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Association Study of Polymorphisms in Genes Relevant to Vitamin B12 and Folate Metabolism with Childhood Autism Spectrum Disorder in a Han Chinese Population

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Statistical Analysis C
Data Interpretation D
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Background: Both genetic and environmental factors play a role in the development of autism spectrum disorder (ASD). This case-control study examined the association between childhood ASD and single-nucleotide polymorphisms (SNPs) in genes involved with vitamin B12 and folate metabolism.

Material/Methods: Genotypes of transcobalamin 2 (TCN2) rs1801198, methionine synthase (MTR) rs1805087, methionine synthase reductase (MTRR) rs1801394, and methylene tetrahydrofolate reductase (MTHFR) rs1801133 were examined in 201 children with ASD and 200 healthy controls from the Han Chinese population.

Results: Our results showed no association of all examined SNPs with childhood ASD and its severity.

Conclusions: None of the examined SNPs were a risk factor for the susceptibility to childhood ASD and severity of the disease in a Han Chinese population.

MeSH Keywords: **Autistic Disorder • Child Development Disorders, Pervasive • Polymorphism, Single Nucleotide**

Abbreviations: **ASD** – autism spectrum disorder; **CARS** – child autism rating scale; **CNV** – copy number variations; **MTR** – methionine synthase; **MTRR** – methionine synthase reductase; **MTHFR** – methylene tetrahydrofolate reductase; **SNP** – single-nucleotide polymorphism; **TCN2** – transcobalamin 2

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Background

Autism spectrum disorder (ASD) is an early-onset neurodevelopmental disorder characterized by struggles in social relationships, deficiency in language and speech, and stereotypical behaviors [1]. Due to increasing prevalence and no current effective treatments, ASD brings huge economic and emotional burdens to affected families and societies [2]. Studies in this field are of great clinical benefit.

Both genetic and environmental factors play a role in the development of ASD [3–7]. Family and twin studies provide strong evidence supporting the contribution of genetics in the development of the disease [7,8]. Molecular genetic studies have discovered that ASD is possibly caused by diverse genetic variants such as gene mutations, single-nucleotide polymorphisms (SNPs), chromosomal abnormalities, and copy number variations (CNVs). Owing to the high heterogeneity of ASD, single genetic variants are found in only a small proportion of ASD cases [9]. The interactions between genetic predisposition and environmental factors have been proposed as the major mechanisms in the etiology of ASD [5,10].

Vitamin B12 (cobalamin) and folate participate in the methylation cycle as well as in DNA and RNA biosynthesis. Metabolic abnormalities of vitamin B12 and folate have been associated with the risk of ASD. Deficiency of vitamin B12 has been associated with many psychiatric and neurological disorders [11]. ASD patients were found to have lower serum vitamin B12 compared to healthy controls [12]. A clinical trial revealed that methyl B12 supplementation improved symptoms and reduced oxidative stress in a subgroup of autistic children [13]. Furthermore, children with brain folate deficiency had a higher risk of being diagnosed with ASD [14]. Folic acid supplementation at about the time of conception have been linked to a lower incidence of ASD in offspring [15,16].

Enzymes and transporter proteins play important roles in metabolism of vitamin B12 and folate. Transcobalamin II (TCN2) is the transporter protein that carries vitamin B12 (cobalamin) into cells within target tissues. Using cobalamin as a cofactor, methionine synthase (MTR) converts homocysteine into methionine and transfers methyl groups from 5-methyltetrahydrofolate to homocysteine, producing tetrahydrofolate for nucleic acid synthesis and methionine for methylation reactions. Methionine synthase reductase (MTRR) is responsible for the regeneration of MTR functions. It converts 5,10-methylenetetrahydrofolate to 5-methylenetetrahydrofolate and regulates the intracellular flow of folate. Methylene tetrahydrofolate reductase (MTHFR) catalyzes the irreversible conversion of 5,10-methylenetetrahydrofolate into 5-methyltetrahydrofolate (Figure 1). Polymorphisms in genes related to the metabolism of vitamin B12 and folate have been examined

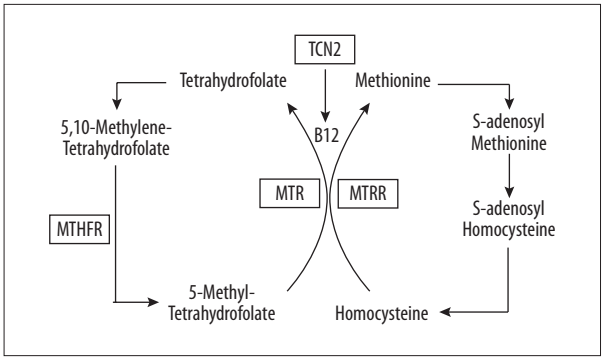

Figure 1. Enzymes (TCN2, MTR, MTRR, and MTHFR) are important in B12 and folate metabolism. TCN2 transports vitamin B12 (cobalamin) to cells. MTR converts homocysteine into methionine and 5-methyltetrahydrofolate to tetrahydrofolate. MTRR is essential for regenerating functional MTR. MTHFR converts 5,10-methylenetetrahydrofolate into 5-methyltetrahydrofolate. TCN2 – transcobalamin; MTR – methionine synthase; MTRR – methionine synthase reductase; MTHFR – methylene tetrahydrofolate reductase.

individually or in combination in previous studies [17–22], but the results are still ambiguous or inclusive. Particularly, the polymorphisms in these genes have not been well defined in the Chinese population.

The present study examined genotypes of SNPs TCN2 rs1801198, MTR (rs1805087), MTR (rs1801394), and MTHFR rs1801133 among children with ASD and healthy controls from the Han Chinese population. The purpose of our study was to examine the association of these SNPs with the risk of childhood ASD.

Material and Methods

Patients with ASD and controls

All patients and controls were recruited from Xiaoshan District of Zhejiang Province from September 2012 to June 2016. A total of 201 Han Chinese children with ASD and 200 healthy children were included, with detailed information described previously [23]. According to the Childhood Autism Rating Scale (CARS), patients with scores of <36 were classified as mild-to-moderate and ≥36 as severe. The Medical Ethics Committee of Zhejiang Xiaoshan Hospital approved this study. Informed consent was signed by parents or guardians of all children.

Genotyping of SNPs

DNA was extracted from whole blood cells using the Qiagen Blood DNA mini kit (Qiagen China, Shanghai, China). TaqMan

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Table 1. Hardy-Weinberg equilibrium tests (*P* values) of SNPs in case and control groups.

SNPs	Cases	Control
rs1801198	0.0776	0.6458
rs1801394	0.9758	0.7129
rs1805087	0.2048	0.0730
rs1801133	0.5873	0.0991

probes were obtained from Applied Biosystems (Beijing, China). Assay IDs for rs1801198, rs1801394, rs1805087, and rs1801133 were C__325467_10, C__3068176_10, C__12005959_10, and C__1202883_20, respectively. Genotypes of SNPs were examined using a TaqMan probe-based real-time PCR approach using the protocol described in previous studies [2,24].

Statistical analysis

All data were analyzed using SAS 9.3 software (SAS Institute Inc., Cary, NC). Hardy-Weinberg equilibrium was examined by the chi-square test. The association between SNPs and the risk of ASD was tested by the logistic regression model. Data were presented as odds ratios (ORs) and 95% confidence intervals (CIs). A P value <0.05 was considered to be statistically significant.

Results

Our data revealed that genotypic distributions of TCN2 rs1801198, MTR rs1805087, MTRR rs1801394, and MTHFR rs1801133 were in Hardy-Weinberg genetic equilibrium (Table 1).

Table 2. Correlation between SNP genotypes and allele frequencies with childhood ASD.

SNPs	Genotype/Allele	Cases n (%)	Controls n (%)	OR	95% CI	*P* value
rs1801198						
	C/C	43 (21.4)	38 (19.0)	1		
	C/G	113 (56.2)	102 (51.0)	0.98	0.59–1.63	0.9353
	G/G	45 (22.4)	60 (30.0)	0.66	0.37–1.19	0.1667
	C	199 (49.5)	178 (44.5)	1		
	G	203 (50.5)	222 (55.5)	0.82	0.62–1.08	0.1564
rs1801394						
	A/A	121 (60.2)	123 (61.8)	1		
	A/G	70 (34.8)	68 (34.2)	1.05	0.69–1.59	0.8313
	G/G	10 (5.0)	8 (4.0)	1.27	0.49–3.33	0.6259
	A	312 (77.6)	314 (78.9)	1		
rs1805087						
	A/A	168 (83.6)	155 (77.5)	1		
	A/G	33 (16.4)	45 (22.5)	0.68	0.41–1.12	0.1252
	A	369 (91.8)	355 (88.8)	1		
	G	33 (8.2)	45 (11.2)	0.71	0.44–1.13	0.1477
rs1801133						
	A/A	32 (15.9)	42 (21.1)	1		
	A/G	101 (50.3)	86 (43.2)	1.54	0.90–2.65	0.1179
	G/G	68 (33.8)	71 (35.7)	1.26	0.71–2.22	0.4295
	A	165 (41.0)	170 (42.7)	1		
	G	237 (59.0)	228 (57.3)	1.07	0.81–1.42	0.6324

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Table 3. SNP genotype distributions and corresponding risk assessments for ASD using genetic models of inheritance.

SNPs/Models	Genotype	Cases n (%)		Controls n (%)		OR	95% CI	*P* value
rs1801198								
Dominant	C/C	43	(21.4)	38	(19.0)	1		
	G/G+C/G	158	(78.6)	162	(81.0)	0.86	0.53–1.41	0.5513
Recessive	C/C+C/G	156	(77.6)	140	(70.0)	1		
	G/G	45	(22.4)	60	(30.0)	0.67	0.43–1.05	0.0838
rs1801394								
Dominant	A/A	121	(60.2)	123	(61.5)	1		
	G/G+A/G	80	(39.8)	77	(38.5)	1.06	0.71–1.58	0.7896
Recessive	AA+AG	191	(95.0)	192	(96.0)	1		
	G/G	10	(5.0)	8	(4.0)	1.26	0.49–3.25	0.6379
rs1801133								
Dominant	A/A	32	(15.9)	42	(21.0)	1		
	G/G+A/G	169	(84.1)	158	(79.0)	1.40	0.84–2.33	0.1910
Recessive	AA+AG	133	(66.2)	129	(64.5)	1		
	G/G	68	(33.8)	71	(35.5)	0.93	0.62–2.22	0.1410

Logistic regression analysis showed no significant differences in the genotypic distributions and allele frequencies of all examined SNPs between case and control groups (Table 2).

The role of these SNPs in childhood ASD was further analyzed using dominant and recessive models. Our study showed that MTRR rs1801394 and MTHFR rs1801133 were not significantly associated with childhood ASD in any of the models (Table 3).

One hundred and twenty-two patients had mild-to-moderate ASD and 79 had severe ASD among all these children with ASD. There was no significant association between the examined SNPs and severity of childhood ASD (Table 4).

Discussion

In this current case-control study, we analyzed polymorphisms of SNPs in genes related to vitamin B12 and folate metabolism among children with ASD and healthy controls from the Chinese Han population. There were no significant differences in genotypic distributions and allele frequencies of SNPs rs1801198 in TCN2, rs1805087 in MTR, rs1801394 in MTR, and rs1801133 in MTHFR between children with ASD and healthy controls. No significant correlation was observed between the examined SNPs and the severity of the disease.

The TCN2 gene is positioned at chromosome 22. SNP rs1801198 (C776G) affects the folding of the protein and thus alters its binding affinity for B12 [25]. This polymorphism in the TCN2 gene has been associated with lower circulating levels of vitamin B12 and increased circulating levels of homocysteine [26]. The disturbed methionine-homocysteine metabolism caused by SNP rs1801198 (C776G) in the TCN2 gene may lead to the development of ASD. A previous study reported a significant difference in the genotypic distribution and allele frequency of rs1801198 between ASD patients and healthy controls [27]. SNP rs1801198 has been associated with peripheral neuropathy [28]. In contrast, our data reveal that rs1801198 in the TCN2 gene is not a risk factor for childhood ASD.

The MTR gene is located at chromosome 1. The polymorphism rs1805087 (A2756G) in the MTR gene influences the activity of its encoding enzyme, leading to elevated circulating homocysteine [29]. Haghiri et al. [17] performed a case-control study with 108 autistic children and 130 healthy controls from an Iranian population. Although no significant difference in the genotypic distribution of rs1805087 (A2756G) was observed between cases and controls, the G allele of the rs1805087 was associated with a higher risk for ASD compared to the A allele. In addition, homozygosity for the A allele was associated with greater severity of dementia [18]. The present study found no significant association between rs1805087 and the risk of ASD in the Han Chinese population.

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Table 4. Correlation between SNP genotypes and allele frequencies and severity of childhood ASD.

SNPs	Genotype/Allele	Moderate-severe n (%)	Severe n (%)	OR	95% CI	*P* value
rs1801198						
	C/C	25 (20.5)	18 (22.8)	1		
	C/G	71 (58.2)	42 (53.2)	0.82	0.40–1.68	0.5906
	G/G	26 (21.3)	19 (24.0)	1.02	0.44–2.37	0.9726
	C	121 (49.6)	78 (49.4)	1		
	G	123 (50.4)	80 (50.6)	1.01	0.68–1.51	0.9651
rs1801394						
	A/A	75 (61.5)	46 (58.2)	1		
	A/G	40 (32.8)	30 (38.0)	1.22	0.67–2.23	0.5104
	G/G	7 (5.7)	3 (3.8)	0.70	0.17–2.84	0.6162
	A	190 (77.9)	122 (77.2)	1		
	G	54 (22.1)	36 (22.8)	1.04	0.64–1.68	0.8777
rs1805087						
	A/A	100 (82.0)	68 (86.1)	1		
	A/G	22 (18.05)	11 (13.9)	0.74	0.34–1.62	0.4436
	A	147 (93.0)	222 (91.0)	1		
	G	11 (7.0)	22 (9.0)	0.76	0.36–1.60	0.4648
rs1801133						
	A/A	22 (18.0)	10 (12.7)	1		
	A/G	59 (48.4)	42 (53.2)	1.57	0.67–3.65	0.2986
	G/G	41 (33.6)	27 (34.2)	1.45	0.59–3.53	0.4151
	A	103 (42.2)	62 (39.2)	1		
	G	141 (57.8)	96 (60.8)	1.13	0.75–1.70	0.5541

The MTRR gene is located at chromosome 5. The rs1801394 (A66G) in the MTRR gene leads to reduced affinity for the substrate [30,31]. A case-control study found that the A allele of rs1801394 in the MTRR gene was associated with reduced risk of ASD [21]. Our data showed no significant association between SNP rs1801394 and childhood ASD or its severity. rs1801394 in the MTRR gene has been identified as a risk factor for several neuropsychiatric disorders [32].

The MTHFR gene is located on chromosome 1. rs1801133 (C677T) in the MTHFR gene influences enzymatic activity and serum homocysteine levels [33,34]. Synergistic interactions between MTHFR C677T and MTRR A66G increase homocysteine, which is considered a significant risk factor for autism [35]. A previous study was conducted with 186 cases and 186 controls from the Han Chinese population. The results found that both the TT genotype and the T-allele of rs1801133 were associated with a significantly increased risk for childhood ASD [22]. A recent meta-analysis analyzed geographical and ethnic distributions of MTHFR C677T among Chinese populations. MTHFR C677T was found to be significantly correlated with the risk of ASD [36]. The SNP rs1801133 was associated with the risk for autism in Indians [21] and North Americans [20]. In contrast, no association between rs180113 and ASD was observed zin our study, and no such association was found in Brazilian [37], Turkish [38], or Egyptian [39] populations.

The limitations of the current study should be addressed, including its case-control design and its relatively small sample size. Only 4 SNPs on related genes were examined in this study. In addition, metabolites of vitamin B12 and folate are involve in redox and DNA methylation relevant to the development of ASD [10]. Measurement of metabolites of folate was able to separate ASD subjects from controls and to predict severity

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of the disease [40]. However, the levels of vitamin B12, folate, and their related metabolites were not examined in these children. Metabolic disorders of the vitamins might interact with certain polymorphisms in these genes to increase risk of ASD. The role of such interactions was not examined in this study.

Conclusions

Our study reveals that TCN2 rs1801198, MTR rs1805087, MTRR rs1801394, and MTHFR are not risk factors for susceptibility to childhood ASD or the severity of the disease in the Han Chinese population.

Conflicts of interest

None.

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