Reviewer's report

Title: Association between a frequent variant of the FTO gene and anthropometric phenotypes in Brazilian children

Version: 1 Date: 22 August 2012

Reviewer: D. Michael Hallman

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Major compulsory revisions

1) Only the lower age range of the “replication” sample actually overlaps the age range of the primary sample. Thus, it is not clear how comparable the two samples really are.

2) Page 9, “No statistically significant differences were observed... for allelic and genotypic frequencies....” To assess the validity of combining the groups, one would like to see a more comprehensive set of comparisons. Groups with quite similar allele frequencies may differ substantially in other respects. Were no other measured variables compared between the two groups?

3) Page 9, “The mean anthropometric and dietary variables were compared... at the ages of 1, 4 and 8 years old.” Since longitudinal data were available, a better analytical approach might be to use multilevel models that explicitly account for the longitudinal measurements. (See Hallman et al., (2012) Int J Obesity 36:61-68, for an application involving the FTO rs9939609 polymorphism in a longitudinal sample with an age range similar to that of the replication sample here.)

4) Page 9, the paragraph beginning, “When we analyzed the diet composition....” It’s hard to know what to make of the findings reported here. Calories from lipids were higher in the T/T group than the T/A group (though apparently the comparison with the A/A group was not significant), but BMI z-score at 4 years of age was intermediate in the T/T group (and the z-score was much higher in the A/A group than in either of the others), which is not what one would expect if the connection between lipid intake and BMI were direct. After adjusting for BMI, the difference in lipid intake was no longer significant (though one should hesitate in saying that it “disappeared”, given a p-value of 0.055). Shouldn’t the question of interest be the converse— that is, was the difference in BMI significant after adjusting for lipid intake? One would probably not posit causality in the opposite direction.

5) Page 10 (“Likewise, at 8 years of age....”) and Table 2. That the BMI z-score point estimates were lowest in the T/A group at both 4 and 8 years of age seems anomalous. That the standard deviations of the z-score estimates are consistently much higher than the means suggests that the z-score distributions were non-normal. Were transformed z-scores used in the analyses? The Table 2
footnotes suggest not.

6) Page 12, “According to these data, out longitudinal analysis shown [sic] a greater BMI variation....” As noted above, the analytical methods used aren’t explicitly longitudinal. The closest thing to truly longitudinal analyses here are the tests of differences between 1 and 4 and 4 and 8 years of age. But it is not obvious how to interpret the pattern in 8-year-olds, since again, heterozygotes show the smallest differences.

7) Page 12, “Furthermore, these results were replicated in an independent sample of scholars....” (Note that “schoolchildren” would be more accurate than “scholars” in this context.) The replication cohort seems quite different from the primary one— and is, of course, because the ages of the subjects in the two cohorts differ substantially. The only direct comparisons that could be made would be to look at 8-year-olds in both cohorts, though one suspects the number of 8-year-olds in the replication cohort would be quite small. But one need only compare the genotype-specific BMI z-scores reported in Table 3 with those reported for 8-year-olds in Table 2 to see that the associations between genotypes and z-scores in the two cohorts are quite different.

Minor essential revisions

1) Page 8, “The variables with abnormal distribution....” These variables actually have “non-normal” distributions. There’s nothing necessarily abnormal about a non-normal distribution.

2) Page 9, “The genotypic frequencies (Table 1) agreed....” As only one p-value is reported, it would appear that only one test of Hardy-Weinberg equilibrium was conducted, with white and non-white samples combined. If there is any chance that these groups represent distinct ethnicities, tests of HWE should be conducted separately in each group.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Needs some language corrections before being published

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

**Declaration of competing interests:**

I declare that I have no competing interests.