Reviewer’s report

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

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Reviewer: Yvonne Böttcher

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Interaction between obesity and HIF3A rs3826795 polymorphism in relation with plasma ALT

The study was conducted to investigate a potential association of the HIF3A polymorphism with ALT in Chinese children (obese cases (705) and non-obese controls (1325)). Moreover, the authors aimed to analyze whether obesity interacts with the single variant on ALT.

The authors describe a significant interaction between obesity and rs3826795 polymorphism on ALT, expressed by association in obese children only, while the G risk allele increases ALT levels. Further, the authors performed methylation analyses in 110 severely obese children and 110 non-obese children and find that these effects are mediated via DNA methylation at the CpG site 46801699 within first HIF3A intron.

This is a nicely written, concise and clear manuscript. The authors discussed several limitations of their study. I raise here a few issues that should be considered:

1. The authors may want to further elaborate on what the potential mechanism of the meQTL (rs3826795 on methylation at 46801699) might be.

2. The authors describe an additive genetic model to assess the association between the polymorphism and ALT which is non-significant in the entire cohort. What about the dominant mode of inheritance for the G-allele?

3. The authors should describe the statistics behind the mediation analysis in more detail.

4. The sample characteristics for the 110 extremely obese and 110 matched controls should be given in another table.

5. There is some redundancy between the introduction and the discussion which should be removed or re-written.

6. As the authors acknowledge in their limitations they have analyzed peripheral blood samples while they had obviously no access to e.g. adipose tissue etc. Nevertheless, it would be good to describe such studies in the introduction or discussion. For example, the authors may want to cite the following reference in their introduction:
Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

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.

Yes

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