Association Between Methylenetetrahydrofolate Reductase Gene Polymorphisms and Risk of Vitiligo: A Systematic Review and Meta-Analysis

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Accepted Feb 25, 2020; Epub ahead of print Mar 12, 2020

Methylenetetrahydrofolate reductase (MTHFR) is an important enzyme that converts 5,10-methylenetetrahydrofolate into 5-methylenetetrahydrofolate, which provides the methyl group to convert homocysteine to methionine. Two common *MTHFR* gene polymorphisms, C677T (rs1801133) and A1298C (rs1801131), are associated with decreased MTHFR enzyme activity, and several studies have demonstrated the involvement of these polymorphisms in susceptibility to diseases, including autoimmune diseases (1). Vitiligo is a common cutaneous hypopigmentation disease resulting from the loss of functional melanocytes due to autoreactive $CD8^+$ T cells or oxidative stress in genetically predisposed individuals (2). Available studies have reported inconsistent results regarding the relationship between *MTHFR* polymorphisms and vitiligo; therefore this study investigated this topic in a systematic review and meta-analysis.

METHODS AND RESULTS

A systematic search was performed of PubMed, Embase, Cochrane Library, and Web of Science for case-control studies published before 9 December 2019 that compared the expression of *MTHFR* polymorphisms in patients with vitiligo and healthy controls. The keywords were "methylenetetrahydrofolate reductase" or "MTHFR" combined with "vitiligo." Study quality was assessed using the Newcastle–Ottawa Scale. A random effects model was employed for pooled analysis. Heterogeneity across studies was assessed using the I^2 statistic, and the risk of publication bias was assessed using Egger's test. Odds ratios (ORs) and 95% confidence intervals (CIs) were utilized as summary statistics and were calculated using Comprehensive Meta-Analysis Version 3 (Biostat, Inc., Englewood, NJ, USA). A p-value <0.05 was considered statistically significant.

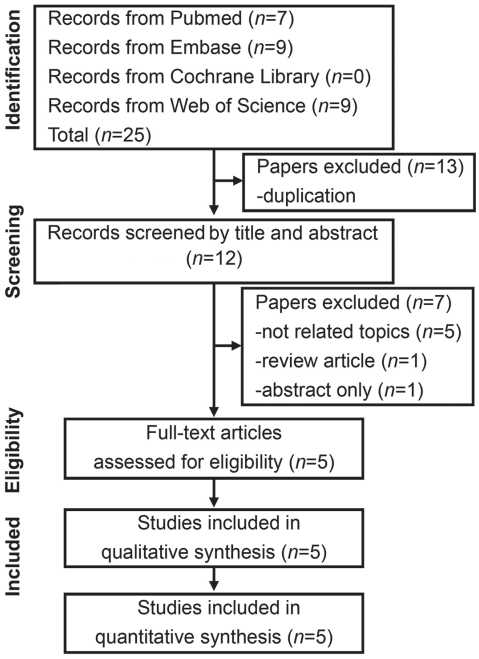

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow-chart of study selection.

Twenty-five relevant studies were initially identified, most of which were sequentially excluded because they were duplicates, concerned an unrelated topic, or were a review (**Fig. 1**). A final total of 5 case-control studies, which had recruited 1,703 patients with vitiligo and 1,708 controls, were included in the meta-analysis (3–7). **Table I** presents the basic characteristics of the included studies, all of which investigated the association between the *MTHFR* polymorphisms of C677T and A1298C and vitiligo susceptibility. **Fig. 2** presents the results of combined analysis for codominant, homozygous, dominant, recessive, and allele

Table I. Basic characteristics of included studies for meta-analysis

Studies	Country	Groups	Age, years Mean±SD/ range	C677T (*n*)					A1298C (n)					Significant results from original study	Quality of study*
				CC	CT	TT	C	T	AA	AC	CC	A	C		
Yasar et al., 2012 (3)	Turkey	Case	27.77±13.44	25	13	2	63	17	10	25	5	45	35	AC of A1298C with higher susceptibility	7
		Control	25.42±4.48	20	15	5	55	25	18	11	11	47	33		
Chen et al., 2014 (4)	China	Case	24.9±12.8	422	471	107	1,315	685	701	272	27	1,674	326	TT of C677T with lower susceptibility	8
		Control	25.9±10.8	363	477	160	1,203	797	719	262	19	1,700	300		
Jadeja et al., 2018 (5)	India	Case	5–60	377	131	12	885	155	181	241	98	603	437	CC of A1298C with higher susceptibility	8
		Control		406	136	16	948	168	211	274	73	696	420		
Benincasa et al., 2019 (6)	Italy	Case	NA	9	29	5	47	39			NA			CT/TT of C677T with higher susceptibility	5
		Control		17	12	1	46	14							
El Tahlawi et al., 2020 (7)	Egypt	Case	34.96±13.84	71	20	9	162	38	56	40	4	152	48	CT/TT of C677T with higher susceptibility	8
		Control	Matched	40	40	0	120	40	30	42	8	102	58	AC/CC of A1298C with lower susceptibility	

*Newcastle-Ottawa Scale, total score: 9. SD: standard deviation; NA: not available.
C: cytosine; T: thymine; A: adenine; CC/AA: wild type homozygosity; CT/AC: heterozygosity; TT/CC: mutant homozygosity.

doi: 10.2340/00015555-3448
Acta Derm Venereol 2020; 100: adv00087

Analysis	Studies	Model	Genotype	OR (95% CI)	*p*	I^2 (%)
C677T						
	5	Co-dominant	CT vs CC	0.868 (0.539–1.400)	0.563	82.231
	5	Homozygous	TT vs CC	0.930 (0.415–2.082)	0.860	61.887
	5	Dominant	CT+TT vs CC	0.880 (0.573–1.351)	0.558	79.692
	5	Recessive	TT vs CC+CT	0.866 (0.438–1.712)	0.679	51.025
	5	Allele	T vs C	0.914 (0.680–1.228)	0.550	71.633
A1298C						
	4	Co-dominant	AC vs AA	1.042 (0.708–1.533)	0.835	74.316
	4	Homozygous	CC vs AA	1.079 (0.598–1.946)	0.801	59.466
	4	Dominant	AC+CC vs AA	1.029 (0.728–1.454)	0.872	71.082
	4	Recessive	CC vs AA+AC	0.945 (0.501–1.782)	0.862	67.882
	4	Allele	C vs A	1.008 (0.784–1.296)	0.951	68.653

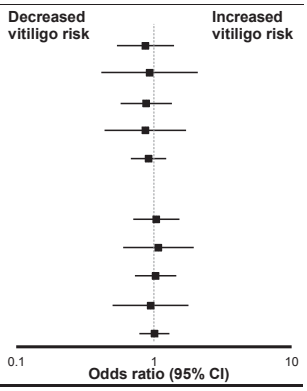

Fig. 2. Meta-analysis of the association between *MTHFR* gene polymorphisms and risk of vitiligo in different genetic models. CI: confidence interval; OR: odds ratio.

models (8). Pooled analysis of 5 included studies revealed no difference in the prevalence of *MTHFR* C677T gene polymorphisms in patients with vitiligo from that in controls, and meta-analyses of the prevalence of *MTHFR* A1298C gene polymorphisms also showed no significant difference between patients with vitiligo and controls. High heterogeneity across the studies was found for all analyses. No publication bias was detected in any measurement.

DISCUSSION

The interaction between genetic susceptibility and environmental factors contributes to the central pathophysiology of vitiligo. Decreased MTHFR enzyme activity in the heterozygous and homozygous *MTHFR* variants of C677T and A1298C is associated with hyperhomocysteinaemia and folate deficiency (1). A previous meta-analysis found significantly higher homocysteine levels, but the same serum folate levels, in patients with vitiligo compared with controls (9). Elevated homocysteine levels may trigger several events related to the pathophysiology of vitiligo, including the production of inflammatory cytokines, oxidative stress, endoplasmic reticulum stress, and neo-self-antigen formation (5). All the included studies drew different conclusions regarding the association between the *MTHFR* gene polymorphisms and the risk of vitiligo in the original study (Table I), and pooled analysis found no significant association between *MTHFR* C677T or A1298C gene polymorphisms and vitiligo susceptibility. Consistently, previous reports by genome-wide association study of vitiligo had also not identified *MTHFR* gene as one of the susceptible genes (10, 11). In addition to the *MTHFR* gene, several non-immune-related genes have been identified as risk factors for vitiligo. These genes are responsible for the development and function of melanocytes, cell growth and survival, and defence against oxidative stress. Although genetic risk is not the only determining factor for vitiligo, these candidate genes increase vitiligo susceptibility by coordinating biological networks involved in immune-mediated melanocyte destruction (12).

The limitations of this analysis include the lack of information for other *MTHFR* polymorphism variants and insufficient data on different ethnicities or vitiligo subtypes.

In conclusion, this meta-analysis demonstrated no significant association between *MTHFR* C677T or A1298C gene polymorphisms and the risk of vitiligo.

The authors have no conflicts of interest to declare.

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