Reviewer's report

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

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Reviewer: Claudia Langenberg

Reviewer's report:

Thank you for the opportunity to read this manuscript investigating the metabolic effects of two common genetic variants in PCSK1 previously shown to affect obesity levels. The authors use data from 1,498 men and women from the Tuebingen Family Study, a cross-sectional study of non-diabetic individuals at increased risk of type 2 diabetes, to investigate associations with obesity and a range of OGTT derived measures of glucose metabolism, including insulin secretion and proinsulin levels.

Similar to another earlier report, the authors fail to replicate associations for the 2 common PCSK1 SNPs with obesity or other measures of adiposity, but demonstrate significant differences in proinsulin secretion by genotype.

I hope the authors find the following comments helpful:

The manuscript addresses an interesting question and extends previous work by investigating measures of proinsulin secretion/conversion – obvious outcomes of interest when studying genetic variation in PCSK1. My main comments relate to the design of the study and choice of parameters used to assess and compare associations with the different outcomes.

Study design/power: As the authors acknowledge themselves, this study is underpowered. Of all common genetic loci identified to be associated with obesity levels to date, FTO is by far the strongest – according to the authors’ calculations the current study is not even adequately powered to detect effects of FTO, let alone any variants with weaker effects, as would be expected for the two SNPs in question. Effect sizes for BMI and waist do actually appear rather large (e.g. table 2), despite the lack of statistical significance, this should be acknowledged. The absence of significant associations does therefore not allow any inference about a potential lack of effects of these PCSK1 variants, an important limitation. In general, due to the on average small effects sizes of individual genetic variants influencing complex traits and lack of power of single studies, the past few years have seen growing efforts of different research groups to join forces in order to increase power and minimise false negative reports. I would encourage the authors to consider this option given the significant lack of power of the present study. Likewise, I do not see why the current study needs to end with the conclusion that further replication is needed. This should be actively pursued in the current study.
Effect sizes versus significance: Throughout the report, the authors focus on statistical significance instead of effect sizes and directions, a shortcoming particularly when considering the limited power of this study. It would be preferable to compare the effect sizes observed in the present study to those from earlier reports and to consistently describe and discuss effects on the different traits for the obesity “risk” alleles.

Minor comments:
Could the authors please state why one tailed t-tests were used?