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: 8 November 2007

Reviewer: Harold Snieder

Reviewer’s report:

This study investigates 10 single-nucleotide polymorphisms (SNPs) in candidate genes for obesity (measured as BMI) in a sample of 5000 children (2500 twin pairs) with BMI data at 4, 7 and 10 years. It has a number of strengths such as the large sample size, multiple measurements at different time points and the use of FDR. I have a number of concerns.

1. The introduction is very short and very similar to the abstract. I propose the authors extend this section and include information on previous genetic association studies carried out in children. Also they could justify why they chose BMI which is surrogate marker of adiposity as the only phenotype for this study and clarify why the study was carried out in such a young population.

2. Introduction, first line obesity rather than BMI should be mentioned as a complex trait.

3. Methods section, the authors could give details on sampling procedure, selection process and demographics of the population. Also, total number of subjects, as well as number of boys and girls. Some of this information could be included in a Table.

4. In the same section, second paragraph, the authors mention that the BMI, weight and height were converted into age- and gender-specific standard deviation scores (SDS, Z-scores) of their distribution in the British 1990 reference data. However, children were categorized into normal, overweight or obese based on IOFT criteria. My suggestion to the authors is that it would be more appropriate to use the UK1990 BMI-for-age growth charts for classifying the children as overweight (85th-95th percentile) and as obese (#95th percentile). IOFT definitions of obesity have been shown to have low sensitivity and they are highly sex-specific in comparison to national definitions (Chinn, Eur J Clin Nutr, 60, 1189-1194, 2006; Reilly, IJO, 30, 595-597, 2006).

5. Maybe the authors could give more details on the genotyping methods, eg what was the genotype success rate?.

6. The allele frequencies for all the SNPs could also be given.

7. It could be interesting if more phenotypes such as body fat measurements or circumferences were included in the analysis, since BMI maybe a less direct measurement of adiposity in children. In this context, the authors could include a section with the advantages and limitations of this study and compare these
findings with those in previous association studies in young children.

8. The analysis does not seem to make optimal use of the longitudinal developmental nature of the data. This needs to be discussed as a limitation. For example, in a recent similar study investigating candidate genes for obesity in youth, Podolsky et al (IJO, 2007) used a growth curve approach to capture the development in adiposity over time.

9. It is not entirely clear whether FDR was applied within each age category (10 tests) or across all age categories (30 tests). Please clarify.

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: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

'I declare that I have no competing interests'