Reviewer’s report

Title: 118 SNPs of Folate-Related Genes and Risks of Selected Congenital Anomalies

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Reviewer: Liborio Stuppia

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The manuscript of Shaw et al. “118 SNPs of Folate-Related Genes and Risks of Selected Congenital Anomalies” describes a study aimed to investigate the influence played by 118 SNPs associated with the complex folate pathway on the risk of spina bifida or conotruncal heart defects.

Obtained results showed few odds ratios revealing sizable departures from 1.0 with respect to spina bifida, and no odds ratios with confidence intervals that did not include 1.0 for any of the studied SNPs with conotruncal heart defects. Authors conclude that these results do not implicate a particular folate transport or metabolism gene to be strongly associated with risks for spina bifida or conotruncal defects.

The study appears well designed, and the manuscript well written. Authors demonstrate to have clear also the limits of the study, the main of which being represented by the lack of data about the mothers’ genotypes, which likely play a crucial role in the folate metabolism.

Minor essential revisions

1) My only major criticism to this study is related to the conclusions. Authors seem to suggest that their study “failed” to evidence a gene-only effect on risk of spina bifida and conotruncal heart defects. However, hundred of studies in the last years have already demonstrated that the contribute of the variants in the genes involved in folate metabolism to the risk of congenital diseases must be considered as a typical example of “poligenic effect”, with several genes playing a limited role. In this view, the results obtained by the authors are exactly those expected, while the detection of the presence of a single gene with major effects should have been unexpected.

Therefore, I strongly suggest to the authors to concentrate their discussion on this point.

2) In the Abstract session, the Conclusion is represented by the sentence “We did not observe any ORs with confidence intervals that did not include 1.0 for any of the studied SNPs with conotruncal heart defects. Haplotype reconstruction showed associations with TYMS, MTHFR, BHMT and MTR for spina bifida.”

In my opinion, this is not a conclusion of the study, but just a portion of the
results. The conclusion should be represented by a short comment on the obtained results.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:
'I declare that I have no competing interests'