Reviewer's report

Title: Non-replication of an association of CTNNBL1 polymorphisms and obesity

Version: 1 Date: 27 November 2008

Reviewer: Harald Staiger

Reviewer's report:

General comment

The manuscript presented by Vogel et al. describes lack of association of formerly reported obesity candidate SNPs in CTNNBL1 (and three other genes) with childhood/adolescence obesity in a case-control GWA study, lack of association with BMI in a population-based GWA study, and lack of overtransmission of the risk allele of CTNNBL1 SNP rs6013029 to obese children in a family study. In times where nearly every week new candidate genes for complex traits are published, it appears very important to publish well-designed replication studies including those presenting negative results. Even though this negative report is interesting and timely and appears sufficiently powered, the study also reveals serious flaws.

Major Compulsory Revisions

1. I have serious concern with the selection of the control group in the case-control GWA study. First, the controls are adults (mean age: 26 y), whereas the cases are children/adolescents (mean age: 14 y). When studying obese children/adolescents, it appears imperative to study controls of comparable age. Second, the controls have a mean BMI of 18.31 ±1.10. This suggests that the control group also includes anorectic subjects. Both points could introduce relevant bias into the study.

2. In addition to BMI, more parameters of body adiposity and body fat distribution, such as fat mass measured by bioimpedance, waist circumference, and waist-hip ratio, should be available in the KORA cohort. In order to substantiate their negative findings, the authors should perform additional regression analyses with these parameters and include the data in the manuscript (or provide them as supplementary material).

3. Since the risk alleles of the CTNNBL1 SNPs are known and, thus, the direction of the SNP effects is given, one-sided statistical tests are justified. Even though the data presented by the authors appear to point in the opposite direction, as compared to the initial study by Liu et al., the authors should add one-sided p-values to the table to further stress that the initially described SNP effects are not seen in these cohorts.

4. The authors report lack of association between SNPs in FLJ42133, SH3PXD2B, and SLIT3 with obesity as ‘data not shown’. Please, include these data in the manuscript (or provide them as supplementary material).
Minor Essential Revisions
How was the combined power of all three studies calculated? Please, provide information about this in the Methods section.

Discretionary Revisions
1. Even though the information about the power of the studies is sufficient, wouldn’t it be more informative to indicate these studies’ minimal effect sizes/odds ratios detectable with sufficient power (1-##0.8)?

2. Methods section, paragraph ‘Participants and Genotyping’: standard deviations should not be presented with higher precision than the mean values.

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.