Progress in Neuro-Psychopharmacology & Biological Psychiatry 46 (2013) 78–85

Contents lists available at ScienceDirect

Progress in Neuro-Psychopharmacology & Biological Psychiatry

journal homepage: www.elsevier.com/locate/pnp

Association between MTHFR C677T polymorphism and depression: An updated meta-analysis of 26 studies

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ARTICLE INFO

Article history:
Received 8 April 2013
Received in revised form 20 June 2013
Accepted 21 June 2013
Available online 4 July 2013

Keywords:
Depression
Meta-analysis
Methylenetetrahydrofolate reductase
MTHFR
Polymorphism

ABSTRACT

Background: Previous studies concerning the association between the 5,10-methylenetetrahydrofolate reductase (MTHFR) C677T gene polymorphism and depression have provided inconclusive findings. A meta-analysis was therefore performed to investigate a more reliable estimate.
Methods: This meta-analysis recruited 26 published studies which were selected by a search of electronic databases up to January 2013, including 4992 depression cases and 17,082 controls. Odds ratios (ORs) with 95% confidence intervals (CIs) were used to assess the association between MTHFR C677T polymorphism and depression susceptibility using random effect models.
Results: Meta-analyses results suggested that MTHFR C677T polymorphism contributed to the increased depression risk in overall populations (for T vs. C: OR = 1.19, 95%CI = 1.07–1.32; for TT + CT vs. CC: OR = 1.15, 95%CI = 1.01–1.31; for TT vs. CC: OR = 1.42, 95%CI = 1.16–1.75; for TT vs. CT + CC: OR = 1.38, 95%CI = 1.16–1.63). Subgroup analysis by ethnicity indicated an association in Asian populations (for T vs. C: OR = 1.36, 95%CI = 1.11–1.66; for TT + CT vs. CC: OR = 1.32, 95%CI = 1.03–1.69; for TT vs. CC: OR = 1.88, 95%CI = 1.26–2.79; for TT vs. CT + CC: OR = 1.76, 95%CI = 1.30–2.38); and a marginal association in White populations (for TT vs. CT + CC: OR = 1.15, 95%CI = 1.01–1.31). However, the association between the MTHFR C677T polymorphism and depression was not observed in the elderly.
Conclusion: The MTHFR C677T polymorphism was associated with an increased risk of depression, especially in Asian populations. However, there was no evidence indicating a correlation in the elderly.

Contents

Abbreviations: MTHFR, 5,10-methylenetetrahydrofolate reductase; ORs, Odds ratios; CIs, confidence intervals; HWE, Hardy–Weinberg equilibrium.

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0278-5846/$ – see front matter
http://dx.doi.org/10.1016/j.pnpbp.2013.06.015

1. Introduction

Depression is a common and important cause of morbidity and mortality (Lewis et al., 2006). About 10% to 15% of the general population is estimated to experience clinical depression during their lifetime (Wang et al., 2013). Depression is a clinically heterogeneous disorder thought to result from an interaction of multiple genes with environmental factors and developmental epigenetic components (Pan et al., 2009). Family and twin studies showed that genetic factors play important roles in the development of depression (Rhee and Waldman, 2002).

The MTHFR is an essential enzyme in metabolizing folate, it is involved in 1-carbon metabolism and responsible for the final step in the conversion of dietary forms of folate to 5-methyltetrahydrofolate (Gaysina et al., 2008). It has been identified that genetic variant of a C to T substitution at position 677 in the MTHFR gene leads to an amino acid change from alanine to valine, resulting in a thermolabile variant of enzyme with reduced activity and elevated plasma homocysteine levels (Frosst et al., 1995). The T allele and TT genotype occur with a frequency of 45% and 11%, respectively (Almeida et al., 2005). The alterations of MTHFR's activity may influence the pathogenesis of conditions such as depression and schizophrenia via by hindering 1-carbon metabolism (Frankenburg, 2007). A study showed MTHFR C677T polymorphism may be associated with depression because both folate deficiency and hyperhomocysteinemia are prospective risk factors for depression (Kim et al., 2008).

Case-control studies investigating the association between the MTHFR C677T polymorphism and depression have given controversial results. Even previous meta-analyses about this topic also had conflicting conclusions. A meta-analysis conducted by Gilbody et al. (2007) indicated that the MTHFR 677TT homozygous genotype increased a risk for depression. However, no association between the MTHFR C677T polymorphism and depression was observed in meta-analyses carried out by Zintzaras (2006) and Gaysina et al. (2008). Reasons may be due to small sample sizes or different populations. Therefore, this comprehensive meta-analysis was conducted including several updated original studies performed after the last meta-analysis and eligible articles published in the Chinese language to clarify if MTHFR C677T polymorphism showed a significant association with depression. Zintzaras (2006) showed that demographic differences influenced the association between MTHFR C677T polymorphism and psychiatric disorders. Hence, potential modifying effects of ethnicity, age, and source of controls were considered in this meta-analysis.

2. Materials and methods

2.1. Identification and selection of studies

A comprehensive literature search was conducted on PubMed, Springer Link, OvidSP, CBM (Chinese Biomedical Database), CNKI (Chinese National Knowledge Infrastructure), VIP (Chinese) database and Wanfang (Chinese) Database to collect data from all the eligible studies investigating the association between MTHFR C677T polymorphism and depression. All the studies were published before January 2013. We used the following search strategy ('Methylenetetrahydrofolate reductase' or 'MTHFR' or 'C677T') and ('polymorphism' or 'polymorphisms' or 'mutation' or 'mutations') and 'depression' or relevant Chinese technical terms for the Chinese Databases to search for published articles. Furthermore, references of all relevant articles and reviews were retrieved to search for additional eligible studies. Articles just providing abstracts were excluded.

2.2. Inclusion and exclusion criteria

The studies meeting the following criteria were included: (1) concerning the relationship between MTHFR C677T polymorphism and depression; (2) case-control studies; (3) providing complete data of cases and controls for calculating an odd ratio (OR) with 95% confidence interval (CI); (4) the distribution of the genotypes in control groups was in Hardy–Weinberg equilibrium (HWE); (5) if there were multiple publications from the same population, only the most recent was included. The studies not reported the genotype frequencies were excluded.

2.3. Data extraction

Two reviewers (Yi-Le Wu and Xiu-Xiu Ding) independently extracted the following information from all eligible studies: author, year of publication, country, ethnicity (categorized as Asian and White populations), source of controls, the number of different genotypes in cases and controls. Disagreements were resolved through discussion.

2.4. Statistical analysis

The strength of association between MTHFR C677T polymorphism and depression was assessed by ORs with 95% CIs. The allele model (T vs. C), the dominant model (TT + CT vs. CC), the homozygote model (TT vs. CC) and the recessive model (TT vs. CT + CC) were used to evaluate the risk. Chi-square test was used for Hardy–Weinberg equilibrium of genotypes in control group of each reviewed research, and a P value less than 0.05 was considered statistically significant. Given the potential between-study heterogeneity (e.g. depression is an etiologically heterogeneous group of brain disorders and different assessment methods for depression in included studies may generate heterogeneity), the random-effects model (DerSimonian and Laird, 1986) was used in this meta-analysis. Meta-regression was implemented to investigate effects of the possible modifiers of ethnicity (White populations vs. Asian populations), source of controls (Hospital-based vs. Population-based), and age (elderly yes vs. no; elderly, aged 60 years or older). Subgroup analyses were conducted by stratification of ethnicity and age. Sensitivity analyses were performed to assess the stability of the meta-analysis results by sequential omission of individual studies. Funnel plots and Egger's linear regression test were used to estimate evidence for potential publication bias (Egger et al., 1997). All statistical analyses were conducted using Stata 9.0 (StataCrop, College station, Tex). A P value less than 0.05 was considered statistically significant.

3. Results

3.1. Characteristics of eligible studies

Fig. 1 described the steps of study selection. A total of 26 publications (cases, 4992; controls, 17082) were identified after initial literature search and subsequent screening (Almeida et al., 2005, 2008; Arinami et al., 1997; Bjelland et al., 2003; Cao et al., 2010; Chen et al., 2005; Chojnicka et al., 2012; Feng et al., 2010; Gaysina et al., 2008; Hickie et al., 2001; Hong et al., 2009; Kelly et al., 2004; Kim et al., 2009; Kunugi et al., 1998; Lewis et al., 2006; Lizer et al., 2011; Pan et al., 2009; Qiao et al., 2012; Reif et al., 2005; Słopien et al., 2008; Tan et al., 2004; Yang et al., 2009; Yuan et al., 2007, 2008; Zeman et al., 2010; Zhao et al., 2008). In terms of ethnicity, 13 studies were performed in Asian populations; while 13 studies were conducted in White populations. All control samples from included studies were in HWE. Detailed characteristics of included studies were summarized in Table 1.

3.2. Quantitative synthesis

As shown in Table 2, the combined results based on all studies showed that T variant of MTHFR C677T gene polymorphism was significantly associated with an increased risk of depression in overall populations (for T vs. C: OR = 1.19, 95%CI = 1.07–1.32; for TT + CT vs. CC: OR = 1.15, 95%CI = 1.01–1.31; for TT vs. CC: OR = 1.42,