Reviewer's report

Title: Distinct DNA methylation patterns of cognitive impairment and Trisomy 21 in Down Syndrome

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Reviewer: Fabio Coppedè

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Review of Manuscript:

“Distinct DNA Methylation patterns of cognitive impairment and Trisomy 21 in Down Syndrome”

by Meaghan J Jones et al.

The search of distinct patterns of DNA methylation in individuals with Down syndrome (DS) is a timely topic and the present manuscript has some value. However, there are several points that need to be clarified.

Major compulsory revision:

1) Case-Control cohort: the number of controls is really low. I would encourage to add at least five additional subjects to match it with that of DS individuals. Are cases and controls really matched for age? Please show mean, S.D. and P-values.

2) Sample contamination. The authors suggest that buccal specimens could have some degree of blood DNA contamination. Therefore they have corrected their analyses with blood DNA of 5 unrelated subjects. It is not clear why the authors have not corrected with blood DNA from the same subjects. This referee wants to see buccal and blood data from the 15 subjects enrolled from the present study as it is not clear who are the 5 unrelated subjects: healthy individuals? age/gender matched? Ethnically matched? Moreover, a comparison of blood and buccal DNA from the same subjects would allow to identify DS specific DNA methylation signatures.

3) Manuscript organization. There is a weak description of some of the genes showing different methylation patterns between DS and controls only in the results section, but not in the discussion. Please, discuss properly those genes in the discussion section, highlighting their potential contribution to the DS phenotype and/or cognitive decline.

4) Discussion. The discussion is weak (see also major concern 3). The authors speculate on the possible contribution of their findings to DS or cognitive impairment. Do their findings match genome-wide observations in people with AD (for example post-mortem brains?). Is there something known in MCI individuals?
5) Conclusions. The authors wrote the title section “Conclusions”, but forgot to wrote the conclusion, again demonstrating scarce capabilities of manuscript organization.

6) References. Also the reference stile shows scarce formatting, with some references in capital letters (example refs: 2,6,11,12 etc), and others in another style (ex: 1,3, etc), likely due to distraction or multiple submissions.

7) The name of human genes should be in “Italics”

Statistical review

The manuscript needs to be seen by a statistician for the following reasons:
The number of cases/controls is very low, and this referee wonders if the study has the statistical power to detect significant differences. The authors mention some corrections, such as Bonferroni’s one, but it is not clear how this was done. I statistical point of view is highly recommended as this referee is not a statistician.

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