The Genetic Risk Of Methylene Tetrahydrofolate Reductase Single Nucleotide Polymorphism On Blood Homocysteine is Dependent On Sex, Race and Supplement Use - a Systematic Review and Meta Analysis

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Overviews
- The MTHFR C677T (rs1801133) polymorphism has been widely accepted as a risk marker of elevated blood homocysteine (tHcy) 1, and has been used in genetic testing for risk prediction. Yet, there is a lack of consistency in terms of the penetrance and effect size of this genetic variant.
- There are reports of effect modifiers on rs1801133, such as age, sex, race, supplement use, smoking, alcohol drinking, etc.2-4 However, the results are inconsistent and few studies reported how the covariates affect tHcy collectively.
- There are few studies that investigated how rs1801133 contributes the risk of hyperhomocysteinemia in combination with other covariates.
- It is challenging to study the effect of rs1801133 with exhaustive inclusion of all covariates. Meta analysis offers a good alternative by combining data available in the literature.

Methods
- A thorough literature review to gather data from available publications that report the effect of rs1801133 on tHcy.
- Extract the association results of publications that report the effect of rs1801133 on tHcy (Table 1).
- Stratify the genetic association result based on the inclusion status of potential covariates.
- Analyze stratified data by linear multivariate regression and fully hierarchical moderator analysis.

Table 1: Characteristics of Homocysteine Levels for Each Genotyping in Three Different Groups (Table 1)

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of Articles</th>
<th>N Total</th>
<th>CC_N</th>
<th>CC_Mean (SD)</th>
<th>CT_N</th>
<th>CT_Mean (SD)</th>
<th>TT_N</th>
<th>TT_Mean (SD)</th>
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<tbody>
<tr>
<td>Overall</td>
<td>252</td>
<td>137428</td>
<td>67615</td>
<td>9.61 (1.52)</td>
<td>53810</td>
<td>9.9 (1.48)</td>
<td>16003</td>
<td>11.95 (1.61)</td>
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<tr>
<td>Meta Regression</td>
<td>115</td>
<td>64424</td>
<td>28067</td>
<td>9.64 (1.4)</td>
<td>27831</td>
<td>10.16 (1.43)</td>
<td>8344</td>
<td>12.2 (1.53)</td>
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<tr>
<td>Fully Hierarchical Analysis</td>
<td>41</td>
<td>8559</td>
<td>3498</td>
<td>8.52 (1.88)</td>
<td>3632</td>
<td>8.39 (1.04)</td>
<td>1429</td>
<td>10.01 (1.52)</td>
</tr>
</tbody>
</table>

1. Characteristics of Homocysteine Levels for Each Genotyping in Three Different Groups (Table 1)

2. The Effect of rs1801133 on tHcy in General Population is Highly Heterogeneous

- Figure 1: Overall Forest Plot and Funnel Plot

3. Gender, race and Supplement Use Affect the Effect of rs1801133 on tHcy Significantly

- Figure 2: Fully Hierarchical Matrix of ∆tHcy

- Figure 3: Regression Model and Fully Hierarchical Analysis of tHcy

Conclusions
- It is important to predict the effect of rs1801133 on tHcy under the context of the multiple covariates.
- Well-designed statistical analyses based on the available data are also necessary for this purpose.

References