Reviewer's report

Title: Folate network genetic variation, plasma homocysteine, and global genomic methylation content: a genetic association study

Version: 2 Date: 14 June 2011

Reviewer: Abee L Boyles

Reviewer's report:

1. Is the question posed by the authors well defined?
The authors provide clear justification for their research and do not promise more than they deliver.

2. Are the methods appropriate and well described?
The methods used are appropriate and accurately described. Online Supplement 3 provides additional details on methods that would be useful to someone who would like to perform a similar study, but the main manuscript contains sufficient information to interpret and evaluate the paper.

3. Are the data sound?
The data are sound – this is a well-established cohort and many of the components of the phenotypes have been previously described and published. The other laboratory methods used are standard procedures performed with appropriate controls.

4. Does the manuscript adhere to the relevant standards for reporting and data deposition?
Online Supplements 1 and 2 provide the full information on the SNPs tested and I am not aware of any intention to make these genotypes available in a public repository.

5. Are the discussion and conclusions well balanced and adequately supported by the data?
The discussion and conclusion focus on the most relevant results and provide the reader with sufficient information to weigh these results with previous publications. The conclusions do not overstate the significance of the findings but put them in an appropriate context - stressing to readers that MTHFR rs1801133 is only part of the relevant genetic variation in folate metabolism.

6. Are limitations of the work clearly stated?
The authors have included a balanced presentation of the study’s limitations within each section of the discussion and in the conclusions.

7. Do the authors clearly acknowledge any work upon which they are building, both published and unpublished?
The authors have included appropriate citation of previous research in this area. I am unaware of any unpublished relevant results.
8. Do the title and abstract accurately convey what has been found?

The title and abstract are accurate reflections of the content of the paper — although their very extensive analysis is difficult to distill into a succinct abstract without removing some relevant information. The first 2 sentences of the abstract conclusion sound more like results (in that these genes were not mentioned by name previously).

9. Is the writing acceptable?

The writing is clear, descriptive, and to the point.

Minor Essential Revisions:

1. Please provide an appropriate citation for the statistical methods. There is only one reference in the paragraph describing the methods (page 6-7), but this work does not appear to describe the same methods or consider adjusting for population substructure. Please ensure that there are no additional works that should be cited.

2. Why was a lower nominal significant threshold used for MTHFR interactions than for gene-nutrient interactions while both had the same FDR adjusted threshold (page 7)? Please correct if this is a typo, or explain the difference.

Level of interest: An article of outstanding merit and interest in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare that I have no competing interests.