Reviewer's report

Title: Association of an INSIG2 obesity allele with cardiovascular phenotypes is gender and age dependent: a retrospective cohort study

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Reviewer: Funda Orkunoglu-Suer

Reviewer's report:

This paper is of potential interest because of there are very few studies focused on the INSIG2 variant associated with CAD/MI patients, in a predominantly White population. This paper also found association with the INSIG2 variant and hypercholesterol in the young adult female subjects. However there are some revisions necessary;

Major revisions

1. Subjects section should include more information about study subjects (for example; total number, gender, age, and BMI, ethnicity, weight, smoking, hypertension, hypercholesterolemia, LDL, SBP, DBP, CAD event, drug treated etc.). Clinical characteristic and demographics of subjects may be summarized in a table. Sample details provided in the first paragraph of the results should placed in subjects.

2. All clinical parameters results (given in Table 3); other than significant ones should be indicated as negative findings in results section.

3. Were Nominal p values given significant remaining after multiple test correction? What was the significant p value after multiple test correction? Since there were 30 clinical parameters tested against genotype, the significant p value after correction should be decreased and indicated in results.

4. Given that there are few association studies of CAD with INSIG2 reported, the recent articles on this topic should be referred in the intro and discussed. Such as:

   Weidman et. all, Obesity 17, 1390–1395 (1 July 2009) |
   doi:10.1038/oby.2008.669 Lack of Association between a Common Polymorphism near the INSIG2 Gene and BMI, Myocardial Infarction, and Cardiovascular Risk Factors
   http://www.biomedcentral.com/1471-2350/10/56 Bresler J et al; which has INSIG2 genotyping within Coronary Artery Risk Development in Young Adults (CARDIA) Study and Atherosclerosis Risk in Communities (ARIC) Study cohorts

5. In the discussion it is stated that there was no association found between rs566605 with CAD/MI risk factors such as obesity, T2D, hypertension, hypercholesterolemia and smoking. Such factors included in this study should be defined in the materials and methods and the findings in results section as well.

Minor revisions
1. In the abstract method section should be included the name of the technique used such as; RT-PCR/TaqMan/allelic discrimination.

2. In the abstract obesity risk allele which is “C” in this case needs to be added in parenthesis.

3. Gene names should be Italicized such as; INSIG2

4. The version of the SDS software should be included in the genotyping section.

5. Diagnosis criteria used (such as MONICA? Or other guideline used), and exclusion criteria from the study should be given in subjects section.

6. As there is no control sample used, this should to be declared in subject section.

7. Genotypic data commonly ethnicity specific and therefore Table 1 and Table 2 should be merged and stratified by ethnicity. Genotype data in different ethnicities can be compared with HapMap and NCBI dBSNP databases and should be indicated in the results.

8. The p value after race in Table 3 needs to be clarified? (Was it for only Caucasian?)

9. The grant number is missing in acknowledgements (such as ;NHLBL-RO1XXXX)

10. In the discussion INSIG2 association with cholesterol should be discussed in detail. There is another study available in Korean population which can be support and should be discussed, and some supportive data in mice as well, please find below details.

   http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2759923/ (Association analyses of the INSIG2 polymorphism in the obesity and cholesterol levels of Korean populations)

   J Clin Endocrinol Metab. 2008 May; 93(5):1995-2001. Epub 2008 Mar 4. (A study with double-knockout mice in relation to both Insig1 and Insig2, where mice given a cholesterol-rich diet gained more weight compared to a control group)

11. In the third paragraph of the discussion the term “lower risk allele” is very poor use of this term. It should be clarified either the risk (C) or protective allele (G) associated with hypercholesterolemia in young adult females in predominantly white MI/CAD study cohort.

**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 have no competing interests.