Reviewer’s report

Title: Interaction between obesity and the Hypoxia Inducible Factor 3 Alpha Subunit rs3826795 polymorphism in relation with plasma alanine aminotransferase

Version: 0 Date: 12 Jan 2017

Reviewer: Andrew Walley

Reviewer’s report:

I have a few points about the manuscript that need to be sorted out before it should be considered acceptable for publication:

* The only new laboratory work in this manuscript appears to be the SNP typing. However, the last paragraph of the introduction suggests the methylation data is new as well when it looks like it is from the authors' previous publication in PLoS ONE 2015. This should be much clearer in all parts of the manuscript. For example, the DNA methylation method should not be included. The methods do point the reader to the previous paper but only for the study design when it looks like this is exactly the same dataset.

* Equally, in this paper the DNA methylation data is not described in sufficient detail. For example, it is not possible to know what the distribution of methylation is for the cases and controls. This is presumably because it has been described before and, if so, the authors should cite the previous work in the results to ensure the reader can investigate this dataset further. If it is not the same dataset then it needs more detail in the results, such as distribution, success rates, etc.

* Abbreviations in the title (HIF3A and ALT) need to be spelled out in full.

* Lg is used in the statistical analysis section. This is not a normal abbreviation, it looks like it is being used as an abbreviation for logarithm, in which case it should be logALT

* I am not a statistical expert so it is impossible for me to confirm that the mediation analysis is appropriate. It would be very helpful if the authors included a reference to mediation analysis.

* It is not clear why the authors are adjusting for age-squared when this is not commonly done in statistical genetics analysis. Some statement in the methods section of why they are doing this would be helpful.

* It is also not clear why the authors' selection process resulted in obese and non-obese groups with significantly different proportions of male subjects. The fact that the controls are not gender-matched may be the source of the weakly positive associations they are seeing. Some discussion of this point is needed.
* No mention of multiple testing correction is made and this as a clear weakness of the study. Any correction of the reported p-values reported is likely to render them non-significant and the discussion should mention this.

**Are the methods appropriate and well described?**
If not, please specify what is required in your comments to the authors.

No

**Does the work include the necessary controls?**
If not, please specify which controls are required in your comments to the authors.

Yes

**Are the conclusions drawn adequately supported by the data shown?**
If not, please explain in your comments to the authors.

No

**Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?**
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I recommend additional statistical review

**Quality of written English**
Please indicate the quality of language in the manuscript:

Acceptable

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