Reviewer's report

Title: Performance of a blockwise approach in variable selection using linkage disequilibrium information

Version:3**Date:**10 December 2014

Reviewer number:2

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In the submitted manuscript, Dehman et al. propose a testing method for genome-wide association studies (GWAS), which can take advantage of linkage disequilibrium (LD) structure of SNPs. Their method computes LD blocks automatically, and then performs Group Lasso regression to seek LD blocks associated with the trait. I think the method is elegant. However, I am not yet convinced if the method can be useful for GWAS for the reasons listed below. I think these points need be addressed to publish the method as an alternative way to analyze GWAS.

Major Compulsory Revisions

1. The settings of simulation (section 3.1.1) is not realistic.

They assume the strength of association between a causal SNP and the trait to be $R2 = 0.2$, which is too strong. For most of the GWAS hits, $R2$ is below 0.01 (see http://www.genome.gov/gwastudies/). I think 0.01 or some smaller value should be used.

In addition, assuming all SNPs to have minor allele frequency 0.5 is not realistic.

2. The method does not provide study-wise p-value.

The authors mention this as a future direction of investigation (section 4). However, I think significance assessment is indispensable for practical use.

3. The computation time in realistic settings needs to be mentioned.

The smallest size would be 1000 individuals for 500,000 SNPs. Nowadays, people test around a few million SNPs imputed using 1000 Genomes Project data.

Minor Essential Revisions

4. Figure numbers are very confusing.

Some of the "left panels" and "right panels" seem to be renumbered as separate figures.

For example, "left panel of Figure 13" seems to be Figure 12.

Discretionary Revisions

5. I am interested to know if Group Lasso regression performs better than combining single-locus p-values in the LD block. One approach for combining p-values is GATES by Li et al. (2011) Am J Hum Genet 88:283.

6. To pursue SNPs with modest effect-size, it is now common to perform meta-analysis of GWAS. It would be nice to comment if the proposed method can be applied in meta-analysis setting.

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.