Author's response to reviews

Title: Methylene tetrahydrofolate reductase gene variant (MTHFR C677T) and migraine: a case control study and meta-analysis

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Author's response to reviews: see over
Response to Reviewer’s comments

We have the pleasure in resubmitting our revised manuscript “Methylenetetrahydrofolate Reductase Gene Variant (MTHFR C677T) and Migraine: A Case Control Study and Meta-analysis” for further consideration for publication in BMC Neurology.

We would like to thank the reviewer for the helpful comments and suggestions and we have revised the manuscript incorporating changes requested. All changes are in track.

In particular:

1. “All data should be analyzed separately”: We have updated tables 4 and 5 and changed figure 1 to 1A and 1B to show the data for MA and MO separately.

2. “Data on all migraine is uninteresting”: Our case-control study hypothesis was that MTHFR gene was associated with migraine (regardless of the type). Therefore our exploratory analysis in table 2 included all migraine and MA. At this stage of the study we wanted to show if there were any differences between any migraine and MA and therefore we believe this table is necessary to describe the data as stated.

3. “Some of the studies are quite small with wide CI”: We agree with the reviewer and acknowledge such limitation in the manuscript.

4. “I would like the authors to discuss the importance of their findings in relation to MA as it is only a very minor effect that is observed”: In studies of complex disorders, the finding of OR >1.2 is considered a significant effect. In this study we found 30=42% increase risk, which is at least a moderate effect. We have added further discussion to our findings (pages 14-15) in track. The main 2 points are that studies of this gene variant and other disorders must take into account the comorbidity with migraine and interventions aimed at population at risk may add further the increasing interests in personalized medicine.

5. “The discussion should be focused on methodological short comings of association studies”: we agree with the reviewer that several methodological aspects of previous studies (in addition to small sample size) may have contributed significantly to the findings reported. We have discussed case selection, ethnic variations and presented a figure to show publication bias (figure 2). Added discussion re-migraine diagnosis is on page 13 in track.

Thank you again for the helpful input.

Sincerely,
Dr. Zena Samaan, on behalf of co authors