Reviewer's report

Title: PKLR rs3020781 and NOS1AP rs7538490 in relation to type 2 diabetes, obesity and related metabolic phenotypes in a Danish large-scale study: case-control studies and analyses of quantitative traits

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Reviewer: Jana van Vliet-Ostaptchouk

Reviewer's report:

In this manuscript, Andreasen and colleagues examine two common variants within two genes: one in the PKLR gene encoding liver pyruvate kinase and another – in the NOS1AP gene encoding the nitric oxide synthase 1 (neuronal) adaptor protein [CAPON] for association with type 2 diabetes. Both polymorphisms - rs3020781 in PKLR and rs7538490 in NOS1AP - were identified by high-density association mapping of the well known T2D linkage peak at the chromosome 1q21-24 by Prokopenko et al. In that study, both snps showed the same association pattern in 4 different populations of European origin. Andreasen et al. aimed to validate these findings and also to investigate the effect of the snps on metabolic traits and obesity in a large sample of Danes. The authors found no evidence of association between the PKLR rs3020781 and the NOS1AP rs7538490 snps and type 2 diabetes and related quantitative phenotypes.

This manuscript is generally well and laconic written, the results are clearly presented. The results of this paper are of the interest for researchers in the field of genetics of type 2 diabetes, however there are several minor points that needed to be addressed.

Although the present study is adequately powered to detect a moderate effect and, thus, represents a well performed replication study to confirm the observed association by Prokopenko et al., the authors can not exclude the between-study heterogeneity as a possible cause of the negative replication. Were the allele and genotype frequencies in the studied sample of Danes comparable to the results of Prokopenko et al.?

Unfortunately, no detailed information on the LD blocks of the two associated clusters in the 1q region identified by Prokopenko et al. is available to conclude whether additional snps from the clusters should be included in the replication study. The authors should comment upon this in a sentence or two in the discussion.

Also, the discussion could be considerably improved by referring to the recently published paper by Hasstedt et al. entitled “Type 2 diabetes susceptibility genes on chromosome 1q21-24” (Ann Hum Genet. 2008 Mar). In this study the authors tested, individually and in pairs, the variants in few candidate genes (also in the PKLR gene) in the 1q region to detect evidence for interactions among putative
1q susceptibility genes.

Minor comments.
Perhaps revising the title of the manuscript from “PKLR rs3020781 and NOS1AP rs7538490 in relation to type 2 diabetes, obesity and related metabolic phenotypes in a Danish large-scale study: case-control studies and analyses of quantitative traits” to “Lack of association of PKLR rs3020781 and NOS1AP rs7538490 with type 2 diabetes, obesity and related metabolic phenotypes” (or similar) would be useful. It would clearly indicate that the current study is a negative replication.

**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.