Reviewer's report

Title: Evaluation of Four Novel Genetic Variants Affecting Hemoglobin A1c levels in a Population-Based Type 2 Diabetes Cohort (The HUNT2 Study)

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Reviewer: Hélène Choquet

Reviewer’s report:

Review of the paper “Evaluation of Four Novel Genetic Variants Affecting Hemoglobin A1c levels in a Population-Based Type 2 Diabetes Cohort (The HUNT2 Study).”

In this report, J. Hertel and colleagues evaluated the effect of four SNPs (located near the BNC2, SORCS1, GSC and WDR72 loci) previously associated with HbA1c in a context of type 1 diabetes on glycemic control in type 2 diabetes (T2D). They tested association between the four polymorphisms and HbA1c and non-fasting glucose levels in 1,486 subjects with T2D issued from a Norwegian population-based cohort.

The paper is well written and the data clearly presented. However, the current study may be significantly improved.

Minor points:

1. It might be interesting to test others polymorphisms previously reported associated with HbA1C levels in diabetic patients in the HUNT2 Study, such as the -429T>C promoter polymorphism of the RAGE gene (Laki J et al., Mol immunol, 2007).

2. It would be relevant to test others common variants previously reported associated with HbA1C levels in non-diabetic populations. For example, the SNPs from these two papers (Soranzo N et al., Diabetes, 2010 and Pare G et al, Plos Genet, 2008) might be tested in the HUNT2 Study.

3. Did the authors have access to other glycemic control-related traits such as fasting glucose?

4. Results subsection: In the reviewer’s view, the sentence “However, the results for SORCS1 (rs1358030) demonstrated the largest effect sizes ... and direction consistent with decreased glucose level” must be discarded knowing that “none of the risk alleles reached statistical significance with either increased HbA1c measures or increased non-fasting serum glucose levels”.

Major points:

1. In this report, the authors suggest that “further studies in other populations are needed to elucidate whether these novel sequence variants affect glycemic
control in type 2 diabetes”. In these days of meta-analysis and collaborations it would be sound to use data from genome-wide association studies to confirm the lack of effect of these four SNPs on HbA1C levels in T2D subjects in a large meta-analysis.

2. Subgroup analyses have been performed (subjects with HbA1c > or # 7.0%). Given the sample size (N=1,486 subjects), the reviewer suggests not to apply such subgroup analyses for statistical power issues. Analyses in not adequately powered subsamples strongly increase the risk of false positive associations.

**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