Gene 512 (2013) 179–184

Contents lists available at SciVerse ScienceDirect

Gene

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

Association between MTHFR C677T polymorphism and primary open-angle glaucoma: A meta-analysis

Yan Huo [a], Huan Zou [a], Min Lang [a], Shu-Xing Ji [a], Xiao-Lei Yin [c], Zheng Zheng [a], Wei Liu [a], Chun-Lin Chen [a], Rong-Di Yuan [b,*], Jian Ye [a,**]

[a] Department of Ophthalmology, Institute of Surgery Research, Daping Hospital, Third Military Medical University, Chongqing, China
[b] Department of Ophthalmology, Xinqiao Hospital, Third Military Medical University, Chongqing, China
[c] Department of Ophthalmology, 305 Hospital of PLA, Beijing, China

ARTICLE INFO

Article history:
Accepted 25 October 2012
Available online 1 November 2012

Keywords:
Primary open-angle glaucoma
Methylenetetrahydrofolate reductase
Polymorphism
Meta-analysis

ABSTRACT

Epidemiological studies have evaluated the association between methylenetetrahydrofolate reductase (MTHFR) C677T polymorphism and primary open-angle glaucoma (POAG) risk. However, the results remain conflicting. The aim of this study was to investigate the association between MTHFRC677T polymorphism and POAG risk. All genetic association studies on MTHFR C677T polymorphism and POAG were systematically searched by the electronic databases PubMed, Embase and Web of Science. Study selection, data abstraction and study quality evaluation were conducted in duplicate independently. The strength of association between MTHFR C677T polymorphism and POAG was measured by odds ratios (ORs) and 95% confidence intervals (CIs). Publication bias was tested by Begg's funnel plot and Egger's regression test. A total of 10 studies including 1224 cases and 1105 controls were included in our final meta-analysis. There was no evidence of significant association of the overall population (for allelic model: OR = 1.17, 95% CI = 0.94–1.46; for additive model: OR = 1.15, 95% CI = 0.85–1.57; for dominant model: OR = 1.19, 95% CI = 0.92–1.55 and for recessive model: OR = 1.11, 95% CI = 0.83–1.49). Significant associations were found between MTHFR C677T polymorphisms and POAG in allelic model (OR = 1.39, 95% CI = 1.05–1.83) and additive model (OR = 1.88, 95% CI = 1.04–3.43) for population-based (PB) subgroup. This meta-analysis suggested that there were significant associations between MTHFR C677T polymorphism and POAG in allelic model and additive model for PB subgroup which indicated that the T allele or TT genotype might increase the risk of POAG, whereas no evidence of significant association was shown of the overall studied population. However, this conclusion should be interpreted cautiously. More large sample-size and multi-ethnicity studies with well-defined POAG patients and well-study design are needed in the future study.

1. Introduction

Glaucoma, one of the causes of blindness worldwide, is characterized by a progressive loss of retinal ganglion cells (RGCs) and subsequent optic nerve degeneration (Quigley and Vitale, 1997). It was reported that glaucoma would affect 79.6 million by 2020 (Quigley and Broman, 2006). Primary open-angle glaucoma (POAG), which is defined as a chronic and progressive optic neuropathy, is the most common form of glaucoma in most populations such as European and African ancestry (Tielsch et al., 1991) and those of East Asia, including Korea (Kim et al., 2011) and Japan (Iwase et al., 2004). By now, the pathogenesis of POAG is still unclear. Various factors including elevated intraocular pressure, older age, genetic, myopia, and thinner central cornea play a critical role in the development of POAG (Anderson, 1989; Francis et al., 2008; Kuzin et al., 2010; Leske et al., 2008; Sommer et al., 1991; Suzuki et al., 2006; Tielsch et al., 1994). Recently, it has been shown that homocysteine was correlated with glaucoma that is caused by inducing vascular injury or by direct toxicity to RGCs (Bleich et al., 2002; Fingert et al., 2006; Pianka et al., 2000).

Methylenetetrahydrofolate reductase (MTHFR), the predominant circulatory form of folate, is required for the remethylation of homocysteine to methionine by catalyzing the reduction of 5, 10-methylenetetrahydrofolate to 5-methyltetrahydrofolate. It is demonstrated that concentrations of homocysteine could be affected by the C677T polymorphism in the MTHFR gene, which is the most common genetic determinant of elevated levels of homocysteine (Miner et al., 1997). Studies showed that the C677T mutation was common in the general population, with the variable frequency

Abbreviations: POAG, primary open-angle glaucoma; MTHFR, methylenetetrahydrofolate reductase; HWE, Hardy-Weinberg equilibrium; OR, odds ratio; CI, confidence interval; PB, population-based; HB, hospital-based; NOS, Newcastle-Ottawa Scale.

* Corresponding author. Tel.: +86 23 68755633.
** Corresponding author. Tel./fax: +86 23 68767066.
E-mail addresses: yuanrongdi@126.com (R.-D. Yuan), yejian1979@163.com (J. Ye).

0378-1119/$ – see front matter © 2012 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.gene.2012.10.067

of heterozygous mutations ranging from 32 to 40% (Frosst et al., 1995; Rady et al., 2002). To date, numerous studies have reported the correlation of MTHFR C677T polymorphism and POAG, but the results are inconclusive (Bleich et al., 2002; Clement et al., 2009; Fingert et al., 2006; Junemann et al., 2005; Mabuchi et al., 2006; Michael et al., 2008, 2009; Mossbock et al., 2006; Nilforoushan et al., 2012; Zetterberg et al., 2007). Moreover, single study may be limited by sample size and other limitations of research design. Meta-analysis has the benefit to overcome this limitation by increasing the sample size, which has been widely used in genetic association studies (Marini et al., 2012; Zhang et al., 2012). The aim of this study was therefore designed to clarify the association between MTHFR C677T polymorphism and POAG.

2. Materials and methods

2.1. Literature search and inclusion criteria

This meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) criteria (Moher et al., 2009) and searched the electronic databases PubMed, Embase and Web of Science (up to June 10, 2012) following search strategy: 'mutation or variant or polymorphism or genotype' AND 'methylenetetrahydrofolate reductase or MTHFR' AND 'glaucoma' to investigate the association between MTHFR C677T polymorphism and POAG. Hand-searching of the references of included articles identified by electronic search and the abstracts presented at related scientific societies' meetings were also performed to identify other relevant studies. Studies had to comply with the following criteria: (1) studies on the relationship between MTHFR C677T polymorphism and POAG; (2) studies on an original research study with full text articles, not a review, case report, or editorial comment; and (3) study on sufficient data and the original data from case–control studies. Two investigators (Huo Y and Zou H) independently screened the information including the titles, abstracts and full texts to determine inclusion carefully. If the two reviewers disagreed with each other, a third reviewer (Ye J) may be sought.

2.2. Data extraction

Data were collected independently by the same two investigators (Huo Y and Zou H). Following data were independently extracted from each study: first author's name, publication date, country, ethnicity, study design, and evidence of Hardy–Weinberg equilibrium (HWE) ($p<0.05$ of HWE was considered significant), respectively. The subgroup was classified by different ethnicities such as Caucasian, Asian, African, Amerindian, and mixed and by study design including population-based (PB) studies and hospital-based (HB) studies.

2.3. Statistical analysis

The Stata 11.0 software examines the ORs and 95% CIs for four model: allelic model (T allele vs. C allele), additive model (T/T vs. C/C), dominant model (C/T + T/T vs. C/C) and recessive model (T/T vs. C/T + C/C), which were used to assess the strength of association between MTHFR C677T polymorphism and POAG. The pooled ORs were calculated respectively through a Mantel–Haenszel fixed effects model if there was no heterogeneity (Mantel and Haenszel, 1959). Otherwise, a random effects model was adopted (DerSimonian and Kacker, 2007). In this study, heterogeneity was assessed by the Q-test and I^2 test. When $p<0.10$ and $I^2>50\%$, heterogeneity was considered significant (Cochran, 1954; Higgins and Thompson, 2002). The strength between reviewers regarding study selection of agreement was evaluated by Kappa statistic. Furthermore, this meta-analysis analyzed the subgroup of ethnicity (Caucasian and Asian) and source of control (PB and HB). The Newcastle–Ottawa Scale (NOS) (Wells et al., 2011) was used to evaluate the qualities of studies. Two authors (Huo Y and Zou H) of this article independently assessed the quality of each study. Studies with NOS score ≥ 7 were considered to be of high quality. Sensitivity analysis was conducted by limiting the high quality studies (NOS score ≥ 7) and agreement with HWE ($p \geq 0.05$). Publication bias was analyzed by Begg's funnel plot and Egger's test ($p<0.05$ was considered representative of statistically significant publication bias) (Egger et al., 1997).

3. Results

3.1. Study characteristics

Literature search identified a total of 70 potentially eligible articles. Finally, a total of 10 studies (Bleich et al., 2002; Clement et al., 2009; Fingert et al., 2006; Junemann et al., 2005; Mabuchi et al., 2006; Michael et al., 2008, 2009; Mossbock et al., 2006; Nilforoushan et al., 2012; Zetterberg et al., 2007) were involved in this meta-analysis based on our inclusion criteria. The study selection detail process is shown in Fig. 1. There was perfect inter-rater reliability for the selection of studies to be included in the meta-analysis, with Kappa values of 0.91 based on titles and abstracts and 1.00 based on full texts. The detailed characteristics of the association between MTHFR C677T polymorphism and POAG are shown in Table 1: The average score of NOS results was 7.6 (range 6 to 9), indicating a generally good methodological quality of studies. Among the selected studies, six studies related to Caucasian population and four studies related to Asian population. There were three studies in PB and seven studies in HB. One study score is ≤ 6 and one study did not follow the HWE.

3.2. Quantitative synthesis

There were 1224 cases and 1105 controls in our meta-analysis and no evidence of significant association between MTHFR C677T polymorphism and POAG when all 10 studies were pooled into the meta-analysis (for allelic model: OR = 1.17, 95% CI = 0.94–1.46; for

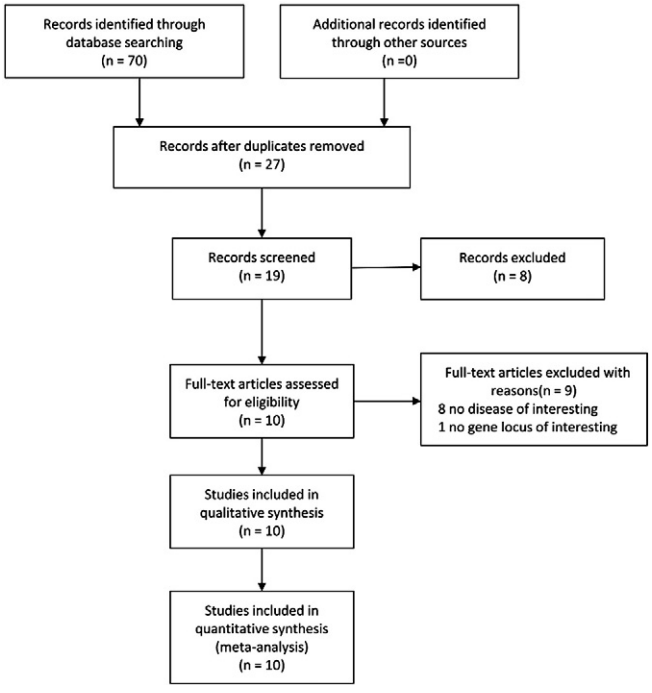

Fig. 1. Flow diagram of the study selection process.