Reviewer's report

Title: Epistatic study reveals two interactions involved in Blood Pressure genetic regulation

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Reviewer: Scott Williams

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This manuscript reports interesting analyses of the role that gene-gene interactions play in blood pressure. The results for epistasis are replicated and interestingly only one of the 9 SNPs that associates with BP is in the epistasis results, indicating different pathways for BP regulation.

Minor Essential Points:

1) Although the results are clearly presented for the most part, the methods could be better explained. Specifically, how many independent tests were performed – there were 100 SNPs in 65 genes but how many had LD \( r^2 > 0.8 \). The correction would indicate there are several.

2) How exactly were results compared to GWAS studies? Is it via imputation from GWAS data? This is not clear and this comparison may be of use.

3) Statements such as:

   “To our knowledge, no previous study has assessed the epistasis of cardiovascular candidate genes on BP regulation in European individuals.” should be removed especially since the paper cited below has such an interaction as does Rana et al 2007 Hypertension 49: 96-106.

4) Some of the writing is a bit hard to follow. Specific sentences that I had trouble with are:

   “may be responsible for BP defects modifying their plasma protein levels, whereas rs1800590 in LPL and rs2228570 in VDR, possibly functional, may act via altering protein structure.”

After reading the text I understand this but it should be rephrased.

Also:

“Our imputation analyses showed that any of these significant SNPs have been reported or were in LD \( r^2 < 80\% \) with genetic variants highlighted in previous GWAS [14, 15].” Do the authors mean many. If so then they should be specified.

5) Also, it would be useful to know how the differences in the discovery and replication data sets affect the results. For example, ages are quite different as are the male:female ratios. I am particularly interested to see if the sex makes a differences as it has been previously replicated in subjects of European descent that multiple SNP models may differ (e.g. Velez et al 2006 Am. J. Hypertension
19: 1278-85). Testing for interaction with gender may be revealing and then if significant may justify a stratified analysis.

6) The discussion is highly repetitive with the results. It might be of more use to expand on ideas of epistasis and how it can mask single gene effects. There are numerous papers discussing this in the genetics literature.

7) Finally, the argument that there is evidence for protein structure variants affecting BP or even regulation is a bit of a stretch as the SNPs chosen already exhibit bias.

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

**Quality of written English:** Needs some language corrections before being published

**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'