Reviewer's report

Title: BMI-independent association of obesity risk SNPs in PCSK1 with insulin sensitivity and proinsulin conversion

Version: 1 Date: 30 March 2010

Reviewer: Emma Ahlqvist

Reviewer's report:

In this article Heni, Haupt et al. investigate the effect of two coding SNPs, in the PCSK1 gene, that have previously been implied in obesity, on weight and diabetes related traits. They find an association with proinsulin conversion, but also an unexpected effect on insulin sensitivity. While the study is small and clearly needs replication it is an interesting finding that should stimulate new investigations. However, there are some minor concerns that need to be addressed before publication.

Major revisions

- It is not stated whether one or two-sided tests were used for the linear regression, only that one-sided tests were used for the power calculations. Two-sided tests should be used for all calculations. Power should be calculated for the statistical tests that were used or at least a close approximation. The effect sizes calculated seem to be Cohen’s d, which should be stated, and should be expressed in standard deviations.

- Also, please clarify which phenotypes were ln-transformed, in the methods part is says only the ones that were not normally distributed; in the tables it says all.

- It says in the methods that the subjects were selected from a larger study. How was this selection done?

Minor revisions

The first sentence of the abstract gives the impression that the role of PCSK1 in neuropeptide processing is the main focus of the manuscript.

- “First-phase insulin was determined from the OGTT as described earlier [19] by calculating $1283 + 1.829 \times \text{Ins30} - 138.7 \times \text{Glc30} + 3.772 \times \text{Ins0}$.” Please cite the original article instead.

- “Insulin sensitivity during the OGTT was estimated as proposed by Matsuda and DeFronzo [20].” Please write the full formula.

- “The similar findings with two different measurements of insulin sensitivity as well as the inverse influence on 120-min blood glucose argue against a mere statistical type 1 error.”

These are related phenotypes and not independent evidence.