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

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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 I² 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.

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* |
|--------------------|---------|--------|----------------------------|-----------|------------|---------------------------------------|------------------|
| Yasar et al., 2012 | Turkey  | Case   | 27.77 ± 13.44              | 25        | 13         | 2                                    | AC of A1298C with higher susceptibility | 7                 |
| Chen et al., 2018  | China   | Control| 25.42 ± 4.48               | 20        | 15         | 5                                    | TT of C677T with lower susceptibility | 8                 |
| Jadeja et al., 2018| India   | Case   | 5–60                       | 377       | 131        | 12                                   | CC of A1298C with higher susceptibility | 8                 |
| Benincasa et al., 2019 | Italy   | Case   | NA                         | 9         | 29         | 5                                    | CT/TT of C677T with higher susceptibility | 5                 |
| El Tahalwi et al., 2020 | Egypt  | Control| 34.96 ± 13.84              | 71        | 20         | 9                                   | CT/TT of C677T with higher susceptibility | 8                 |

*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.
models (8). Pooled analysis of 5 included studies revealed no difference in the prevalence of MTHFR C677T gene polymorphisms in patients with vitiligo compared to 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 hyper-homocysteinaemia 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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| Analysis | Studies | Model       | Genotype | OR (95% CI)      | p     | I² (%) | Decreased vitiligo risk | Increased vitiligo risk |
|----------|---------|-------------|----------|------------------|-------|--------|-------------------------|------------------------|
| 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    | TT+CC vs CC | 0.880 (0.573–1.531) | 0.558 | 79.692 |                         |                        |
|          | 5       | Recessive   | TT+CC vs 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    | CC+AC vs AA | 1.029 (0.728–1.454) | 0.872 | 71.082 |                         |                        |
|          | 4       | Recessive   | CC+AA vs 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 |                         |                        |