Association of MTHFR A1298C Polymorphism with Preterm Birth: A Meta-Analysis

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ABSTRACT

Background: A few studies have been conducted to explore the association of MTHFR A1298C (rs1801131) polymorphism with preterm birth risk, the results remain inconsistent. Therefore, we conducted a meta-analysis to derive a more systematic estimation of the association.

Method: Relevant studies were searched by PubMed, EMBASE, CNKI, and Google Scholar up to June 2018. The strength of the association of MTHFR A1298C polymorphism with preterm birth was calculated by odds ratios (OR) with 95% confidence interval (95%CI).

Results: A total of nine case-control studies with 1,609 cases and 14,981 controls were included. Pooled results showed that there was no significant association between MTHFR A1298C polymorphism and preterm birth risk under all five genetic models in overall. However, in the stratified analysis of ethnicity, a significant association between MTHFR A1298C polymorphism and preterm birth risk was observed in the Asians under four genetic models, i.e., allele (C vs. A: OR = 0.960, 95% CI 0.543-0.871, P = 0.002), heterozygote (CA vs. AA: OR = 0.887, 95% CI 0.024-0.457, P = 0.003), dominant (CC+CA vs. AA: OR = 0.965, 95% CI 0.534 -0.935, P = 0.015) and recessive (CC vs. CA+AA: OR = 0.923, 95% CI 0.026-0491, P = 0.004), but not in Caucasians.

Conclusion: This meta-analysis suggested that MTHFR A1298C polymorphism is not associated with preterm birth risk in overall population. However, MTHFR A1298C polymorphism plays an important role in preterm birth development in Asian population.

Introduction

Preterm birth or preterm delivery is the most important cause of neonatal mortality and the second-leading cause of death before age of 5 (after pneumonia) worldwide.[1,2] It has been reported that the rate of preterm birth has risen in both developed and developing countries over the last decade.[3,4] More than 10% of all babies are born preterm worldwide, with lowest prevalence in Northern European countries and highest in sub-Saharan African countries.[5,6] About one third of preterm births are medically induced before labour for maternal or fetal indications.[7,8] Maternal indications include pre-eclampsia, eclampsia, HELLP syndrome, previous caesarean section or uterine rupture, and maternal diseases.[9–12] Common fetal indications are intrauterine growth restriction, oligohydramnion, intrauterine infection, poor umbilical blood flow, abnormal fetal heart rate, placental abruption, and placenta previa.[11,12]

The etiology of preterm birth is poorly understood, risk factors associated with the development of the preterm birth include both genetic and environmental factors.[13,14] Several epidemiological studies were conducted to investigate the role of variants in several genes such as TNF-alpha, IL-1 beta, IL-6, MTHFR, MMP-1 and etc., in association with preterm birth.[13,14] For example, the association of MTHFR A1298C (rs1801131) polymorphism with polymorphism and preterm birth risk has been evaluated since the first case-control study performed in 2006 by Engel et al. But, those studies in the following years in different regions and designs turned out with inconsistent and inconclusive results, due to the small sample size. Meta-analysis is a useful technique for finding true and powerful results from individual studies. Therefore, we performed a systematic review and meta-analysis to investigate the association between MTHFR A1298C (rs1801131) polymorphism with polymorphism and preterm birth risk.

Materials and Methods

Publication Search: A comprehensive literature search was performed using PubMed and EMBASE, Web of Science, China Biological Medicine Database, and China National Knowledge Infrastructure (CNKI) to identify studies that evaluated the association between MTHFR A1298C (rs1801131) polymorphism and the risk of preterm birth up to June 30, 2018. The following MeSH terms and keywords were used in various combinations in this search: (''preterm birth'' OR ''preterm delivery'') AND (''Methylenetetrahydrofolate reductase'' OR ''MTHFR'' OR ''A1298C'' OR ''rs1801131'') AND (''polymorphism'' OR ''variant'' OR ''variation'' OR ''SNP'').

Inclusion and Exclusion Criteria: The following criteria were used for study selection in the meta-analysis: (1) case-control study or a cohort studies; (2) evaluating the association of the MTHFR A1298C (rs1801131) polymorphism with preterm birth risk; (3) sufficient data for estimating an odds ratio (OR) with 95% confidence interval (CI). Accordingly, studies with the following characteristics were excluded: (1) not case-control study or cohort study; (2) no control population; (3) studies with insufficient available data or lacking of genotypes distribution data; (4) abstracts, comments, case reports, letters, editorials, reviews, and systematic reviews; (5) published studies containing duplicate data. If studies had the same or overlapping data, only the largest study should be included in the final analysis. If the same data appeared in different works, the result was only used once.

Data extraction: Data was carefully extracted from all the eligible studies by two authors independently according to the selection criteria. The following data were collected from each study: first author, publication year, country, ethnicity, source of controls, genotyping method, numbers of cases and controls, genotype frequency of cases and controls, minor allele frequencies, MAFs in control subjects, and the result of Hardy–Weinberg equilibrium (HWE) test.

Statistical Analysis: The association

between MTHFR A1298C (rs1801131) polymorphism and preterm birth was estimated using the odds ratio (OR) corresponding to a 95% confidence interval (CI). The significance of the pooled OR was determined using the Z-test and P < 0.05 was considered statistically significant. The pooled ORs were performed under five genetic models, i.e., allele (G vs. C), homozygote (GG vs. CC), heterozygote (GC vs. CC), dominant (GG+GC vs. CC) and recessive model (GG vs. GC+CC), respectively. The presence of between study heterogeneity was calculated by the Chi-square-based Q-test, in which significance was set at the P-value < 0.05. In addition, the I^2 value was used to quantify the variation caused by the heterogeneity, in which $I^2 > 50\%$ represents heterogeneity. The fixed effects model was used to pool ORs and 95% confidential interval (CI) when there was no significant heterogeneity. Otherwise, the random effects model (the DerSimonian and Laird method) was used. Fisher's exact test was used to assess the Hardy–Weinberg equilibrium (HWE) with the significance set at P < 0.05. Sensitivity analyses were conducted to identify individual study' effect on pooled results and test the reliability of results. In addition, Sensitivity analyses were performed by removing those studies did not in agreement with HWE. The presence of publication bias was examined by Begg's funnel plot and the Egger' linear regression test and a P < 0.05 was considered significant.

Results

Characteristics of studies: A total of nine case-control studies with 1,609 cases and 14,981 controls were selected in this meta-analysis. The essential data for each study are listed in Table 1. Out of all the studies included, four case-control studies were on Caucasians, three case-control studies were on Asians, and two studies were on Africans. All the included studies were published between 2006 and 2018 and sample size ranged between 50 and 774. The included studies were conducted in Korea, China, Turkey, USA, and Norway. Genotyping methods used

included PCR-RFLP, TaqMan and Real time PCR. The distributions of genotypes in the controls of the studies were in Hardy-Weinberg equilibrium except for three studies.

Quantitative Data Synthesis: Table 2 listed the main results of the meta-analysis of MTHFR A1298C (rs1801131) polymorphism and preterm birth risk.

There was no significant association between MTHFR A1298C (rs1801131) polymorphism and preterm birth risk under all five genetic models, i.e., allele (C vs. A: OR = 0.960, 95% CI 0.879-1.048, p = 0.716), homozygote (CC vs. AA: OR = 0.887, 95% CI 0.464-1.694, p = 0.716), heterozygote (CA vs. AA: OR = 0.992, 95% CI 0.872 -1.129, p = 0.905), dominant (CC + CA vs. AA: OR = 0.965, 95% CI 0.860-1.082, p = 0.542) and recessive (CC vs. CA+AA: OR = 0.923, 95% CI 0.751 -1.135, p = 0.446). In the subgroup analysis by ethnicity, a significant association between MTHFR A1298C (rs1801131) polymorphism and preterm birth risk was found in the Asians under four genetic models, i.e., allele (C vs. A: OR = 0.960, 95% CI 0.543-0.871, P = 0.002), heterozygote (CA vs. AA: OR = 0.887, 95% CI 0.024-0.457, P = 0.003), dominant (CC + CA vs. AA: OR = 0.965, 95% CI 0.534 -0.935, P = 0.015) and recessive (CC vs. CA + AA: OR = 0.923, 95% CI 0.026-0491, P = 0.004), but not in Caucasians (Table 2).

Heterogeneity Test and Sensitivity analysis: Between studies, heterogeneity was found under only homozygote model (GG vs. CC: I^2 = 54.93, P_H = 0.007). To examine the potential source of heterogeneity, subgroup was performed by ethnicity. The results revealed that ethnicity did not relate to heterogeneity in the present meta-analysis. Leave-one-out sensitivity analysis was performed to explore individual study's influence on the pooled data. The results revealed that no individual study affected the pooled OR significantly since no substantial change was found (data not shown). Furthermore, we also performed a sensitivity analysis by excluding all four studies departure from HWE among controls and

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

First Author	Country (Ethnicity)	Source of Controls	Genotyping Technique	Case/Control	Cases					Controls					MAFs	HWE
					Genotypes			Allele		Genotypes			Allele			
					AA	AC	CC	A	C	AA	AC	CC	A	C		
Hwang 2018 [16]	Korea(Asian)	HB	PCR-RFLP	98/128	69	29	0	167	29	84	40	4	208	48	0.188	0.772
Nan 2015 [17]	China(Asian)	HB	TaqMan	108/108	71	36	1	178	38	61	38	9	160	56	0.259	0.383
Uvuz 2009 [18]	Turkey(Caucasian)	HB	RT-PCR	50/50	17	27	6	61	39	24	21	5	69	31	0.31	0.897
Gargano 2009 [19]	USA(Caucasian)	HB	PCR-RFLP	152/408	70	82	-	222	82	189	219	-	597	219	0.277	-
Gargano 2009	USA(African)	HB	PCR-RFLP	71/328	48	23	-	119	23	220	108	-	548	108	0.277	-
Du 2013 [20]	China(Asian)	NA	TaqMan	220/220	155	65	0	375	65	136	80	4	352	88	0.2	0.043
Nurk 2004 [21]	Norway(Caucasian)	HB	Real-time PCR	774/13166	354	347	73	1055	493	6003	5764	1399	17770	8562	0.325	0.781
Engel 2006 [22]	USA(Caucasian)	HB	TaqMan	69/335	23	30	16	76	62	123	140	72	386	284	0.424	0.001
Engel 2006	USA(African)	HB	TaqMan	67/238	2	27	38	31	103	24	95	119	143	333	0.7	0.437

HB: hospital based; PB: population based; RFLP: restriction fragment length polymorphism; MAF: minor allele frequency; HWE: Hardy–Weinberg equilibrium.

Table 2. Results of the association of MTHFR A1298C polymorphism with preterm birth

Subgroup	Genetic Model	Type of Model	Heterogeneity		Odds Ratio				Publication Bias	
			I^2 (%)	P_H	OR	95% CI	Z_{test}	P_{OR}	P_{Beggs}	P_{Eggers}
Overall	C vs. A	Fixed	40.04	0.101	0.960	0.879-1.048	-0.916	0.716	1.000	0.995
	CC vs. AA	Random	54.93	0.038	0.887	0.464-1.694	-0.364	0.716	0.764	0.611
	CA vs. AA	Fixed	26.48	0.226	0.992	0.872 -1.129	-0.119	0.905	0.072	0.595
	CC+CA vs. AA	fixed	27.82	0.197	0.965	0.860-1.082	-0.610	0.542	0.466	0.661
	CC vs. CA+AA	Fixed	40.93	0.118	0.923	0.751 -1.135	-0.763	0.446	0.230	0.243
By ethnicity										
Asian	C vs. A	Fixed	0.000	0.828	0.682	0.543 -0.871	-3.060	0.002	1.000	0.485
	CC vs. AA	Fixed	0.000	0.981	0.105	0.024-0.457	-3.000	0.003	0.296	0.568
	CA vs. AA	Fixed	0.000	0.822	0.776	0.584-1.032	-1.743	0.081	0.296	0.191
	CC+CA vs. AA	Fixed	0.000	0.880	0.707	0.534 -0.935	-2.432	0.015	0.296	0.585
	CC vs. CA+AA	Fixed	0.000	0.985	0.113	0.026-0491	-2.910	0.004	0.296	0.486
Caucasians	C vs. A	Fixed	0.000	0.575	0.994	0.901-1.096	-0.126	0.899	0.089	0.091
	CC vs. AA	Fixed	54.31	0.112	0.943	0.735-1.212	-0.456	0.649	0.296	0.207
	CA vs. AA	Fixed	0.000	0.401	1.046	0.904 -1.209	0.602	0. 547	0.296	0.301
	CC+CA vs. AA	Fixed	0.000	0.530	1.020	0.896-1.162	0.306	0.760	0.089	0.161
	CC vs. CA+AA	Fixed	0.000	0.712	0.913	0.729 -1.145	-0.788	0.431	1.000	0.210

their exclusion did not substantially affect the results of the meta-analysis.

Publication Bias: Begg's funnel plot and Egger's test were performed to assess the publication bias. The shapes of the funnel plots did not show any evidence of obvious asymmetry under all five genetic models. Moreover, Egger's linear regression also did not found significantly statistical evidence of publication bias under all five genetic models, i.e., allele (C vs. A: P_{Beggs} = 1.000 and P_{Eggers} = 0.995), homozygote (CC vs. AA: P_{Beggs} = 0.764 and P_{Eggers} = 0.611), heterozygote (CA vs. AA: P_{Beggs} = 0.072 and P_{Eggers} = 0.595), dominant (CC+CA vs. AA: P_{Beggs} = 0.466 and P_{Eggers} = 0.661), and recessive (CC vs. CA+AA: P_{Beggs} = 0.230 and P_{Eggers} = 0.243).

Discussion

Up to now, the etiology of preterm birth is still unclear, and relevant researches have put forward multiple potentially relevant aspects, involving genetic and environmental factors. Hyperhomocysteinemia is a risk factor for pregnancy outcomes.[15] Increased levels of homocysteine may be due to inadequate dietary intake of folate and vitamin B12 and inherited defects within the methionine-homocysteine pathway such as MTHFR C677T and A1298C polymorphism. The MTHFR plays a role in processing amino acids, the building blocks of proteins. In addition, MTHFR is important for a chemical reaction involving forms of the vitamin B9.

In this meta-analysis, a total of nine case-control studies with 1,609 cases and 14,981 controls were included. In our meta-analysis, MTHFR A1298C (rs1801131) polymorphism showed no association with preterm birth risk in overall population. It is well known that MTHFR polymorphisms vary widely by ethnicity. In subgroup analyses, we performed meta-analysis in Caucasian and Asian populations. The result was inconsistence with overall population. There was an association between MTHFR A1298C (rs1801131) polymorphism and preterm birth risk in Asians, but not in Caucasians.

To the best knowledge, we have included significantly more number of studies to the previous meta-analysis study by using a strict searching strategy which combination online databases with manual search make the eligible studies included as much as possible. In addition, in this meta-analysis we have well designed and performed the process of literature search, information extraction and statistical analysis. Despite the important findings from the present meta-analysis, several limitations should be taken into consideration when explaining the results: First, as only Caucasian and Asian populations were involved in the present meta-analysis, the results might not suit for other ethnicities. Second, publication bias may exist in the present meta-analysis; however, after adjustment using the "trim and fill" method, the result was stable in the direction of the effect, and still presented a significant association. Third, the result of this meta-analysis was based on unadjusted ORs; due to insufficient information stratified analysis cannot be conducted by age, sex, and other factors. Four, because of the complex nature of preterm birth, it is unlikely that a single polymorphism in MTHFR A1298C would be obviously associated with individual susceptibility to preterm birth, and whether additional polymorphisms of this gene or other susceptible genes, which may lead to underestimation of its overall genetic effect on susceptibility to preterm birth. Finally, the interaction of different susceptibility genes and environment factors leaded to preterm birth, but our study could not assess gene-gene and gene–environment interactions due the limited information of included studies.

In summary, our meta-analysis indicated that the MTHFR A1298C (rs1801131) polymorphism with preterm birth is not a risk factor for preterm birth. Moreover, more well-designed studies with larger sample sizes should be conducted to re-evaluate the associations of MTHFR A1298C polymorphism with preterm birth risk in different ethnicities.

Conflict of Interests

Authors have no conflict of interests.

Acknowledgments

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