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REVIEW

Null association of maternal *MTHFR* A1298C polymorphism with Down syndrome pregnancy: An updated meta-analysis

Vandana Rai *, **Upendra Yadav**, **Pradeep Kumar**

Human Molecular Genetics Laboratory, Department of Biotechnology, VBS Purvanchal University, Jaunpur 222003, India

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Abstract *Background:* Methylenetetrahydrofolate reductase (MTHFR) is an important enzyme of folate/homocysteine pathway and is essential for DNA synthesis and methylation. *MTHFR* gene polymorphisms have been reported as risk factors for congenital defects and several metabolic and neurological disorders. Several studies have investigated an association between maternal *MTHFR* A1298C polymorphism and Down syndrome (DS) child. However, results have been inconclusive.

Aim: A meta-analysis of published case–control studies up to December, 2015 was performed to investigate this association.

Methods: Electronic databases were searched for case–control studies and odds ratios (ORs) with 95% confidence intervals (CIs) were estimated to assess the association. Total twenty-one case–control studies with 2004 cases and 2523 controls were included in the present meta-analysis.

Results: Results of meta-analysis showed a significant association between maternal A1298C polymorphism and DS pregnancy with homozygote model (CC vs. AA: OR = 1.26, 95% CI = 1.01–1.58, $p = 0.04$), but no such association was found in any other genetic models (C vs. A: OR = 1.07, 95% CI = 0.93–1.23, $p = 0.32$; CC + AC vs. AA: OR = 1.08, 95% CI = 0.96–1.23, $p = 0.18$; CC vs. AC + AA: OR = 1.11, 95% CI = 0.90–1.36, $p = 0.30$; AC vs. AA: OR = 1.06, 95% CI = 0.93–1.21, $p = 0.34$).

Conclusion: Subgroup and sensitivity analysis results showed that this polymorphism is a risk factor for DS pregnancy in Asian populations but not in Caucasian population as well as in overall meta-analysis.

* Corresponding author. Fax: +91 05452 252244, +91 05452 252344.
E-mail address: raivandana@rediffmail.com (V. Rai).

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Contents

1. Introduction

Down syndrome (DS) is the commonest chromosome abnormality in humans, characterized by trisomy 21. It is a major cause of abortion and fetal mental retardation, with an incidence of 1–2/1000 live birth [1]. Advanced maternal age is the only well-reported risk factor for maternal nondisjunction [2], while the underlying mechanism remains unexplained. Numerous studies have suggested an association between DS and maternal folate pathway gene polymorphism. In 1999, James et al. [3] were the first to propose the hypothesis that abnormal DNA methylation patterns resulting from aberrant folate metabolism may increase DNA hypomethylation in centromeric regions, increasing the risk of trisomy 21 [4]. Folate plays an important role in genetic material distribution during cell division, because of its part in the cellular methylation reactions, which, epigenetically regulate chromosome segregation [5,6]. 5,10-Methylenetetrahydrofolate reductase (MTHFR) is a key enzyme of folate pathway and several studies reported significant association between maternal *MTHFR* polymorphisms and DS [3,7–10], whereas some others studies could not find any association [11–13].

MTHFR enzyme catalyzes the synthesis of 5-methylenetetrahydrofolate, which remethylates homocysteine to methionine. Methionine is the main precursor for S-adenosylmethionine (SAM), the main methyl donor for DNA, RNA and protein methylation [1]. Insufficient periconceptional folic acid intake on one hand and deficient folate metabolism in mothers and fetuses on the other hand have been acknowledged as risk factors for DS and several other congenital defects [7,14,15]. It has been suggested that genetic predisposition to impaired folate metabolism in mothers could promote DNA hypomethylation and meiotic nondisjunction resulting in trisomy 21 [7,14].

Several polymorphisms have been reported in *MTHFR* gene, out of which C677T and A1298C are clinically important [16,17]. C677T polymorphism makes MTHFR enzyme thermolabile. A cytosine to thymine nucleotide substitution at 677 position (C677T) reduces MTHFR enzyme activity and increases plasma homocysteine concentration [16,18,19]. The second polymorphism A1298C involving alanine to cytosine nucleotide substitution in *MTHFR* gene has also been reported to reduce enzyme activity [17]. Mutant allele (C) frequency differs greatly in various ethnic groups of the world. The prevalence of the A1298C homozygote variant (CC) ranges from 7% to 12% in the White populations of North America and Europe. Lower frequencies have been reported in Hispanics (4–5%), and Asian populations (1–4%) [20,21]. Several studies have been conducted and demonstrated *MTHFR* polymorphism as a risk factor for congenital defects like NTD [22], oral clefts [23], congenital heart defects [24], adult disease conditions like cardiovascular and cerebrovascular diseases [20]. The present meta-analysis was carried out to assess the association of maternal *MTHFR* A1298C polymorphism with Down syndrome pregnancy.

2. Method

2.1. Selection of studies

Studies were identified by a search of PubMed, Google Scholar, Elsevier, and Springer Link databases up to July, 2015. The following terms were used: 'methylenetetrahydrofolate reductase', 'MTHFR', 'A1298C', and 'Down syndrome' to identify eligible articles for meta-analysis. The distribution of the genotypes in the control group was tested for the Hardy–Weinberg equilibrium (HWE).

2.2. Inclusion and exclusion criteria

Included studies had to meet the following criteria (i) study should be a case–control association study, (ii) study should have reported the genotypes of *MTHFR* A1298C