Reviewer’s report

Title: The contribution of FTO and UCP-1 SNPs to extreme obesity and cardiovascular risk in Brazilian individuals

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Reviewer: Cecile Lecoeure

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In this study, the aim is to replicate association between obesity and related disorders with one SNP of FTO and 3 SNPs of UCP1 in Brazilian individuals. For that they included 126 obese and 113 controls. The 239 participants were also characterized for lipids and glycaemic measurements as well as blood pressure. The results show a significant association with obesity and two polymorphisms: rs9939609 in FTO, rs6536911 in UCP1. The rs6536911 shows also a significant association with diabetes, hypertension and dyslipidemia when not adjusted for BMI. The authors also tested the interaction between the two significant SNPs and found no synergistic effect with obesity. Moreover 94 of the obese subjects underwent a bariatric surgery and were weighted 1 year after the surgery. None of the SNPs were shown implied in the weight loss. They also genotyped 40 insertions/deletions to assess the genomic ancestry of the samples. No significant difference in ethnic background was highlighted between cases and controls. The largest part of ancestry comes from European descent.

The question is well defined. And a quality control was correctly applied on the genetic data. However some explanations are needed in the methods and procedure part. And results need more discussion. The authors are aware that this present study needs confirmatory results because of the small sample size.

Major Compulsory Revisions

1. According to the previous studies mentioned by the authors, two variants (A-3826G and A-1766G), located in the 5’ flanking region of UCP1, are shown associated to obesity related phenotypes. If the polymorphisms genotyped here are different from the two mentioned above could the authors explain their choice?

2. Could the authors add the location of the SNPs with regard to their related genes?

3. The lack of association with UCP1 polymorphisms rs12502572 and rs2270565 could be due to low power. Could the authors estimate the power of their study design?

4. Could the authors give the name of the programs used to test the Hardy-Weinberg equilibrium? To estimate the linkage disequilibrium?

5. In “statistical analyses”, first paragraph, the authors mention that the linkage disequilibrium between the three SNPs related to UCP1 is estimated. Could the
authors show the result?

6. In “statistical analyses”, last sentence, the authors declare a test as significant for any p-value < 0.05 but in “results”, fifth paragraph, they conclude to a significant association between diabetes and the rs9939609 with a p-value of 0.05. One may consider this as a borderline association.

7. In “results”, fifth paragraph, the authors conclude that there is a significant association between the FTO variant and BMI but give a p-value of 0.420. Could they check this? They also find a significant association with UCP1. What is the p-value?

8. In table 1, did the authors also use the Mann-Whitney test for comparing the distributions of gender and disease status? In case of dichotomous variables the Chi² test is more appropriate. Could they precise this table includes mean and standard deviation?

9. The authors tested the effect of the variants on BMI. Did they perform the tests in each group or in the overall sample? As mentioned in “statistical analyses”, the gender is used as covariate but that would also be interesting to include the age.

10. In “results”, last paragraph, could the authors give the p-value when testing the proportions of genomic ancestries?

11. When testing rs6536911 with the obesity status, the genotype TC is more frequently observed in cases than in controls. When testing that variant with BMI, the highest mean BMI is observed with the genotype TT. Could the authors discuss that point?

12. In different published studies, the minor allele A of rs9939609 is shown associated with higher BMI mean. In table 3, in the obese group, the lower BMI mean is associated with the minor genotype AA. Could the authors discuss that point?

13. In tables 3 and 4, could the authors indicate that mean is given and add the 95% confidence interval of the mean?

14. Among the samples, some were probably under treatment. How were considered the values observed under treatment when testing? Could the authors say a word about that in the “methods and procedure” part?

Minor Essential Revisions

1. For one SNP of UCP1, one can find three spellings: rs22705565 in the text, rs22700565 in the title of table 2, rs2270565 in table 2. The last one seems the correct one.

2. As the authors tested the effect of the SNPs on diabetes, I suggest not restricting the title to obesity and cardiovascular risk.

3. In the methods part of the abstract, when the authors give the BMI mean of control and case groups please precise this is the mean. Symbol # is not appropriate. At the beginning of the “results” part, please also precise it is the mean of BMI given into brackets.

4. In “statistical analyses”, first paragraph, “permutation tests”.
5. In “statistical analyses”, “Unphased to analyze the polymorphisms and their association…”

6. There’s a discrepancy between the age characteristics of the control group in “results”, first paragraph, and in the table 1 (17.3 vs. 17.1).

7. In “statistical analyses”, no s required to covariate in “with gender as covariate for BMI”.

8. In “discussion”, fifth paragraph, a t is missing in “weighing”, and the term BMI would be more appropriate in reference to the written 3kg/m². Further in the paragraph I think the word year is missing “…weight loss one after…”.

9. Could the authors check spelling of the reference 20 (polymorphism in the plural, the word obesity is missing).

10. Several errors occurred in table 2. There are 262 copies of both alleles for rs12502572 in the case group. Only 252 are expected, and according to the genotypes there are only 111 copies of allele A. The percentage of allele A of rs2270565 in the case group is 7% not 4%. In the legend, the spelling of rs12502572 is not correct.

11. Could the authors check the MAF of rs9939609 given in “results”, third paragraph?

Level of interest: An article of limited interest

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:

I declare that I have no competing interests.