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REVIEW ARTICLE

Methylenetetrahydrofolate reductase C677T polymorphism and susceptibility to epilepsy

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Abstract

Background Methylenetetrahydrofolate reductase (MTHFR) gene C677T polymorphism was reported as risk factor for multiple diseases due to its role in conversion of homocysteine to methionine. The aim of the present meta-analysis was to find out the validity of association of C677T polymorphism with epilepsy susceptibility.

Methods Pubmed, Science Direct, Springer Link and Google Scholar, databases were searched for relevant studies up to January, 31, 2018. The pooled odds ratios (ORs) with 95% confidence intervals (CIs) were performed using five genetic models. All statistical analysis was done by MetaAnalyst and Mix programs.

Results Except recessive model, significant association was found between MTHFR C677T polymorphism and epilepsy risk in other four genetic models (T vs C: OR = 1.29, 95% CI = 1.08–1.52, $p = 0.004$; TT vs CC: OR = 1.48, 95% CI = 1.19–1.82, $p = 0.0003$; TT + CT vs CC: OR = 1.20, 95% CI = 1.05–1.38, $p = 0.008$; TT vs CT + CC: OR = 1.35, 95% CI = 1.11–1.62, $p = 0.002$). Similarly, in the subgroup analysis based on ethnicity, significant association was found in Asian (T vs C: OR = 1.85; 95% CI = 1.15–2.99; $p = 0.03$) and Caucasian populations (TT vs CC: OR = 1.38; 95% CI = 1.10–1.1.73; $p = 0.005$). No evidence of heterogeneity and publication bias was detected in present meta-analysis.

Conclusion In conclusion, results of present meta-analysis suggested that 677T allele of MTHFR is significantly increases the epilepsy susceptibility.

Keywords Epilepsy · Polymorphism · MTHFR · C677T · Homocysteine · Meta-analysis

Introduction

Epilepsy is a common neurological disorder, triggered by abnormal electrochemical activities in the brain, resulting in seizure [2, 67]. Worldwide, about more than 65 million individuals suffer with epilepsy with more than 80% of epileptics residing in low- and middle-income countries [6, 17, 34, 60, 63, 66]. In all epileptics, about 40% cases are of idiopathic epilepsies (IEs). In idiopathic epilepsy, genetics play important role. Epilepsy is genetically heterogenous and showed autosomal dominant and recessive mode of inheritance, which suggests complex inheritance, i.e., involvement of many genes and nongenetic factors also [13, 19, 28, 56, 67].

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Numerous studies have reported that hyperhomocysteinemia is a risk factor for stroke, psychiatric, and neurodegenerative diseases [14, 25]. About 10–40% epileptic patients exhibit hyperhomocysteinemia [1, 8, 10, 25, 27]. Folate is essential for DNA synthesis, methylation, and repair. It provides primary methyl donor for conversion of homocysteine in to methionine. Folate deficiency or folate pathway enzyme variants are the main cause of hyper homocysteinemia. Most of the folate/methionine genes are polymorphic, especially C677T polymorphism of methylenetetrahydrofolate reductase (MTHFR) and A66G polymorphism of methionine synthase reductase (MTRR). The frequency of these polymorphisms (C677T, A1298C and A66G) varies greatly in different populations [53, 54].

MTHFR gene is located on chromosome 1p. Several polymorphisms are reported in MTHFR gene, but C677T polymorphism is the most studied and clinically important polymorphism, in which cytosine is substituted with thymine at position 677, leading to substitution of alanine to valine (A333V). MTHFR mutant homozygous (VV) enzyme has approximately 70% decreased enzyme activity in compare to normal MTHFR enzyme [22]. MTHFR C677T

polymorphism is reported as risk factor for multiple diseases-ischemic vascular disease, psychiatric and neurological diseases including Alzheimer, Parkinson's disease, and migraine [11, 16, 38, 55, 58]. The frequency of T allele varies greatly worldwide [24, 41, 52, 70]. There are conflicting results about the role of MTHFR C677T polymorphism in epilepsy susceptibility. To derive a precise estimation of relationship between MTHFR C677T polymorphism and epilepsy risk, we conducted the present meta-analysis.

Methods

Present meta-analysis was carried out according to meta-analysis of observational studies in epidemiology (MOOSE) guidelines [61].

Literature search

The electronic databases PubMed (http://www.ncbi.nlm.nih.gov/pubmed), Science Direct (http://www.sciencedirect.com), Springer Link (http://link.springer.com), and Google Scholar (http://scholar.google.com) were searched for eligible studies. The search terms used are "Epilepsy" and "Methylenetetrahydrofolate reductase" or "MTHFR" or "C677T."

Inclusion and exclusion criteria

The included studies must meet the following criteria: (i) study should be published, (ii) study should be case–control study, (iii) study should evaluated MTHFR C677T polymorphism in epilepsy patients, (iv) study should report numbers of MTHFR genotypes (CC, CT, and TT) or alleles in cases and controls, and (v) epilepsy patients were diagnosed according to the clinical and electroencephalography criteria of the International League Against Epilepsy (ILAE).

Studies were excluded if (i) MTHFR genotypes/allele numbers in cases and controls were not mentioned in the study, (ii) only cases were reported, and (iii) article was review or editorials or book chapter or linkage studies.

Data extraction

Following information were extracted from each included studies like (i) first author's family name, (ii) country name of participants, (iii) ethnicity of participants, (iv) journal's name, (v) year of publication, (vi) number of cases and controls, (vii) MTHFR genotypes in cases and controls, and (viii) genotyping methods.

Meta-analysis

Pooled odds ratio with 95% CI were used as association measure to assess association between MTHFR C677T genotypes and risk of epilepsy using five genetic models like- additive/allele contrast (T vs C), homozygote (TT vs CC), co-dominant/heterozygote (CT vs CC), dominant (TT + CT vs CC) and recessive (TT vs CT + CC) models. The statistical significance of the pooled OR was determined using a Z test, and $p < 0.05$ was considered statistically significant. The heterogeneity was tested by the Q statistic and was considered statistically significant when $p < 0.05$ [26]. The pooled OR was estimated using the fixed effects model when there was less heterogeneity [36] or random effects model when there was higher heterogeneity [15]. All included studies were tested for genotypic distribution of the MTHFR C677T polymorphism in the control group with the HWE principle using the χ^2 test. Subgroup analysis based on ethnicity was also performed.

Publication bias was evaluated by the funnel plot of precision and standard error. Funnel plot asymmetry was further assessed by the method of Egger's linear regression test [18]; if $p < 0.05$, the publication bias was statistically significant. Meta-analysis was performed using Mix [7] and MetaAnalyst [65] programs.

Results

Characteristics of included studies

PubMed, Science direct, Springer Link, and Google Scholar databases search returned 195 articles. Initial examination involving abstracts and titles leads to the exclusion of 130 non-relevant articles. Of the remaining 65 relevant articles, 48 articles again excluded (articles lack complete genotyping data, comments, letter to editors, not analyzed MTHFR gene, etc.). Seventeen articles were remaining, out of which five articles excluded again, because they were meta-analysis and duplicate articles. Finally, 12 studies which met the inclusion criteria were included in the present meta-analysis [4, 9, 10, 13, 23, 30, 39, 40, 57, 59, 64, 71] (Table 1; Fig. 1).

In total 12 included studies, the numbers of cases and controls were 1931 and 1985 respectively. Largest sample size was 689 [57], and lowest sample size was 18 [4]. In cases, the frequency of CC-homozygous individuals was 39.28%. However, 43.85% of CT-heterozygous individuals and 16.87% of TT-homozygous individuals displayed the C677T polymorphism. In control groups, the frequencies of CC, CT, and TT individuals were 43.4%, 43.39%, and 12.9%, respectively. The T allele frequencies in the case and control groups were 37.83% and 33.35%, respectively. All 12 studies were carried out in different countries—India [4], Italy [9, 10, 23],

Table 1 Characteristics of 12 studies included in the present meta-analysis

Study	Country	Case	Control	Case genotypes CC/CT/TT	Control genotypes CC/CT/TT	Case allele		Control allele		*p* value (HWE)
						C	T	C	T	
[71]	Korea	103	103	25/54/24	37/53/13	104	102	127	79	0.26
[64]	Spain	59	28	19/30/10	7/17/4	68	50	31	25	0.23
[40]	Japan	72	97	24/29/19	43/37/17	77	67	123	71	0.08
[10]	Italy	95	98	26/50/19	33/47/18	102	88	113	83	0.86
[30]	UK	141	226	50/75/16	85/115/26	175	107	285	167	0.17
[13]	UK	170	303	64/80/26	146/128/29	208	132	420	186	0.90
[23]	Italy	60	58	14/3016	18/26/14	58	62	62	54	0.45
[9]	Italy	259	231	68/11972	60/110/61	255	263	230	232	0.47
[59]	Poland	65	55	36/22/7	24/29/2	94	36	77	33	0.06
[57]	USA	689	668	350/262/77	366/246/53	962	416	981	355	0.25
[4]	India	18	18	4/8/6	5/7/6	16	20	17	19	0.35
[39]	Saudi Arab	200*	100*			282	118	180	20	

*Only allele numbers were given

Japan [40], Korea [71], Poland [59], Saudi Arab [39], Spain [64], the UK [13, 30], and the USA [57] (Table 1).

Meta-analysis

In the overall analysis, significant associations were observed for the dominant model using both fixed effect (TT + CT vs CC: OR = 1.20, 95% CI = 1.05–1.38, $p = 0.008$) and random effect models (TT + CT vs CC, OR = 1.20, 95% CI = 1.05–1.38, $p = 0.008$). Meta-analysis of mutant homozygote showed strong significant association between C677T polymorphism and epilepsy risk using both fixed and random effect models (TT vs CC: OR = 1.48, 95% CI = 1.19–1.82, $p = 0.0003$). Results of allele contrast meta-analysis showed

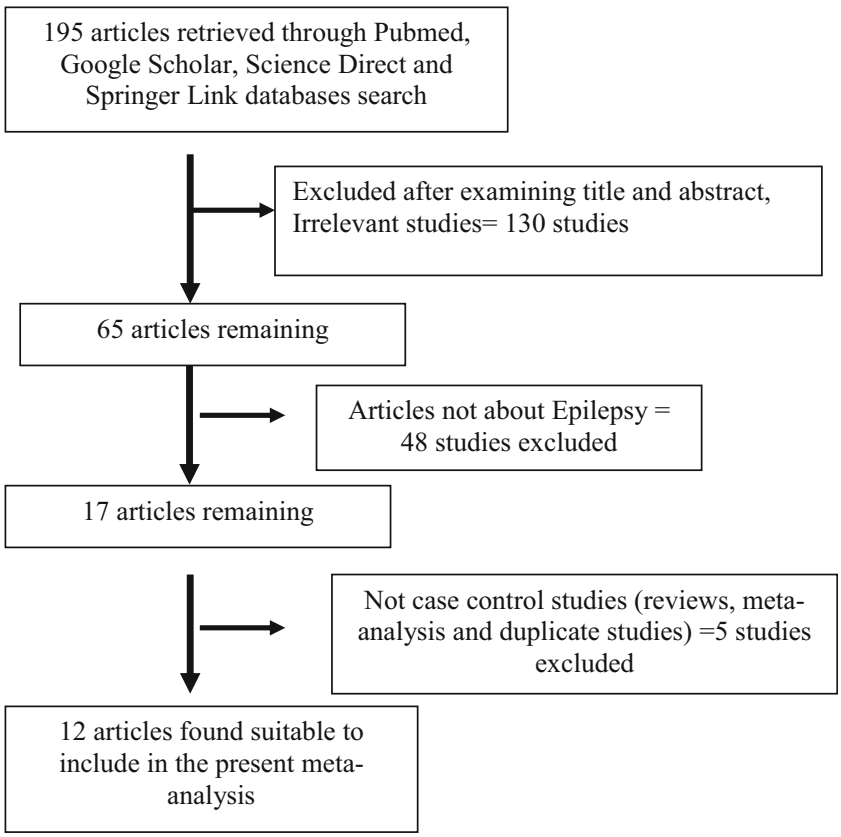

Fig. 1 Flow diagram of study searching and selection process

Table 2 Summary estimates for the odds ratio (OR) of MTHFR C677T in various allele/genotype contrasts, the significance level (p value) of heterogeneity test (Q test), and the I^2 metric and publication bias p value (Egger test)

Genetic models	Fixed effect OR (95% CI), p	Random effect OR (95% CI), p	Heterogeneity p value (Q test)	I^2 (%)	Publication bias (p value of Egger's test)
Total 12 studies meta-analysis					
Allele Contrast (T vs C)	1.26(1.14–1.38), <0.0001	1.29 (1.08–1.52), 0.004	0.03	60.06	0.52
Co-dominant (CT vs CC)	1.13 (0.98–1.30), 0.10	1.13 (0.98–1.30), 0.09	0.5	0	0.92
Homozygote (TT vs CC)	1.48 (1.19–1.82), 0.0003	1.48 (1.19–1.82), 0.0003	0.69	0	0.70
Dominant (TT + CT vs CC)	1.20 (1.05–1.38), 0.008	1.20 (1.05–1.38), 0.008	0.47	0	0.94
Recessive (TT vs CT + CC)	1.35 (1.11–1.62), 0.002	1.34(1.11–1.62), 0.002	0.77	0	0.58
Asian studies meta-analysis					
Allele Contrast (T vs C)	1.85(1.15–2.99), 0.03	1.84(1.14–2.99), 0.03	0.67	0	0.56
Co-dominant (CT vs CC)	1.46(0.92–2.82), 0.10	1.46(0.92–2.82), 0.10	0.98	0	0.82
Homozygote (TT vs CC)	2.19(1.2–3.8), 0.005	2.18(1.25–3.81), 0.006	0.70	0	0.44
Dominant (TT+CT vs CC)	1.64(1.08–2.50), 0.02	1.64(1.08–2.50), 0.02	0.94	0	0.38
Recessive (TT vs CT+CC)	1.72(1.07–2.83), 0.02	1.74(1.06–2.84), 0.02	0.64	0	0.28
Caucasian studies meta-analysis					
Allele contrast (T vs C)	1.15(1.03–1.28), 0.02	1.15(1.03–1.28), 0.02	0.51	0	0.43
Co-dominant (CT vs CC)	1.1(0.94–1.3), 0.24	1.1(0.92–1.3), 0.31	0.35	10.49	0.51
Homozygote (TT vs CC)	1.38(1.10–1.73), 0.005	1.38(1.09–1.73), 0.005	0.72	0	0.97
Dominant (TT + CT vs CC)	1.16(1.00–1.34), 0.04	1.16(1.00–1.34), 0.05	0.42	1.9	0.46
Recessive (TT vs CT + CC)	1.28(1.04–1.57), 0.01	1.28(1.04–1.57), 0.01	0.74	0	0.69

significant association of epilepsy risk with MTHFR T allele with both fixed effect (T vs C: OR = 1.26, 95% CI = 1.14–1.38, $p < 0.0001$) and random effect models (T vs C: OR = 1.29, 95% CI = 1.08–1.52, $p = 0.004$) (Table 2; Fig. 2). Meta-analysis using recessive model results also showed positive association between MTHFR polymorphism and epilepsy risk using both fixed and random effects models (TT vs CT + CC: OR = 1.35, 95% CI = 1.11–1.62, $p = 0.002$), but co-dominant model meta-analysis did not show any association (CT vs CC: OR = 1.13, 95% CI = 0.98–1.30, $p = 0.10$) (Table 2). In cumulative analysis using fixed and random effect models, the association of mutant "T" allele with epilepsy remained statistically significant with the addition of new study (Fig. 3).

Heterogeneity analysis

The between studies heterogeneity of different genetic models was analyzed for 12 case–control studies. The results in allele contrast model ($p = 0.03$; $I^2 = 60.06$), homozygote model ($p = 0.69$; $I^2 = 0$), dominant model ($p = 0.47$; $I^2 = 0$), recessive model ($p = 0.50$; $I^2 = 0$), and heterozygote model ($p = 0.77$; $I^2 = 0$) had no heterogeneity.

Subgroup analysis

Out of 12 included studies, four studies were from Asian population (393 cases/318 controls) and eight studies were from Caucasian population (1538 cases/1667 controls). Meta-analysis of Caucasian studies showed that the T allele was significantly associated with epilepsy risk using homozygote model (TT vs CC: OR = 1.38; 95% CI = 1.10–1.73; $p = 0.005$) and allele contrast model (T vs C: OR = 1.14; 95% CI = 1.04–1.28; $p = 0.02$) (T vs C) (Table 2; Fig. 4). In addition, meta-analysis of Asian population also indicated that the T allele was strongly associated with epilepsy risk using allele contrast (T vs C: OR = 1.85; 95% CI = 1.15–2.99; $p = 0.03$) and homozygote model (TT vs CC: OR = 2.19; 95% CI = 1.2–2.30; $p = 0.005$) (Table 2; Fig. 5).

Publication bias

The shapes of Funnel plots did not reveal any asymmetry (Figs. 6 and 7). p value of Eggers test was > 0.05 and also did not suggest any publication bias (T vs C: $p = 0.52$; TT vs CC: $p = 0.70$; CT vs CC: $p = 0.92$; CT + TT vs CC: $p = 0.94$; and TT vs CT + CC: $p = 0.58$).

Discussion

Twelve case–control studies with 1731 epilepsy cases and 1885 controls were included in the present meta-analysis. The results of current meta-analysis indicated that the T allele of MTHFR gene was significantly associated with risk of epilepsy. The mechanism of epileptogenesis has not been clearly known [12], but several reports supported the

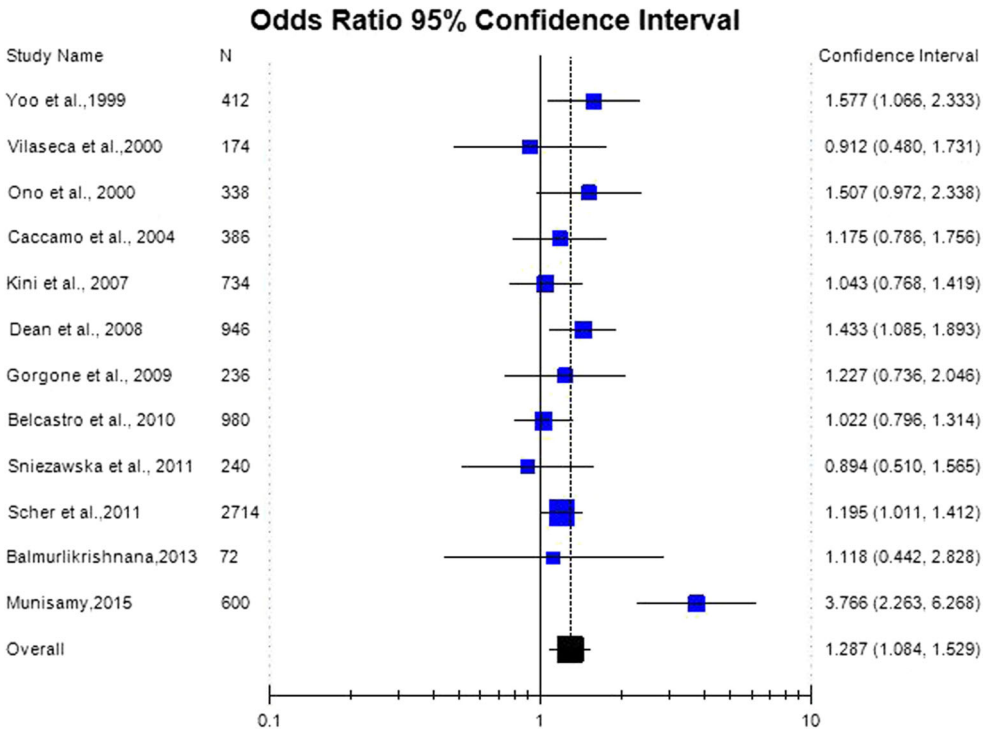

Fig. 2 Forest plots (random effect) showed significant association between MTHFR C677T polymorphism (T vs C) and risk of epilepsy

homocysteine hypothesis of epilepsy [5]. Folate deficiency or reduced activity of MTHFR enzyme may lead to increased serum Hcy levels [29, 62]. MTHFR C677T polymorphism and its association with increased epilepsy risk are due to higher concentration of homocysteine. Higher homocysteine concentration stimulates *N*-methyl-D-aspartate (NMDA) receptors and by mediating excitotoxicity produces free radicals, which causes neuronal death [21, 31]. In addition, metabolite of homocysteine like homocysteic acid and L-Hcy sulfinic acid interacts with glutamate receptor and exhibits excitotoxicity [20, 35]. Experiments with animal models also supported the homocysteine hypothesis of epilepsy like (i) administration of high doses of Hcy produces convulsive seizures, a fact that has been exploited in models of

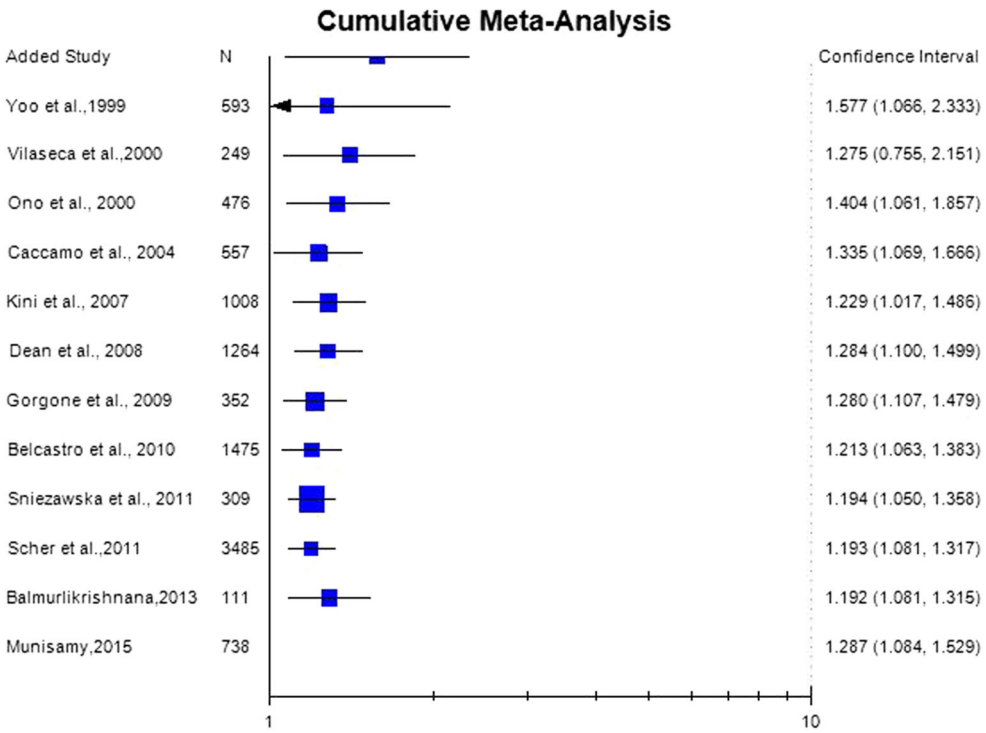

Fig. 3 Forest plots (random effect) showed cumulative meta-analysis (T vs C)

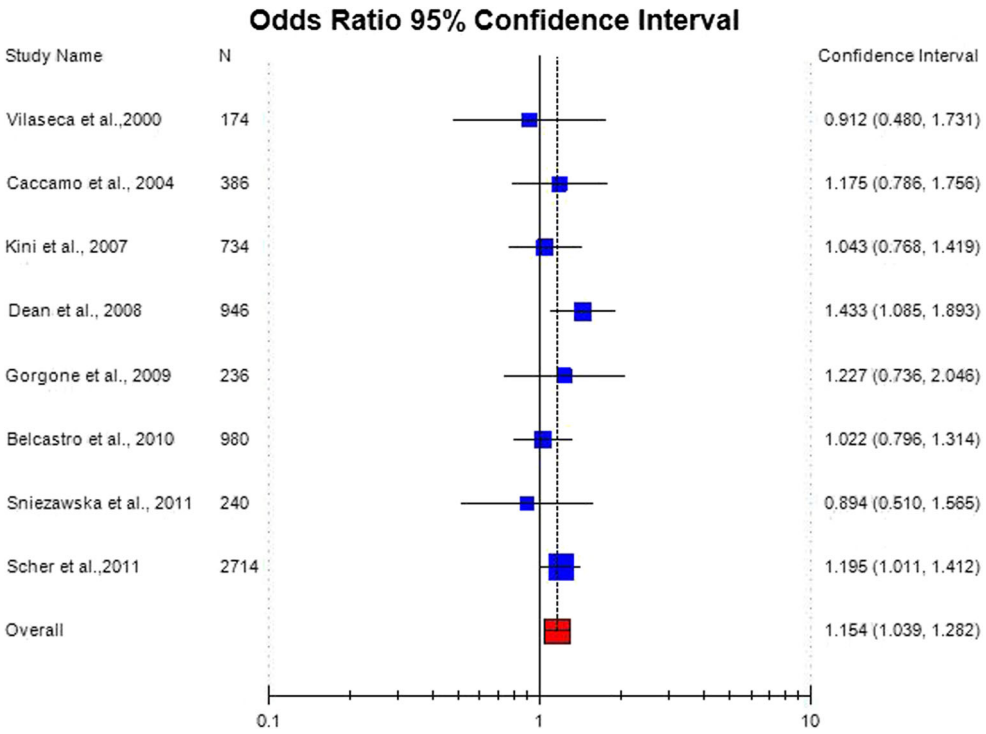

Fig. 4 Forest plots (random effect) showed significant association between MTHFR C677T polymorphism (T vs C) and risk of epilepsy in Caucasian studies

experimental epilepsy [32]; (ii) Hcy sequesters adenosine, an endogenous anticonvulsant [37]; and (iii) Hcy potentiates pilocarpine in inducing status epilepticus [5].

Meta-analysis is an acceptable useful methodology suitable for elucidating genetic factors in different diseases/disorders. The individual studies are usually small and underpowered and, thus, unable to provide a definite answer even in the case where a true association exists [3]. Several meta-analyses were published which evaluated risk of folate pathway genes polymorphism for different disease and disorders like Down syndrome [41], orofacial clefts [49], male infertility [50], recurrent pregnancy loss [45], autism [48], schizophrenia [68], bipolar

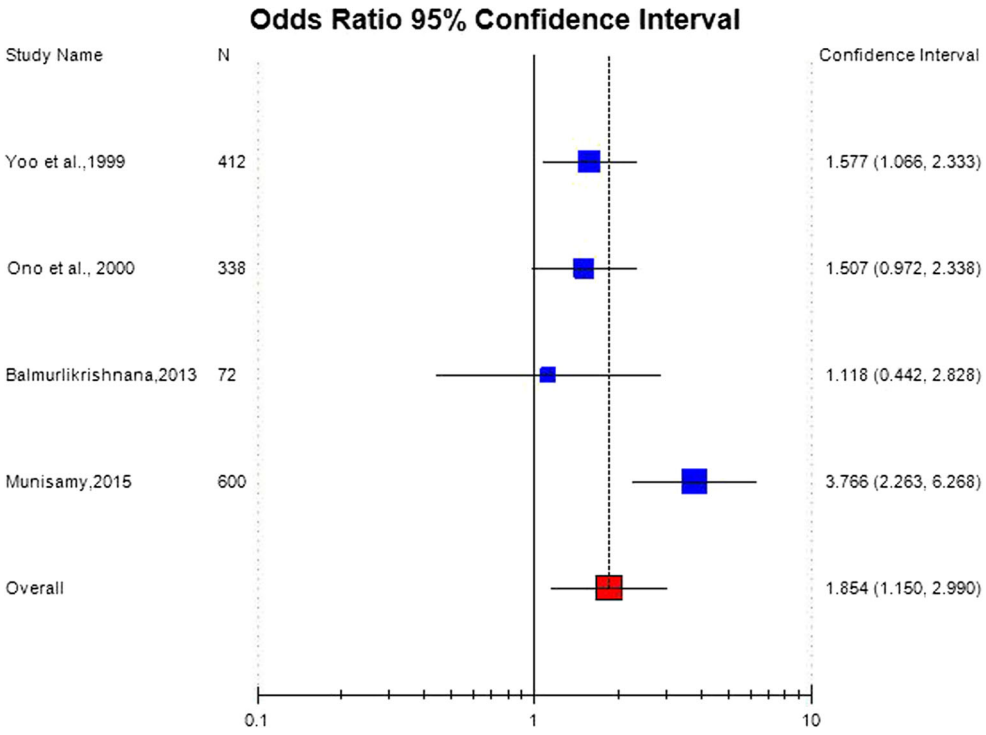

Fig. 5 Forest plots (random effect) showed significant association between MTHFR C677T polymorphism (T vs C) and risk of epilepsy in Asian studies

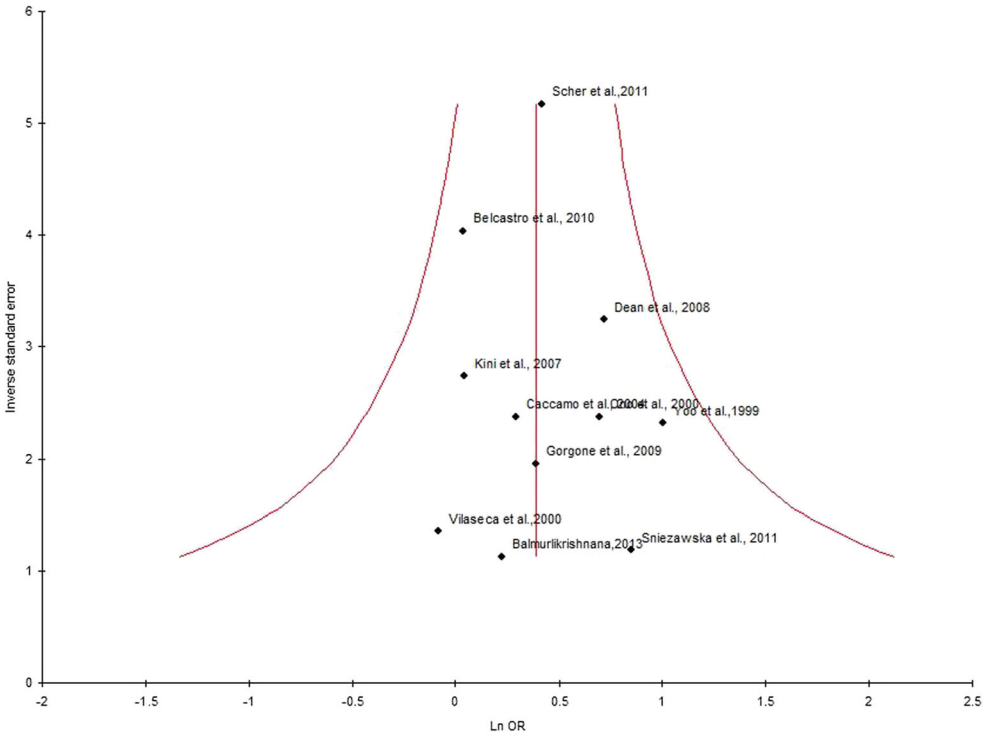

Fig. 6 Funnel plot of precision by log odds ratio (allele contrast model)

[42], depression [44], Alzheimer's disease [47], breast cancer [33, 43], prostate cancer [67], and colorectal cancer [46].

Certain potential limitations exist in our meta-analysis, which should be acknowledged—(i) present meta-analysis based on unadjusted data, (ii) only 12 studies were included, (iii) single gene polymorphism was considered, (iv) interactions between gene–gene and gene–environment could not be included in present meta-analysis due to a lack of relative data, and (v) only four databases were searched, so it might be possible that few relevant studies were left. Besides limitations, present meta-analysis has several strengths also like absence of publication bias and heterogeneity etc.

In conclusion, results of the present meta-analysis suggested that there are strong significant associations between

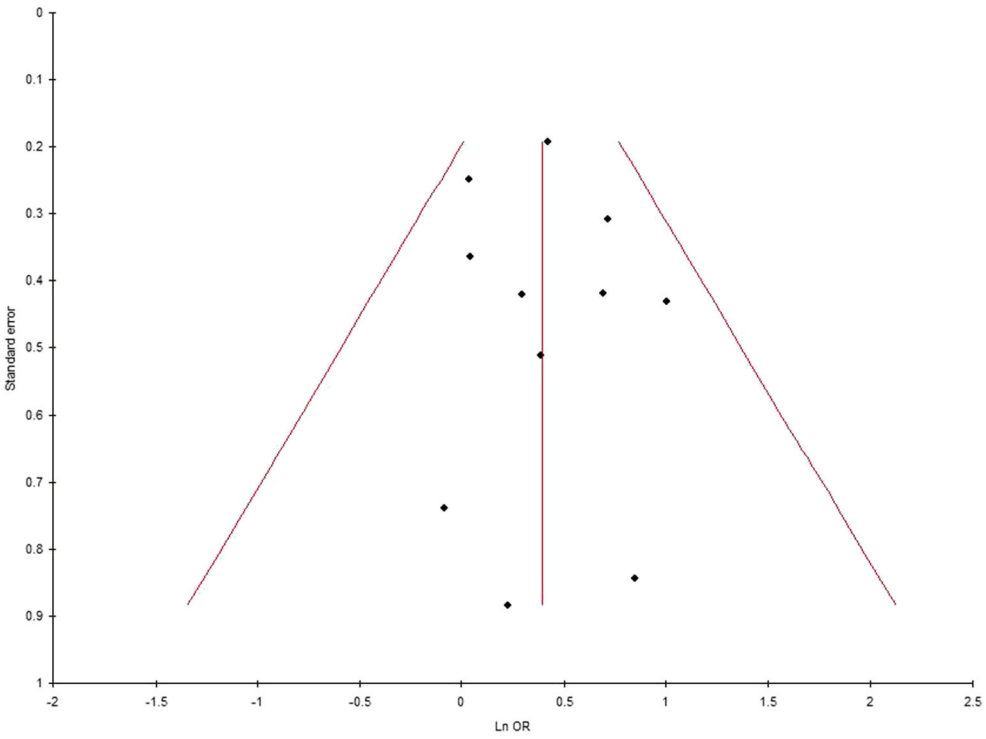

Fig. 7 Funnel plot of standard error by log odds ratio (allele contrast model)

the MTHFR C677T polymorphism and epilepsy susceptibility. Folate deficiency and folate pathway hypofunctional enzymes especially MTHFR are the main risk factor for hyperhomocysteinemia, and C677T polymorphism reduces ~70% enzyme activity; hence, individuals with TT genotype are higher risk of epilepsy due to higher homocysteine concentration. Further studies with large sample sizes and a well designed case–control stratified by ethnicity are warranted to confirm present findings.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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