Reviewer's report

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

**Version:** 1  **Date:** 15 March 2010

**Reviewer:** Paul Nyquist

**Reviewer's report:**

The authors are to be congratulated for engaging in the difficult task of examining the association of the SNP INSIG2 to atherosclerotic disease in the cohort of patient previously studies for coronary artery disease and PCI interventions. This is a retrospective study of a prospective study. It is not clear that the original study group is population based. The authors have found an association with the SNP and PAD in a group of males included in the study over the age of 65 (p=0.01) and stroke in a similar group of woman over the age of 65 (p=0.02).

The study is adequately titled. The manuscript is difficult to read and the reasoning for a number of steps in the manuscript is not clear. The author uses overly long and elaborate sentence structure. The article could be shortened into a more succinct form. In general the grammar and spelling are correct and appropriate.

**Methods:**

The data appear to be well contrived from a well executed clinical study. The PCR techniques appear to be appropriate. It is not clear if they looked at one or several SNPs. If so then a haplotype and linkage analysis would be required. The data were contained in an appropriate data base that was verified by the primary study.

**Compulsary revisions**

1) It is not clear what the primary aim of the original analysis was. It is presumed that the authors had chosen CAD as the original primary phenotype. The report of the secondary phenotypes of PAD and CV in different age and sex cohorts suggests that these results were obtained after many different analysis using different vascular phenotypes as the dependent variable. This can be appropriate but the issue of multiple comparisons as well as selection bias becomes important and must be addressed in the methods section. Additionally was this the only SNP for which associations where tested. If it was not this brings in the issue of more possible multiple comparisons issues. A traditional adjustment for the issue of multiple comparisons could use an adjusted Bonfferoni: dividing the significance threshold of 0.05 by the number of tests run. In this case running as little as 4 tests would have pushed these results above the level of significance which would be .0125 with an adjusted Bonfferoni..

2) The authors did a simple Chi square and did not do any logistic regression or multi-factorial analysis. It would have been important to control for sex, age,
HTN, diabetes and in this case BMI to control for confounding errors in the analysis. Controlling for these issues may have pushed the results into the significant range.

3) The authors did not describe whether the model they used was base on a dominant, codominant or recessive model. It appears the final assessment assumed codominance.

4) Did the authors address the issue of admixture and did they segregate their genetic analysis by race? It is not clear in the manuscript that this was done. If not then why not, and this should have a significant effect on the analysis. If this analysis was not done then it must before the article can be accepted.

5) Finally the authors state the population is in hardy Weinberg equilibrium. They state that this was done with a helix tree software package but not the markers used nor the technique. If their analysis included all racial subtypes it is not likely that they were in hardy Weinberg equilibrium. Did they use a sophisticated marker analysis?

Discussion/Conclusions:

The conclusions of the study are simply not supported by the methods as described. Although the p values stated are significant for regular case control studies they do not meet the level of significance required for a genetic study. The discussion is tangential and should focus on a few basic points. The weaknesses of the study. The body of work that supports or refutes the study. The next step in analysis. None of these issues are directly addressed in the discussion.

This manuscript needs major revisions before it can be accepted. The issues brought up in the methods section must addressed prior to resubmission.

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**

I declare that i have no competeing interests