Reviewer's report

Title: Associations between BMI and 10 candidate genes at ages 4, 7 and 10 in a large UK sample

Version: 2 Date: 23 November 2007

Reviewer: steven wiltshire

Reviewer's report:

General
The study describes an examination of ten SNPs, previously associated with obesity, BMI or waist circumference, for association with BMI in a sample of 5000 twins at the ages of 4, 7 and 10. After correction for multiple testing, using the false discovery rate, the study finds no significant associations. The authors conclude that the stage of biological development of the subjects is important in candidate gene studies.

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Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

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Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

1. More details on the models used in the QTDT analysis are needed. Was the twin-option used (to model shared twin environment)? Were familial correlations due to the major gene modelled with a specific variance component (i.e. using IBDs) or just the polygenic and environmental components? Was population stratification examined, thereby informing the decision to do a total association test rather than the orthogonal test?

2. In the three chi-square analyses of the trichotomised data, how was the relatedness between the each member of a twin pair accommodated, or was just a single twin per pair used in this part of the analysis?

3. What proportion of the twin pairs was dizygotic and what monozygotic?

4. What was the gender-breakdown of the twins? A table addressing this question and question 3 would be helpful.

5. Were the parents genotyped?

6. Regarding the analyses including sex as a covariate, did these use the BMI z-scores that had been standardised against age and sex (in which case would an effect of sex actually be expected)?

7. I think the authors need to include P-values at least for the chi-square analyses, and an indication of the range of significances for the gender-specific
QTDT analyses.

8. In the authors’ discussion, they mention the issue of power and failure to replicate (midway down page 7). Perhaps they could address the possibility that the initial finding of an association is a false positive.

Discretionary Revisions (which the author can choose to ignore)

9. Perhaps add in the title of the manuscript a mention that the UK sample is a sample of twins.

10. Also, given that the authors observe no significant associations (excepting the one with P=0.033) maybe the authors might consider changing the title to “No evidence for association between ...”

11. Would it help the reader for the authors to quote the BMI cutoffs according to these criteria for ages 4, 7 and 10 years?

12. A few more details are needed regarding the power calculations (how, which software etc.) for the benefit of other researchers?

13. It would help the reader for Table 1 to include as a footnote the full name of each gene.

14. What were the heritability estimates for BMI at the three ages?

**What next?**: Accept after minor essential revisions

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

**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.