Austin Journal of Autism & Related Disabilities

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Austin Publishing Group

Research Article

Methylenetetrahydrofolate Reductase A1298C Polymorphism and Autism Susceptibility

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Received: March 22, 2018; **Accepted:** May 09, 2018; **Published:** May 16, 2018

Abstract

Background: Methylenetetrahydrofolate reductase (*MTHFR*) is a key enzyme involved in folate/homocysteine metabolism. A polymorphism A1298C has been reported to be linked with risk of several diseases/disorders like birth defects, metabolic and psychiatric disorders and different cancers. The association between autism and *MTHFR* gene A1298C polymorphism has been investigated in several case-control studies, which rendered contradictory results.

Aim: To shed light on association between *MTHFR* A1298C polymorphism and risk of autism, a meta-analysis of published case control association studies was conducted.

Methods: Four electronic databases: PubMed, Google Scholars, Elsevier and Springer Link were searched up to August, 2016. All statistical analyses were performed using MetaAnalyst and Mix (version 1.7). Odds ratios (ORs) with their 95% confidence intervals (95% CIs) were calculated. Total seven studies with 1,424 cases and 1,513 controls were included in the present meta-analysis.

Results: The results of meta-analysis suggested that there were no significant association between A1298C polymorphism and autism risk using overall comparisons in five genetic models (A *vs* C: OR=0.99, 95%CI=0.80-1.23, p=0.005; AC *vs* AA: OR = 1.04, 95% CI = 0.75-1.43, p = 0.82; CC *vs* AA: OR = 0.16, 95% CI = 0.06-0.45, p = 0.006; CC+AC *vs* AA: OR = 0.45, 95% CI = 0.25-0.80, p = 0.006; CC *vs* AC+AA: OR = 0.15, 95% CI = 0.06-0.37, p<0.0001)). Publication bias was absent.

Conclusion: In conclusion, results of present meta-analysis showed no significant association between *MTHFR* A1298C polymorphism and autism risk.

Keywords: Autism; *MTHFR*; A1298C; Homocysteine

Introduction

Autism is a complex neurodevelopment disorder involving multiple organ systems, primarily immunological, gastrointestinal and neurological ones [1] and appears in the early years of life [2-4]. It is currently estimated that 3-6 children out of 1000 worldwide have autism spectrum disorder (ASD) [5]. The incidence of autism has increased rapidly in recent decades [6,7]. It is a heterogeneous neurological disorder characterized by three core behavior abnormalities-namely, deficits in social interaction, reduced verbal and nonverbal communication, and highly focused stereotyped behaviors that emerge after a period of relatively normal development [8]. A number of factors such as genetic, epigenetic, environmental and autoimmune function have been implicated in the etiology of autism [6,9-14].

One carbon (C1) metabolism is a likely pathway to regulate epigenetic processes in autism [15]. CI metabolism is comprised of three interconnected pathways-folate cycle, methionine cycle and transsulfuration cycle. The folate and methionine pathway mediates de novo nucelotide synthesis for DNA repair and replication and DNA methylations. The transsulfuration pathway balance cellular redox. There are several evidences that in autistic children, DNA methylation and DNA repair are altered [16,17] as well as dysregulation of redox homeostasis [18], which reinforces a critical role for CI metabolism in the etiology of ASDs [15]. One carbon metabolic pathway include several genes and most of them are polymorphic especially methylenetetrahydrofolate reductase (*MTHFR*) and methionine synthase reductase (MTRR) and frequency of mutant alleles varies greatly worldwide [19-25].

Folate facilitates methionine synthesis from homocysteine by acting as a cofactor for methylene tetrahydrofolate reductase (*MTHFR*) which converts 5,10-methylenetetrahydrofolate (CH2THF) to 5-methyltetrahydrofolate (CH3THF). 5-methyltetrahydrofolate donates methyl group for the conversion of homocysteine in to methionine, which further converted in to *S*-adenosyl-methionine (SAM). SAM is universal methyl group donor, which transfer methyl to DNA, RNA, proteins, phospholipids, or neurotransmitters [26]. Consistently global DNA hypomethylation observed in autistic children [27-29]. Methyl deficiency may strongly impact epigenetic remodeling during key periods of development.

MTHFR gene is 20 kb long (20,336 bp) and mapped at 1p36.3

Citation: Rai V and Kumar P. Methylenetetrahydrofolate Reductase A1298C Polymorphism and Autism Susceptibility. Austin J Autism & Relat Disabil. 2018; 4(1): 1048.

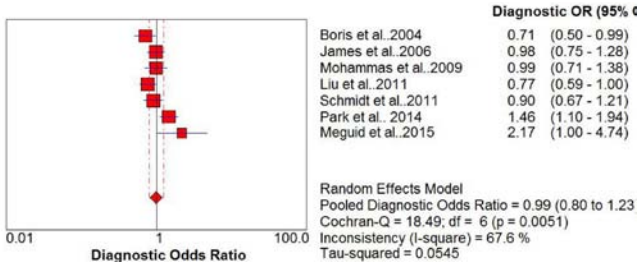

Figure 1: Random effect Forest plot of allele contrast model (C vs. A) of *MTHFR* A1298C polymorphism.

(OMIM 607093), having 11 exons. Several single nucleotide polymorphisms (SNPs) have been identified in *MTHFR* gene. Among which the most commonly studied polymorphisms are C677T in exon 4 and A1298C in exon 7 [30,31]. These two polymorphisms were shown to be associated with reduced enzyme activity and their frequency varies greatly in different geographical regions. The A1298C polymorphism codes for an alanine to glutamine substitution in the C-terminal regulatory domain [32]. Individuals homozygous for the A1298C have approximately the same enzyme activity as those heterozygous for C677T allele [32,33]. The prevalence of the A1298C homozygote variant genotype ranges from 7 to 12% in White populations from North America and Europe. Lower frequencies have been reported in Hispanics (4 to 5%), Chinese (1 to 4%) and Asian populations (1 to 4%) [34,35]. There are conflicting results about the role of *MTHFR* polymorphism A1298C as risk for autism. To derive a precise estimation of relationship between *MTHFR* A1298C polymorphism and autism risk, we conducted present meta-analysis.

Methods

Search strategy, identification of studies and data extraction

A literature search of the PubMed, Google Scholar, Science Direct, and Springer Link databases was conducted using combinations of the following terms: "polymorphism or variant or mutation" and " Autism " and "Methylenetetrahydrofolate reductase or *MTHFR*" and "A1298C". Studies that were included in the present meta-analysis had to meet the following criteria: 1) study should evaluated *MTHFR* gene A1298C polymorphism in autism cases, 2) study should be a case-control, and 3) study should reported sufficient genotype/allele numbers for estimation of odds ratio (OR) with a 95% Confidence Interval (CI).

The following information was extracted from each included study: first author's family name, journal name, year of publication, country name, number of cases and controls. Number of alleles or genotypes in both cases and controls were extracted or calculated from published data to recalculate ORs.

Meta-analysis

Crude odds ratio with 95% CI were used to assess strength of association between *MTHFR* A1298C genotypes and risk of autism in log additive/ allele contrast (C *vs* A), homozygote (CC *vs* AA), co-dominant/heterozygote (AC *vs* AA), dominant (CC+AC *vs* AA) and recessive (CC *vs* AC+AA) models. The statistical significance of the pooled OR was determined using a Z test and p <0.05 was considered statistically significant.

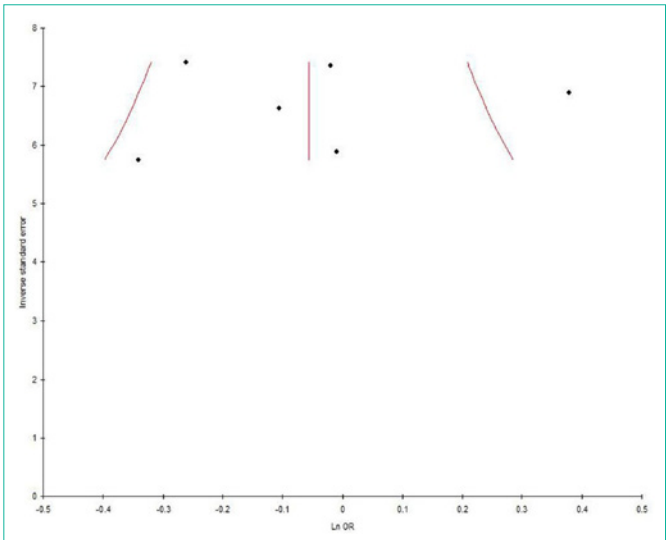

Figure 2: Funnel plots of precision by OR of *MTHFR* A1298C allele contrast model (C vs. A).

The heterogeneity of these studies was tested by the Q statistic and was considered statistically significant when p<0.05 [36]. The pooled OR was estimated using the fixed effects model when there was less heterogeneity [37], or random effects model when there was higher heterogeneity [38]. All included studies were tested for genotypic distribution of the *MTHFR* A1298C polymorphism in the control group with the HWE principle using the x^2-test.

Funnel plots were used to detect publication bias. However, due to the limitations of funnel plotting, which require a range of studies of varying sizes involving subjective judgments, publication bias was evaluated using Egger's linear regression test [40]. All p-values are two tailed with a significance level at 0.05. All statistical analyses were undertaken by MetaAnalyst [41] and MIX version 1.7 [42].

Results

Characteristics of included studies

Seven relevant studies describing the association between *MTHFR* A1298C and autism were identified [41-47] (Table 1). However, in the study of Mohammad et al. [43], the distributions of genotypes in the control groups were not in HWE (p <0.05), indicating genotyping errors and/or population stratification. Except one study [45], six studies were on Caucasians. All the included studies were case-controlled, comprising 1,424 cases and 1,513 controls. In case groups, the frequencies of AA-homozygote, AC hetrozygote and CC homozygote were 51.39%, 38.88% and 9.729% respectively. In control groups, the frequencies of AA homozygote, AC-heterozygote, and CC-homozygote were 52.46, 37.02 and 10.51%, respectively. The C allele frequencies in the case and control groups were 29.55 and 29.11%, respectively (Figure 1).

Meta-analysis

The results of present meta-analysis exhibited high heterogeneity in several genetic models when all eligible studies were pooled together (Table 2). Thus, random effect model was applied to calculate the OR.

Table 1: Distribution of different *MTHFR* genotypes in seven included meta-analysis.

Study	Population	Case/Control	Case genotype			Control Genotype			HWE P- value
			AA	AC	CC	AA	AC	CC	
Boris et al.,2004	Caucasian	168/159	93	65	10	70	75	14	0.33
James et al.,2006	Caucasian	356/204	175	147	34	103	77	24	0.10
Mohammad et al.,2009	Asian	138/138	35	59	44	48	32	58	0.00
Liu et al.,2011	Caucasian	205/382	109	81	15	170	175	37	0.40
Schmidt et al.,2011	Caucasian	296/177	160	117	19	89	76	12	0.43
Park et al., 2014	Caucasian	236/423	147	75	14	298	114	11	0.98
Meguid et al.,2015	Caucasian	24/30	0	23	1	12	16	2	0.27

Table 2: Summary estimates for the odds ratio (OR) of MTHFR A1298C in various allele/genotype contrasts, the significance level (p value) of heterogeneity test (Q test), and the I^2 metric and publication bias p-value (Egger Test).

Genetic Models	Fixed effect OR (95% CI), p	Random effect OR (95% CI), p	Heterogeneity p-value (Q test)	I^2 (%)	Publication Bias (p of Egger's test)
All studies (32)					
Allele Contrast (C *vs* A)	0.95 (0.84-1.07), 0.4	0.99(0.80-1.23),0.0051	0.01	64.81	0.74
Co-dominant (AC *vs* AA)	1.001(0.85-1.17),0.9	1.04(0.75-1.43),0.82	0.001	73.67	0.39
Homozygote (CC *vs* AA)	0.13(0.10-0.15),<0.0001	0.16(0.06-0.45),0.0006	<0.0001	94.87	0.3
Dominant (CC+ AC *vs* AA)	0.44(0.37-0.50),<0.0001	0.45(0.25-0.80),0.006	<0.0001	93.62	0.67
Recessive (CC *vs* AC+AA)	0.12(0.1-0.14),<0.0001	0.15(0.06-0.37),<0.0001	<0.0001	94.15	0.34

The results indicated that *MTHFR* A1298C polymorphism was not associated with autism risk (allele contrast A *vs* C: OR=0.99, 95% CI=0.80-1.23, p=0.005; the heterozygote model AC *vs* AA: OR = 1.04, 95% CI = 0.75-1.43, p = 0.82; the homozygous model CC *vs* AA: OR = 0.16, 95% CI = 0.06-0.45, p = 0.006; the dominant model CC+AC *vs* AA: OR = 0.45, 95% CI = 0.25-0.80, p = 0.006; and recessive model CC *vs* AC+AA: OR = 0.15, 95% CI = 0.06-0.37, p<0.0001). In order to derive a more precise result and to clarify the heterogeneity among studies, author conducted a subgroup meta-analysis stratified with the ethnicity. Six studies were from Caucasian population and only one study was from Asian population, so sub group analysis was performed only on Caucasian studies only. In this subgroup analysis, no significant association between *MTHFR* A1298C polymorphism and autism susceptibility was found in Caucasian population.

Publication bias

The shape of the funnel plots showed that the dots were almost symmetrically distributed and were predominantly in 95% confidence limits (dominant model, Figure 2). The results of Egger's test statistically confirmed the absence of publication bias in the dominant model (p= 0.67).

Discussion

Normal activity of *MTHFR* is required for normal genome methylation and imprinting. The DNA methylation or epigenetic programming is essential for gene imprinting and cell differentiation during embryogenesis [48]. Most critical period of epigenetic programming are prenatal and early post natal, when DNA methylation is essential for development of normal brain and neuron networks [15]. Genetic, epigenetic and environment factors play important role in autism rate and symptom severity [15].

The epigenetic mechanism controls several processes during neurodevelopment which occurs prenatally and early postnatal up to 2 years of age like (i) establishment of neuron networks, (ii) selected cell death, (iii) synaptogenesis and (iv).

Pruning of inappropriate dendritic arbors and synapses etc. High concentration of Hcy and its metabolites inhibit activity of methyl transferases like Catechol-O-methyl transferase (COMT) [49]. And experiments on animal models have showed that COMT activity is high during early embryogenesis at the time of development of sympathetic nervous system [50]. COMT degrades dopamine neurotransmitter by transferring methyl group from SAM to dopamine. Excess dopamine inhibits expression of brain derived neurotrophic factor (BDNF) [51], which is essential for normal brain development [45]. Abnormal methylation due to variant *MTHFR* enzyme reduced the activity of COMT and increased the concentration of dopamine, which consequently inhibit the synthesis of BDNF and abnormal neurodevelopment is resulted [51].

Meta-analysis is an acceptable useful methodology suitable for elucidating genetic factors in different diseases/disorders. Several meta-analysis were published which evaluated risk of folate pathway genes polymorphism for different disease and disorders- like Down syndrome [52-54], orofacial clefts [55,56], recurrent pregnancy loss [57,58], male infertility [59], schizophrenia [60,61], depression [62], autism [63], Alzheimer's disease [64], breast cancer [65,66], prostate cancer [67], colorectal cancer [68] and ovary cancer [69] etc.

Certain limitations exist in the meta-analysis- (i) present meta-analysis based on unadjusted data, (ii) only seven studies and small sample size (2936) limited the ability to draw more solid conclusions, (iii) there is marked heterogeneity among studies, (iv) although the Egger's test did not show any publication bias, selection bias could have occurred, because only published studies were included in present meta-analysis, (vi) interactions between gene–gene and gene–

environment could not be included in present meta-analysis due to a lack of relative data and (vii) only four databases were searched, so it might be possible that few relevant studies were left.

Results of present meta-analysis suggested that A1298C polymorphism of *MTHFR* gene was not a risk factor for autism susceptibility in overall population as well as, in Caucasian populations. Large studies that assess the interrelations between folate intake and *MTHFR* polymorphism are needed to further clarify the role of *MTHFR* polymorphism in the development of autism.

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Austin J Autism & Relat Disabil - Volume 4 Issue 1 - 2018
ISSN: 2472-341X | www.austinpublishinggroup.com

Citation: Rai V and Kumar P. Methylenetetrahydrofolate Reductase A1298C Polymorphism and Autism Susceptibility. Austin J Autism & Relat Disabil. 2018; 4(1): 1048.