Reviewer's report

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

Version: 1 Date: 14 November 2008

Reviewer: HongWen Deng

Reviewer's report:

Title: Non-replication of an association of CTNNBL1 polymorphisms and obesity
Authors: Carla I. G. Vogel, Brandon Greene, André Scherag, Timo D. Müller, Susann Friedel, Harald Grallert, Iris M. Heid, Thomas Illig, H-Erich Wichmann, Johannes Hebebrand and Anke Hinney

Comments:

The CTNNBL1, FLJ42133, SH3PXD2B and SLIT3 genes were recently identified to be associated with obesity phenotypes (BMI and body fat mass) in a genome-wide association study in US Caucasians and a French population (Liu et al. Hum Mol Genet 2008). In this study, the authors aimed to replicate the association of these four genes with obesity in three independent German samples (a case-control sample consisting of 487 extremely obese children and 442 healthy lean individuals, a population-based adult sample consisting of 4261 adults, and a family-based sample consisting of 775 families). The authors claimed that no supportive evidence could be found for association of these reported genes with obesity in the German samples.

Comments:

1) Background:

a) The statement “These genes SH3PXD2B (rs13356223, rs10077897 and rs13436547), SLIT3 (rs17734503 and rs12654448) and FLJ42133 (rs7363432 and rs6095722) however, only showed association with increased BMI or fat mass in the initial sample, but could not be validated in the French sample.” is not correct. In Liu et al. (2008), real replication in the French sample was only performed for the most significant SNPs in the CTNNBL1 gene initially identified in the US Caucasians. Real replication effort for the SH3PXD2B, SLIT and FLJ42133 in the French sample was not pursued.

2) Methods:

b) The cases and controls were not well matched in the case-control sample. The cases were extremely obese children with of age 14.4±3.74, but the controls were healthy lean individual with age of 26.1±5.79 (who were likely to be young adults). This may cause nonreplication of the original association findings.

c) Only 1644 probands of the KORA sample (which comprises 4261 adults) were
genotyped. It is not clear why only a portion of the sample was genotyped for this replication study. It is known that, to achieve sufficient power, the replication sample should be much larger than the initial sample. A replication sample with 1644 subjects may not be sufficiently powerful to replicate the initial association findings.

d) For the family sample, it is not clear how many children and parents were successfully genotyped.

e) What’s the composition in terms of ethnicity for the three study samples?

f) Statistics: potential population stratification was not considered in the case-control sample and the population-based KORA sample.

3) Results and discussion:

a) The statement “Nevertheless, the combined power, that is the probability of at least one of the three tests “re-detecting” an association, was > 90% if the estimated and the true genetic effects correspond” is problematic. The “combined power” defined by the authors seems unreasonable. If none of the three samples is sufficiently powerful for replication purpose, it is not surprising that the initial findings could not be replicated in any of the three samples.

b) It is not “surprising” that Liu et al. (2008) could not show association evidence for FTO. Many factors such as diverse linkage disequilibrium at the FTO locus between populations may result in this.

4) Conclusion:

a) The claim that “no confirmation in a well-powered replication study” needs to be changed, as the study samples were not really sufficiently powerful.