Asian Journal of Psychiatry 20 (2016) 41–51

Contents lists available at ScienceDirect

Asian Journal of Psychiatry

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

Review

Role of *MTHFR* C677T gene polymorphism in the susceptibility of schizophrenia: An updated meta-analysis

Upendra Yadav [a], Pradeep Kumar [a], Sanjay Gupta [b], Vandana Rai [a,*]

[a] Human Molecular Genetics Laboratory, Department of Biotechnology, VBS Purvanchal University, Jaunpur 222 003, UP, India
[b] Department of Psychiatry, IMS, Banaras Hindu University, Varanasi, India

ARTICLE INFO

Article history:
Received 22 June 2015
Received in revised form 31 December 2015
Accepted 5 February 2016

Keywords:
Methylenetetrahydrofolate reductase gene
M*THFR*
C677T
Schizophrenia
Meta-analysis
Homocysteine

ABSTRACT

Methylenetetrahydrofolate reductase (MTHFR) is the key enzyme of folate/homocysteine metabolic pathway. C677T polymorphism of MTHFR gene was reported as risk factor for congenital defects, metabolic and neuropsychiatric disorders. Numerous case-control studies investigated C677T polymorphism as risk factor for schizophrenia but results of these studies were contradictory. To draw a conclusion, a meta-analysis of all available case-control studies was performed. PubMed, Google Scholar, Springer Link and Elsevier databases were searched for eligible case-control studies. Pooled odds ratio with 95%CI was used as an association measure and all statistical analyses were performed by Open Meta-Analyst and MIX software. Total 38 studies with 10,069 cases and 13,372 controls were included in the present meta-analysis. Results of meta-analysis showed significant associated between C677T polymorphism and risk of schizophrenia (OR_{TvsC} = 1.18, 95%CI = 1.10–1.27, $p = < 0.001$; OR_{CTvsCC} = 1.10, 95%CI = 1.04–1.17, $p = <0.001$; OR_{TTvsCC} = 1.40, 95%CI = 1.20–1.64, $p = <0.001$; $OR_{TT+CTvsCC}$ = 1.19, 95%CI = 1.09–1.30, $p = <0.001$). We also performed subgroup and sensitivity analyses. Subgroup analysis was done according to ethnicity and significant association was found between C677T polymorphism and risk of schizophrenia in all three ethnic populations—African (OR = 2.51; 95%CI = 1.86–3.40; $p = <0.001$), Asian (OR = 1.21; 95%CI = 1.10–1.33; $p = <0.001$) and Caucasian (OR = 1.07; 95%CI = 1.01–1.14; $p = 0.01$). In conclusion the results of the present meta-analysis suggested that the *MTHFR* C677T polymorphism is a risk factor for schizophrenia.

Contents

1. Introduction . . . 42
2. Methods . . . 42
   2.1. Search strategy and identification of studies . . . 42
   2.2. Data extraction . . . 42
   2.3. Statistical analysis . . . 42
   2.4. Inclusion and exclusion criteria . . . 42
3. Results . . . 42
   3.1. Eligible studies . . . 42
   3.2. Summary statistics . . . 43
   3.3. Meta-analysis . . . 44
   3.4. Sensitivity analysis . . . 44
   3.5. Subgroup analysis . . . 44
   3.6. Publication bias . . . 45
4. Discussion . . . 45
   Acknowledgements . . . 48
   References . . . 49

* Corresponding author. Tel.: +91 5452252538; fax: +91 5452252244.
E-mail address: raivandana@rediffmail.com (V. Rai).

http://dx.doi.org/10.1016/j.ajp.2016.02.002
1876-2018/

1. Introduction

Schizophrenia (Sz) is a complex psychiatric disorder with 1% prevalence. Although its pathogenesis is still unknown, there is a likely involvement of genetic, neurodevelopmental, neurodegenerative and environmental factors (Morrison and Murray, 2005).

Elevated serum and plasma homocysteine levels have been observed in schizophrenia patients (Levine et al., 2005; Narayan et al., 2014; García-Bueno et al., 2014) and genes involved in folate and homocysteine metabolism has been reported as risk factor for this disease. Methylenetetrahydrofolate reductase (MTHFR) is an essential enzyme in folate mediated one-carbon transfer reactions. MTHFR catalyzes the conversion of 5, 10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, the predominantly circulating form of folate and the methyl donor for conversion of homocysteine to methionine. Methionine is further converted into *S*-adenosylmethionine (SAM), which is the main methyl group donor for cellular methylation of DNA, RNA and proteins. MTHFR variant enzyme due to genetic polymorphisms resulted in less conversion of homocysteine to methionine and consequently increased plasma homocysteine concentration (Mattson and Shea, 2003; Troen, 2005).

Several polymorphisms have been reported in *MTHFR* gene, but the most studied and clinically important variant is C677T (rs1801133) in exon 4 (Frosst et al., 1995). The C677T variant results from a single nucleotide substitution at position 677, in which cytosine is replaced by thymine (Alanine 222Valine). This substitution makes enzyme thermolabile with reduced enzymatic activity (Rozen, 1997). Ample data on the worldwide frequency of C677T polymorphism is currently available (Pepe et al., 1998; Schneider et al., 1998; Rady et al., 2002; Wilcken et al., 2003; Spiridonova et al., 2004; Rai et al., 2010, 2012). The T-allele frequency ranges from 0.20 to 0.55 in Europeans (Pepe et al., 1998), 0.11 to 0.35 in Americans (Schneider et al., 1998), 0.063 to 0.094 in Africans (Schneider et al., 1998), and from 0.04 to 0.38 in Asian population (Spiridonova et al., 2004; Rai et al., 2010, 2012). This polymorphism has been reported to be a genetic factor for various congnital defects and metabolic and neuropsychiatric disorders like—neural tube defcts (Liu et al., 2013), Down syndrome (Coppede et al., 2010), cardiovascular disease (Benes et al., 2001), type II diabetes (Benes et al., 2001), Alzheimer disease (Mansoori et al., 2012), bipolar disorder (Chen et al., 2009), depression (Quiao et al., 2012) etc. Several case-control studies investigated the association between *MTHFR* C677T polymorphisms and the risk of schizophrenia, but the results were inconclusive. Some studies advocated *MTHFR* C677T polymorphism as a risk factor for Schizophrenia (Arinami et al., 1997; Muntjewerff et al., 2005; Kempisty et al., 2006; Feng et al., 2009), whilst other studies reported no genetic association between this polymorphism and schizophrenia (Virgos et al., 1999; Vilella et al., 2005; Philibert et al., 2006; Jönsson et al., 2008; Betcheva et al., 2009). Hence we performed a meta-analysis of case-control studies to evaluate the association of C677T polymorphism and schizophrenia risk.

2. Methods

Meta-analysis was carried out according to MOOSE guidelines (Stroup et al., 2000).

2.1. Search strategy and identification of studies

Eligible studies were identified by searching following databases—PubMed, Google Scholar, Elsevier and Springer link. The following search terms were used: ''*MTHFR*'', ''methylenetetrahydrofolate reductase'', and ''C677T'' in combination with ''schizophrenia''.

2.2. Data extraction

The following information was extracted for each eligible study: first author's family name, journal name, year of publication, country name, number of cases and controls and genotyping method by two authors (UY and PK) and any discrepancies were resolved by discussion. Number of alleles or genotypes in both cases and controls were extracted or calculated from published data to recalculate ORs.

2.3. Statistical analysis

The present meta-analysis examined the overall association of T allele with the risk of schizophrenia. The associations were indicated as odds ratios (ORs) with the corresponding 95%CI. A pooled OR was then estimated on the basis of the individual ORs. The OR was estimated either by using fixed effects (Mantel and Haenszel, 1959) or random effects (DerSimonian and Laird, 1986) model depending upon heterogeneity. The heterogeneity between studies was tested using the *Q*-statistics and quantified using the I^2 statistic (Higgins and Thompson, 2002). If $I^2 > 50\%$ then random effect model was used (Whitehead, 2002). Genetic models were chosen based on the method described by Thakkinstian et al. (2005), briefly calculating and comparing the ORs of T vs. C (allele contrast), TT vs. CC (homozygote), CT vs. CC (co-dominant), TT + CT vs. CC (dominant) and TT vs. CT + CC (recessive) models. We have also done sub-group analysis based on ethnicity and sensitivity analysis. In allele contrast meta-analysis, sensitivity analysis performed by exclusion of the studies in which control population was not in Hardy Weinberg equilibrium and studies with small sample size. The quality score of studies was assessed according to 10-point scoring method of Clark and Baudouin (2006). Two authors (UY and VR) calculated scores. Studies with higher score (>6) were defined as high-quality studies.

Publication bias was investigated by using the funnel plots; viz. funnel plot of standard error by log odds ratio and funnel plot of precision (1/standard error) by log odds ratio. Different statistical tests such as Begg and Mazumdar rank correlation (Begg and Mazumdar, 1994) and Egger's regression intercept (Egger et al., 1997) were adopted to assess the publication bias. All *p*-values are two tailed with a significance level at 0.05. All statistical analyses were undertaken by Open Meta-Analyst (Wallace et al., 2013) and MIX version 1.7 (Bax et al., 2006).

2.4. Inclusion and exclusion criteria

The following inclusion criteria were used: (i) studies should be original, (ii) used case control approach, and (iii) used standard diagnostic criteria for schizophrenia patient diagnosis (Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) or the International Classification of Diseases (ICD). Studies were excluded if: (i) incomplete raw data information and not providing complete information for number of genotype and/or allele calculation, and (ii) Studies based on pedigree data were excluded as they investigate linkage and not association.

3. Results

3.1. Eligible studies

Fig. 1 presents a flow chart of the retrieved studies and the studies excluded, with specifying reasons and the information extracted from the studies included in the meta-analysis is provided in Table 2. Total 105 articles were retrieved using search strategies, but sixty nine articles did not meet the inclusion criteria after reviewing full paper. The excluded articles include two case