | Shao et al. [15] | Chinese | 87 (31.03) | 80 (28.75) | 1.12 (0.70–1.78) | 0.150 |
| 8 | Wu et al. [13] | Chinese | 74 (43.92) | 83 (37.95) | 1.28 (0.82–2.01) | 0.053 |
| 9 | Sawuła et al. [19] | Pole | 202 (8.20) | 200 (6.78) | 1.23 (0.53–2.86) | 0.583 |
| 10 | Zhao et al. [16] | Chinese | 128 (7.43) | 59 (1.00) | 0.70 (0.16–3.16) | 1.000 |

* OR: odds ratio; CI: confidence interval; HWE: Hardy–Weinberg equilibrium.

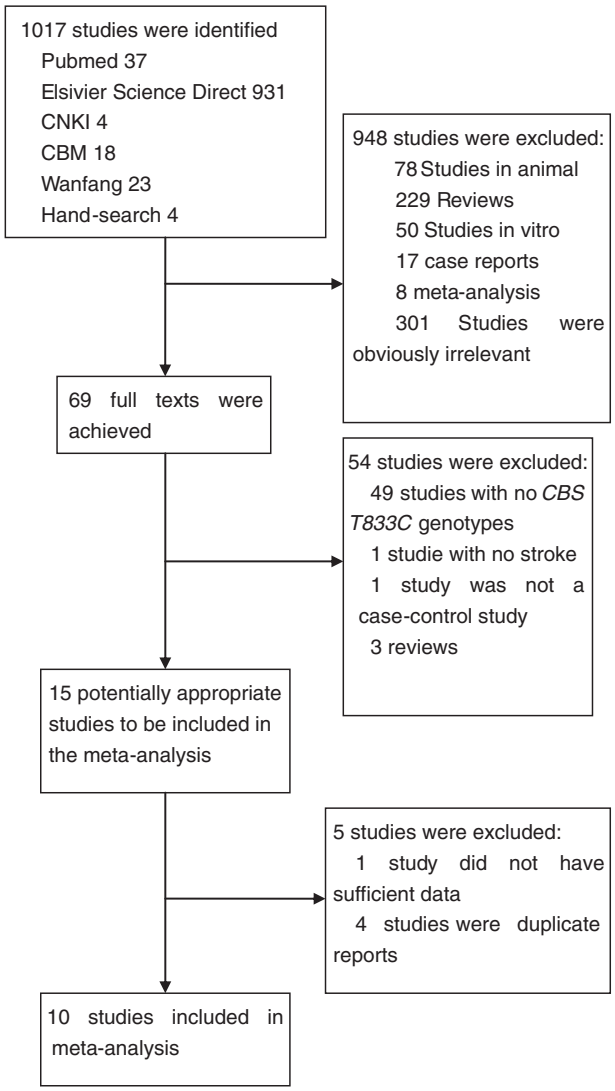


**Fig. 1.** Flow diagram of the study selection process.

$p=0.039$), homozygote comparison (CC vs. TT, OR = 1.79, 95% CI = 1.14–2.82, $p=0.012$), and heterozygote comparison (TC vs. TT, OR = 1.56, 95% CI = 1.01–2.40, $p=0.044$), but not in recessive model (CC vs. TT + TC, OR = 1.49, 95% CI = 0.96–2.32, $p=0.073$) and heterozygote comparison (CC vs. TC, OR = 1.06, 95% CI = 0.65–1.72, $p=0.821$) (Table 2, Fig. 2).

Stratification analysis was further performed by the type of ethnicity to evaluate the effect of CBS T833C polymorphism on the risk of stroke. We found that the increased risk of stroke associated with CBS T833C polymorphism was more pronounced in Chinese (OR = 1.64, 95% CI = 1.00–2.69, $p=0.048$ for TC + CC vs. TT; OR = 1.66, 95% CI = 1.05–2.61, $p=0.030$ for CC vs. TT + TC, OR = 2.02, 95% CI = 1.26–3.24, $p=0.003$ for CC vs. TT; OR = 1.17, 95% CI = 0.71–1.93, $p=0.546$ for CC vs. TC; OR = 1.57, 95% CI = 0.95–2.60, $p=0.076$ for TC vs. TT), but not in Caucasians (OR = 1.31, 95% CI = 0.56–3.08, $p=0.531$ for TC + CC vs. TT; OR = 0.17, 95% CI = 0.02–1.45, $p=0.105$ for CC vs. TT + TC, OR = 0.18, 95% CI = 0.02–1.52, $p=0.115$ for CC vs. TT; OR = 0.14, 95% CI = 0.01–1.66, $p=0.118$ for CC vs. TC; OR = 1.63, 95% CI = 0.65–4.10, $p=0.300$ for TC vs. TT) (Table 2, Fig. 2).

### 3.3. Publication bias

In the present meta-analysis, both Begg's funnel plot and Egger's test were used to assess the publication bias. No obvious asymmetry was observed in any genetic model according to the visual assessment of funnel plot. Egger's test was then used to provide statistical evidence of funnel plot symmetry. The results still did not suggest any obvious evidence of publication bias for all genetic models (Table 3).

## 4. Disscussion

Homocysteine is a thiol amino-acid synthesized during the metabolic conversion of methionine to cysteine [27]. Under normal conditions, about 40–50% or the Hcy is catabolized by methionine synthase (MTR) and betaine-homocysteine methyltransferase (BHMT) to methionine, and about 40–50% or the Hcy is converted to cysteine by CBS and γ-cystathionase [27–30]. As an important enzyme in Hcy metabolism, mutations in CBS gene can result in severe forms of Hyperhomocysteinemia, which is considered as an important risk factor for stroke [3–7].

The association of CBS T833C genetic polymorphism with stroke has been reported by a number of investigators. However, the conclusions remain controversial. In the present meta-analysis, we retrieved 10 studies (2247 cases and 1813 controls) to evaluate the association of CBS T833C genetic polymorphism with stroke. Among these studies, 2 studies (353 cases and 105 controls) were performed involving Caucasian [14,19], and the other 8 studies (1894 cases and 1708 controls) were performed involving Chinese population [10–13,15–18]. As far as we know, this is the first meta-analysis carried out with

**Table 2**
Meta-analysis of the association between the CBS T833C genetic polymorphism and the risk of stroke.

| Polymorphism | Study | Sample size | | No. of studies | Test of association | | | | Test of heterogeneity | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Case | Control | | OR (95% CI) | *z* | *p*-value | Model[a] | $\chi^2$ | *p*-value | $I^2$ (%) |
| CC vs. TT | Overall | 923 | 490 | 8 | 1.79 (1.14–2.82) | 2.52 | 0.012 | F | 10.62 | 0.156 | 34.1 |
| | Asian | 570 | 385 | 6 | 2.02 (1.26–3.24) | 2.92 | 0.003[a] | F | 6.51 | 0.260 | 23.2 |
| | Caucasian | 353 | 105 | 2 | 0.18 (0.02–1.52) | 1.58 | 0.115 | F | 0.01 | 0.918 | 0.0 |
| CC vs. TC | Overall | 923 | 490 | 8 | 1.06 (0.65–1.72) | 0.23 | 0.821 | F | 8.81 | 0.267 | 20.5 |
| | Asian | 570 | 385 | 6 | 1.17 (0.71–1.93) | 0.60 | 0.546 | F | 6.32 | 0.276 | 20.9 |
| | Caucasian | 353 | 105 | 2 | 0.14 (0.01–1.66) | 1.56 | 0.118 | F | 0.07 | 0.790 | 0.0 |
| TC vs. TT | Overall | 2247 | 1813 | 10 | 1.56 (1.01–2.40) | 2.02 | 0.044 | R | 19.31 | 0.023 | 53.4 |
| | Asian | 1894 | 1708 | 8 | 1.57 (0.95–2.60) | 1.78 | 0.076 | R | 19.15 | 0.008 | 63.5 |
| | Caucasian | 353 | 105 | 2 | 1.63 (0.65–4.10) | 1.04 | 0.300 | F | 0.10 | 0.755 | 0.0 |
| CC vs. TC + TT | Overall | 923 | 490 | 8 | 1.49 (0.96–2.32) | 1.79 | 0.073 | F | 8.98 | 0.354 | 22.1 |
| | Asian | 570 | 385 | 6 | 1.66 (1.05–2.61) | 2.17 | 0.030 | F | 5.36 | 0.373 | 6.8 |
| | Caucasian | 353 | 105 | 2 | 0.17 (0.02–1.45) | 1.62 | 0.105 | F | 0.02 | 0.896 | 0.0 |
| TC + CC vs. TT | Overall | 2247 | 1813 | 10 | 1.57 (1.02–2.41) | 2.07 | 0.039 | R | 22.02 | 0.009 | 59.1 |
| | Asian | 1894 | 1708 | 8 | 1.64 (1.00–2.69) | 1.98 | 0.048 | R | 21.39 | 0.003 | 67.3 |
| | Caucasian | 353 | 105 | 2 | 1.31 (0.56–3.08) | 0.63 | 0.531 | F | 0.49 | 0.486 | 0.0 |

[a] F: fixed-effect model; R: random-effect model.

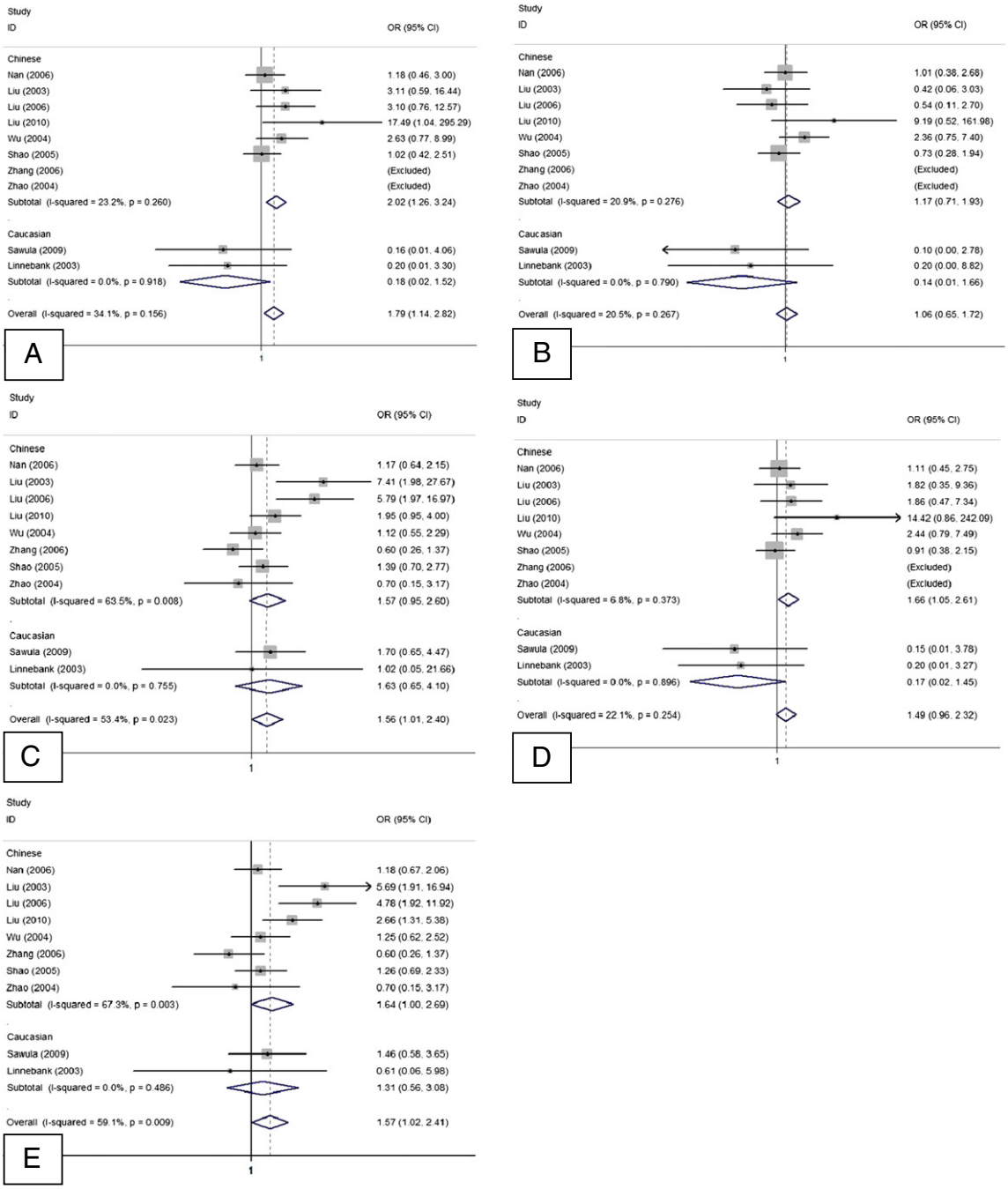


**Fig. 2.** Forest plots of relationship between CBS T833C polymorphism and risk of stroke in different genetic model. A: CC vs. TT; B: CC vs. TC; C: TC vs. TT; D: CC vs TC+TT; E: TC+CC vs TT.

the aim of investigating the relationship between CBS T833C genetic polymorphism and stroke.

In the present meta-analysis, the combined evidence suggests that CBS T833C polymorphism is associated with the risk of stroke, while the results from subgroups of Chinese and Caucasian are different.

**Table 3**
The results of Egger's linear regression test to measure the funnel plot asymmetric*.

| Comparison type | Intercept value | *t*-value | *p*-value | 95% CI of intercept value |
|---|---|---|---|---|
| CC vs. TT | 0.11 | 0.10 | 0.924 | −2.65–2.88 |
| CC vs. TC | −0.65 | −0.69 | 0.517 | −2.96–1.66 |
| TC vs. TT | 1.02 | 0.73 | 0.484 | −2.19–4.23 |
| CC vs. TC + TT | −0.06 | −0.06 | 0.954 | −2.54–2.42 |
| TC + CC vs. TT | 0.29 | 0.18 | 0.863 | −3.44–4.01 |

* CI: confidence interval.

In the Chinese subgroup, our data indicated CBS T833C polymorphism lead to increased incidence of stroke. Statistical significances were shown in homozygote comparison of codominant model (CC vs. TT), recessive model (CC vs. TC + TT), and dominant model (TC + CC vs. TT) (Fig. 2, Table 2). The results suggest that C allele in CBS T833C polymorphism is a risk factor for the risk of stroke. In several studies, serum Hcy level was found higher in patients with stroke than in control people, and hyperhomocysteinemia was found correlated with CBS T833C genetic polymorphism [11,12], suggesting CBS T833C variation may cause decreased enzyme activity of CBS, which result in high serum level of Hcy, and induce stroke in turn. This is confirmed by the study performed by Liu et al. [10], which showed that administration of Vit $B_6$, a cofactor of Cystathionine β Synthase (CBS) [31], resulted in decreased serum level of Hcy significantly in patients with normal CBS genotype but not in patients with CBS

T833C variation. However, our meta-analysis did not detect the association in the Caucasian population. This may due to the fact that the Chinese population and Caucasian are genetically different. Several studies suggested that another CBS polymorphism, CBS 844ins68bp, which may accompanied with CBS T833C polymorphism, may have protective effects against vascular thromboembolic disease [32]. This kind of polymorphism is shown to be fairly prevalent in Caucasian population [33–35], but the prevalence of CBS 844ins68 in Chinese population is much lower [32]. What's more, there are only 2 studies involving Caucasian included in the present study.

Some limitations of this study should be discussed. First, significant between-study heterogeneity was detected, which may distort the meta-analysis. However, this was not a major problem because stroke itself is heterogeneous. Stroke is a complex disease, both environmental and genetic factors are involved in the development of stroke, and most of the studies included in the present meta-analysis did not consider most of the important environmental factors. Moreover, different patient populations may also contribute to the heterogeneity. Second, all eligible studies were published papers. It is possible that some relevant unpublished studies that may have met the inclusion criteria were missed. Thus, some inevitable publication bias may exist in the results, although neither the funnel plots nor Egger's linear regression tests indicated remarkable publication bias in the meta-analysis (Table 3). Third, in the subgroup analysis by ethnicity, only two studies were conducted in Caucasians. Therefore, to conduct a more precise analysis of this functional polymorphism on stroke risk, additional studies with large sample size and involving different ethnicities are warranted.

Despite the limitations, results of the present meta-analysis suggest that there was a significant association between the CBS T833C genetic polymorphism and risk of stroke, and the C allele probably acts as an important stroke risk factor. Further studies with large sample sizes and a case–control design stratified by ethnicity are warranted to confirm our findings.

## Conflict of interest

The authors declare that they do not have any conflict of interest.

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