Reviewer's report

Title: Susceptible Gene of Stasis-Stagnation Constitution from Genome-Wide Association Study Related to Cardiovascular Disturbance and Possible Regulated Traditional Chinese Medicine

Version: 3 Date: 25 February 2015

Reviewer: Kyung-Won Hong

Reviewer's report:

This paper describe the possible genetic risk factors for the Yu-Zhi construction of traditional Chinese medicine (TCM), and they predict possible TCM for the PON2 which is a significant locus of the genome-wide association study.

Major comment

1. In the introduction, the authors listed the previous genetic reports such as Chen et al, Wang et al., Wu et al. Please include the results and discussion for the previously reported SNPs, candidate genes and the up and down regulated gene regions from the GWAS result.

2. Generally, GWAS studies used the highest SNP selection based on the adjusted p-values after controlling the confounding factors. But this paper selected the SNPs from unadjusted p-values and then they adjusted for the selected SNP only. Please check the other GWAS reports.

3. They should display the Manhattan plots and quantile-quantile plots for each genetic model test.

4. It is difficult to understand the rationale that they predict the PON2 protein structure and the TCM. Based on their GWAS results, the most significant SNP was rs8093481 located on the PIEZO2 gene region. Also, their finding of the exonic variant (rs7493) is the nonsynonymous SNP 'Ser311Cys' or 'Ser299Cys', but they discuss the His114 residue for the TCM target. They should explain the reason.

Minor comment

Page 3, Line 6: remove a redundant constitution from 'YZ constitution constitution'.

Page 3, Line 7: 'Whole genome Genotyping ..' should be changed to 'Genome-wide SNP genotypes were obtained using the Illumina HumanHap550 platform'

Page 4, Line 9 - : Please include the reference for the Huang Di Nei Jing textbook.
Page 4, Line 14: Please specify the SNP ID and HLA gene name, and describe the difference the allele frequencies.

Page 4, Line 17: Please include the explanation of the relationship between Yang-deficiency and Yu-Zhi.

Page 8, Line 17: Please describe the median score.

In the Method, Statistical Analysis section: include the statistics software used in this study for GWAS.

In Results, please include the individual numbers for each YZ group.

In table 2, please list the risk allele frequency, effect sizes and the most significant genetic model for each SNP.

In the supplementary materials, please include the questionnaire item.

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

**Quality of written English:** Acceptable

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

**Declaration of competing interests:**

I don’t have any competing interests.