Reviewer’s report

Title: Gene ontology analysis of gene-gene interactions in two genome-wide association studies of sporadic ALS

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Reviewer: Kristel Van Steen

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The subject of the paper was to determine whether patterns of gene-gene interactions aggregate in specific functional groups as defined by GO. My main concern is that it is not straightforwardly clear how the proposed strategy really relates patterns of gene-gene interactions (whereas interactions have been assessed on the snp-level) to functional groups.

Other compulsory comments:

“This permutation-based approach to determining significance corrects for false-positives due to multiple testing. Permutation testing revealed a critical value of the MDR classification accuracy of 0.629 for the detection data and 0.640 for the replication data at a genome-wide #=0.05 significance level.”

The authors state that account is being given for the multiple testing problem. Can some more details be given? The permutation null distribution relates accuracy values that are obtained for the best model in all permutation replicates? Can you comment on the fact that this model may be different from one permutation data set to another?

“Each SNP was assigned a p-value based on its strongest interaction with the other SNPs.”

So the attached p-value to a SNP refers to the most striking evidence for that SNP pairing with another SNP, in whatever region or gene. Could you comment on the fact that the presence of strong main effects may induce spurious results and hence no genuine evidence for interaction? How does the presence of main effects (even though not extreme) affect the procedure?

“Phase 2/3”

Is it correct to say that the reasoning behind these phases is to identify genes of which components (i.e. SNPs) are highly interactive in some sense, hoping that these genes are most likely to be involved in pathways? It would be interesting to provide more intuition about the choices made in the strategy…

In addition, and related to this, what is the effect of window size (SNP-to-gene mapping) on the final results?

Level of interest: An article of limited interest
Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests: 
I declare I have no competing interests