Reviewer’s report

Title: Non-replication of an association of CTNNBL1 polymorphisms and obesity in a population of Central European ancestry

Version: 2 Date: 3 February 2009

Reviewer: HongWen Deng

Reviewer’s report:

Major Compulsory Revisions

This is a revised manuscript reporting non-replication of CTNNBL1 polymorphisms and obesity in a population of Central European ancestry. GWA studies for human complex diseases are being published in an increasing rate. Well-designed powerful replication studies are necessary to confirm/refute the initial association findings. In this replication study, three independent German samples were used, including a case-control sample consisting of 487 extremely obese children and adolescents and 442 healthy lean individuals, an adult cohort including 1,644 individuals, and a family-based sample of 775 independent German families consisted of extremely obese children and adolescents and their parents. The previously reported association between CTNNBL1 gene and obesity could not be replicated in any of these three replication samples.

Comments:

This reviewer has a major concern about the power of the study, although this concern was proposed in the last review and was addressed in this revised version.

1) The “combined power” defined by the authors seems to be misleading. Assuming there are N independent replication samples, the authors define the “combined power” as $1 - (1 - \text{power of the first study}) \times (1 - \text{power of the second study}) \times (1 - \text{power of the third study}) \times \ldots \times (1 - \text{power of the Nth study})$. As a numerical demonstration, suppose there are 6 independent replication samples, each with low statistical power of 30% to replicate initial GWAS findings. According to the authors, the “combined power” of these replication samples (each with low power) to replicate the initial findings is as high as ~90% [i.e., $1-(1-0.30)^6 = 0.89$].

In genetic epidemiology studies, “combined power” generally refers to the power of the combined sample (if the subsamples are really combinable). In this replication study, the three different replication samples, which are case-control, cohort, and family-based samples, respectively, cannot be combined directly for association analyses. The power of replication is actually dependent upon the statistical power of each individual study sample. Since in this replication study only the family-based sample is relatively powerful (80%), it seems to be
overstated that “we detected no confirmation in CTNNBL1 with obesity in a well-powered replication effort”.

2) Due to polygenic inheritance of complex diseases/traits, the chance of replicating a susceptibility variant is much lower than that of initially detecting it. This is because in a GWA study designed to identify quantitative trait loci (QTLs), it is usually easy to detect one of the QTLs, even if the effect of the detected QTL is small and the statistical power of the study is low. As a numerical demonstration, suppose there are 20 QTLs underlie BMI, each explaining 1% BMI variation. Even if a GWA study has only ~10% power to detect a specific QTL among these 20 QTLs, this GWA study has a much higher power of ~88% \((1-(1-10\%)^{20})\) to detect at least one of the QTLs.

However, the probability of replicating the specific QTL detected in the initial GWA will generally be low in subsequent replication studies. The specific QTL identified in the initial GWA can be replicated unless a much larger sample with much higher power is used.

Given the above, this reviewer kindly asks the authors to reconsider their statement of “…a well-powered replication effort”.

**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