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: Anne Marie Minahan

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Hertel JK et al.,

Evaluation of four novel genetic variants affecting haemoglobin A1c levels in a population-based type 2 Diabetes Cohort (The HUNT2 Study)

In the current manuscript the authors describe a study where they examine the impact of SNPs in four gene loci on glycemic control in type 2 diabetes. The gene loci were chosen as they have recently been highlighted as potentially mediating glycemic control in type 1 diabetics. The manuscript is generally well written, with results clearly described and the discussion reflective of the results

1. However, the results are overstated in places, with too much emphasis placed on non-significant findings, which is somewhat misleading. For example in the results section in the main body of the text and in the abstract, you talk about the size effects for the SORCS1 SNP on HbA1c (P=0.013) and glucose (P=0.43). These results are clearly not significant. The text needs to be modified throughout to reduce the emphasis on non-significant findings

2. It would be useful to include in the introduction/discussion a description of the known function of BNC2, SORCS1, GSC and WDR72. If these are unknown then that should be stated.

3. Can you justify why no correction of your P-value was conducted for multiple testing, as would be the accepted procedure

Minor comments

• Not clear what is meant by ‘repeated hemoglobin’ in the second line of the abstract
• Abstract: Last line of the ‘results’ section is vague and unclear what is meant
• Abstract and main text: last line of conclusion. Are you suggesting that all four SNPs should be studied in other type 2 diabetes populations. Your analysis does not provide any evident for an affect of the BCN2 or GSC SNP
• Methods: Although the study population characteristics have been described in other papers, it would be useful is some basic information could be included here. For example, age range, BMI range and how diabetes was defined
• Method, HUNT2 subjects and ethics’: not clear what the term ‘non-premeditated dropout rate from an extensive population based study’ means. This needs to be clarified in the text.
• MODY: put in acronym in full
• Results: Unclear what is meant by ‘The results did not change notably in view of other genetic models’ (not shown)
• You state in your discussion, that a strength of your study is that ‘your genotyping strategy is strong’. Can you clarify in the text what is meant by this. Also the meaning does not emerge from the final sentence of the discussion

Level of interest: An article of importance in its field

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’