Reviewer’s report

**Title:** A Genetic Variant of the Atrial Natriuretic Peptide Gene is Associated with Left Ventricular Hypertrophy in a Non-Diabetic Population - The Malmo Preventive Project Study

**Version:** 3  **Date:** 13 December 2012

**Reviewer:** Carolina Medina-Gomez

**Reviewer’s report:**

In this paper Juji# et al. shown an association of the polymorphism rs5068 with left ventricular hypertrophy after adjustment for sex and age which became borderline not significant after further adjustment systolic blood pressure, antihypertensive and/or cardioprotective treatment, body mass index and fasting plasma glucose in 968 non-diabetic individuals form the Malmo Preventive Project. The authors concluded that rs5068 might might affect susceptibility to left ventricular hypertrophy and support the possible protective role of natriuretic peptides.

This clearly written manuscript reports a well-designed effort seeking the understanding of the effect of a previously described variant associated with blood pressure in cardiomyopathy. Nevertheless, the statistical methods, results and discussion require further clarification.

**Major Compulsory Revisions:**

1. Genotype frequencies of rs5068 (for control and cases) as well as Hardy Weinberg equilibrium significance should be reported. Quality control steps for the genotyping should be specified in one sentence in the methods.

2. The authors show in tables 2 and 3 the results for the different models only for the genetic variant rs5068, which is the main predictor under study. Nonetheless, results from all variables included in the model would enrich the reported results as well as give stronger bases to some of the hypothesis stated on the discussion. I believe the inclusion and further discussion of OR/effect sizes as well as P values for the different variables included in model 1 and 2 for the two outcomes under study are of large importance and might bring opportunities to approach mediators/confounders. The phenotypic variance explained by each model in general and perhaps emphasizing on rs5086 ought to also be reported.

3. In the discussion there is little related to the results for LVM, although you fully describe possible bias introduced for the measurement.

**Minor Essential Revisions:**

1. In the discussion when the authors contrast their work with Ellis and co-workers, did they mean Cannone et al. (reference 14) or both?. In the article
from Cannone it is stated “…The analysis of left atrial volume, LV structure and function as determined by echocardiography (LV ejection fraction, LV dimensions, LV mass, and LV volume index) did not reveal any significant associations with the rs5068 genotype…”.

2. In the abstract and conclusion: “These findings suggest that rs5068, or genetic loci in linkage disequilibrium, might affect susceptibility to left ventricular hypertrophy and support the possible protective role of natriuretic peptides”. Could be better read by changing the word loci to variants.

Discretionary Revisions:

1. In order to prove if congestive heart failure impacts your results, authors could simply do a sensitivity analysis by excluding those four patients and comparing those results with the ones reported in the manuscript.

2. Based on MAF (which I suppose based on literature for the present study will be less than 0.1) and on the previous studies as those mentioned in references 14 and 15 would not the authors increase power using a dominant model?

3. In the statistical models tested, particularly for the logistic regression I would be cautious with multicollinearity between the variables included in the fully adjusted model and recommend you check for this type of issue.

4. Authors could report kappa statistic for inter-observer agreement to emphasize the low levels of subjectivity in the echocardiography reports.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:

I declare that I have no competing interests