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Association between MTR A2756G and MTRR A66G polymorphisms and maternal risk for neural tube defects: A meta-analysis

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ABSTRACT

Background: Methionine synthase (MTR) and methionine synthase reductase (MTRR) genes have been considered to be implicated in the development of neural tube defects (NTDs). However, the results are inconsistent. Accordingly, we conducted a meta-analysis to further investigate such an association.
Methods: Published literature from PubMed and Embase databases was retrieved. All studies evaluating the association between MTR A2756G or MTRR A66G polymorphism and maternal risk for NTDs were included. Pooled odds ratio (OR) with 95% confidence interval (CI) was calculated using the fixed- or random-effects model.
Results: A total of 11 studies (1005 cases and 2098 controls) on MTR A2756G polymorphism and 10 studies (1211 cases and 2003 controls) on MTRR A66G polymorphism were included. Overall, this meta-analysis revealed no significant association between maternal MTR A2756G polymorphism and NTD susceptibility in either genetic model. A significant association between MTRR A66G polymorphism and maternal risk for NTDs was observed for GG vs. AA (OR = 1.31, 95% CI 1.03–1.67) among Caucasians.
Conclusion: The present meta-analysis indicated that MTRR A66G polymorphism, but not MTR A2756G, is significantly associated with maternal risk for NTDs in Caucasians.

1. Introduction

Neural tube defects (NTDs), primarily including anencephaly and spina bifida, are common birth defects of the central nervous system. These birth defects have a multifactorial genesis, with environmental and genetic components. Folic acid supplemented periconceptionally in the mother appears to dramatically reduce the frequency of NTDs (Czeizel and Dudas, 1992; MRC Vitamin Study Research Group, 1991). However, the mechanism underlying this beneficial effect remains unclear. Genes involved in cellular folate transportation may be prime candidates for folate-regulated NTDs (Barber et al., 2000; Shaw et al., 2002). Several studies have indicated that mothers of NTD-affected babies exhibit elevated plasma homocysteine levels, suggesting a disturbed folate-dependent homocysteine metabolism as one of the hypothesized mechanisms (Mills et al., 1995; Steegers-Theunissen et al., 1991, 1994).

Several key enzymes, including methylenetetrahydrofolate reductase (MTHFR), methionine synthase (MTR), and methionine synthase reductase (MTRR), are involved in the homocysteine metabolic pathway. MTHFR catalyzes the reduction of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, which participates in the remethylation of homocysteine to methionine (Brouns et al., 2008). C677T and A1298C are two common variants in the MTHFR gene that have been investigated in three meta-analyses for their roles as genetic risk factors for NTDs (Amorim et al., 2007; van der Put et al., 1997b; Wang et al., 2012).

MTR (EC 2.1.1.13) is a vitamin B12-dependent enzyme essential for the remethylation of homocysteine to methionine. The human MTR gene is located on chromosome 1q43 (Chen et al., 1997). It produces approximately 1265 amino acid residues and weighs 140.5 kDa (Goulding et al., 1997). In MTR, a polymorphism located at nucleotide position 2756 (MTR A2756G; rs1805087) changes aspartic acid into glycine (D919G) (Chen et al., 1997; Leclerc et al., 1996). To date, numerous studies have reported that an association exists between MTR A2756G polymorphism and maternal risk for NTDs. However, their results remain inconsistent (Al Farra, 2010; Candito et al., 2008; Christensen et al., 1999; De Marco et al., 2002; Doolin et al., 2002; Gos et al., 2004; Johanning et al., 2000; Lucock et al., 2000; Morrison et al., 1998; O'Leary et al., 2005; van der Put et al., 1997a; Zhu et al., 2003).

MTRR (EC 2.1.1.135) is an enzyme that helps in the regeneration of inactive MTR via the reductive methylation of cobalamin. The human MTRR gene was mapped to chromosome 5p15.2–15.3 (Leclerc et al., 1998). In MTRR, a polymorphism located at nucleotide position 66 (MTRR A66G; rs1801394) converts isoleucine to methionine residue (I22M). Some studies reported that maternal MTRR A66G polymorphism is an increased risk for NTDs (Candito et al., 2008; Gos et al., 2004; O'Leary et al., 2005; Pietrzyk et al., 2003; Relton et al., 2004a; van der Linden et al., 2006; Wilson et al., 1999; Zhu et al., 2003), whereas others reported otherwise (Lucock et al., 2001; Naushad and Devi, 2010;

Abbreviations: CI, confidence interval; GCP II, glutamate carboxypeptidase II; HWE, Hardy-Weinberg equilibrium; MTR, methionine synthase; MTRR, methionine synthase reductase; MTHFR, methylenetetrahydrofolate reductase; NTD, neural tube defect; OR, odds ratio.

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O'Leary et al., 2005). A 2006 meta-analysis (van der Linden et al., 2006) suggested that MTRR A66G polymorphism is associated with the maternal risk for NTDs. However, this study did not address the association between maternal MTR A2756G polymorphism and NTD susceptibility, and since then two more studies (Candito et al., 2008; Naushad and Devi, 2010) about maternal MTRR A66G and NTD risk have been reported.

Therefore, in this study, we further performed a meta-analysis to assess the association between MTR A2756G and MTRR A66G polymorphisms and maternal risk for NTDs.

2. Materials and methods

2.1. Literature and search strategy

We searched literature databases including PubMed and Embase (last updated on Jan 31, 2012). The search strategy involved the identification of all possible studies using combinations of the following keywords: ("methionine synthase," "MTR," "methionine synthase reductase," or "MTRR"), ("polymorphism" or "variant"), and ("neural tube defect," "NTD," "anencephaly," "spina bifida," or "encephalocele"). The reference lists of reviews and retrieved articles were manually searched. Supplementary data were searched for missing data points. All searches were limited to studies published in English. If more than one article were published using the same case series, only the study with the largest sample size was selected.

2.2. Inclusion criteria and data extraction

The studies included in the meta-analysis were required to meet all the following inclusion criteria: evaluation on the association between MTR A2756G or MTRR A66G polymorphism and maternal risk for NTDs, case–control design, and sufficient data for calculation of odds ratio (OR) with 95% confidence interval (CI). The following information was extracted from each study: name of the first author, year of publication, country of origin, ethnicity, source of control subjects, number of cases and controls, and number of genotypes for two polymorphisms in cases and controls. Two authors independently assessed the articles for compliance with the inclusion/exclusion criteria, resolved disagreements, and reached a consistent decision.

2.3. Statistical analysis

The association between the two polymorphisms of MTR or MTRR genes and maternal risk for NTDs was estimated by calculating the pooled OR and 95% CI under codominant, dominant, recessive genetic models, and the multiplicative model. The significance of the pooled OR was determined via Z-test; $P<0.05$ was considered to indicate statistical significance. Q-test was performed to determine whether the variation was caused by heterogeneity or chance. A random- (DerSimonian–Laird method (Dersimonian and Laird, 1986)) or a fixed- (Mantel–Haenszel method (Mantel and Haenszel, 1959)) effect model was used to calculate pooled effect estimates in the presence ($P\leq0.10$) or absence ($P>0.10$) of heterogeneity, respectively. Stratified analyses were performed by ethnicity. Sensitivity analysis was performed to evaluate the stability of the results by removing the studies not in Hardy–Weinberg equilibrium (HWE). Publication bias was assessed via Egger's test (Egger et al., 1997); $P<0.05$ was considered to indicate statistical significance. Data analysis was performed using STATA version 11 (StataCorp LP, College Station, Texas, USA).

3. Results

3.1. Characteristics of studies

Based on the keywords and inclusion criteria, 31 articles were preliminarily identified (Al Farra, 2010, 2011; Boyles et al., 2006; Brouns et al., 2008; Candito et al., 2008; Christensen et al., 1999; De Marco et al., 2002; Doolin et al., 2002; Doudney et al., 2009; Gos et al., 2004;

Table 1
Characteristics of studies included in the meta-analysis.

First author	Year	Country	Ethnicity	Source of controls	Genotype distributions						Variant allele frequencies(G)	P^{a}_{HWE} for controls
					Case			Control			case/control	
					AA	AG	GG	AA	AG	GG		
MTR A2756G polymorphism												
Van der Put	1997	Netherlands	Caucasian	HB	48	19	2	258	94	12	0.17/0.16	0.347
Morrison	1998	UK	Caucasian	HB	45	19	4	101	43	4	0.20/0.17	0.821
Christensen	1999	Canada	Caucasian	HB	40	20	1	55	34	1	0.18/0.20	0.087
Johanning	2000	USA	Caucasian	HB	59	18	0	70	13	1	0.12/0.09	0.658
Lucock	2000	UK	Caucasian	HB	13	6	0	21	5	5	0.16/0.24	0.002
De Marco	2002	Italian	Caucasian	PB	62	9	4	148	61	1	0.11/0.15	0.044
Zhu[b]	2003	USA	Caucasian	HB	86	NA	NA	94	NA	NA	NA	NA
Gos	2004	Poland	Caucasian	NA	14	19	1	149	109	4	0.31/0.22	0.001
O'Leary	2005	Ireland	Caucasian	HB	232	134	20	310	156	21	0.23/0.20	0.807
Candito	2008	French	Caucasian	HB	55	20	2	40	17	4	0.16/0.20	0.258
Al Farra	2010	Jordan	Caucasian	Mix	11	6	0	194	35	5	0.18/0.10	0.033
MTRR A66G polymorphism												
Wilson	1999	Canada	Caucasian	HB	10	27	21	22	44	23	0.59/0.51	0.917
Lucock[c]	2001	UK	Caucasian	HB	NA	NA	NA	NA	NA	NA	0.53/0.46	NA
Pietrzyk	2003	Poland	Caucasian	PB	40	54	12	66	29	15	0.37/0.27	0.001
Zhu[b]	2003	USA	Caucasian	HB	49	NA	NA	73	NA	NA	NA	NA
Gos	2004	Poland	Caucasian	NA	1	28	5	33	158	71	0.56/0.57	0.000
Relton	2004	UK	Caucasian	HB	28	107	68	58	263	211	0.60/0.64	0.073
O'Leary	2005	Ireland	Caucasian	HB	149	215	83	178	222	76	0.43/0.39	0.626
van der Linden	2006	Netherlands	Caucasian	HB	18	45	53	53	135	76	0.65/0.54	0.620
Candito	2008	French	Caucasian	HB	16	39	22	22	25	14	0.54/0.43	0.195
Naushad	2010	India	Caucasian	NA	0	33	17	0	52	28	0.67/0.68	0.000

PB, population-based; HB, hospital-based; NA, not available.
[a] *P*-value for Hardy–Weinberg equilibrium test in controls.
[b] This study merely presented the odds ratio with 95% confidence interval for GG+AG vs. AA, which were 1.19 (0.68–2.08), 1.89 (1.14–3.13) in MTR A2756G and MTRR A66G polymorphism, respectively.
[c] This study merely presented the odds ratio with 95% confidence interval for G vs. A, which was 1.28 (0.56–2.93).