Reviewer's report

Title: Pathway-Based Outlier Method Reveals Heterogeneous Genomic Structure of Autism in Blood Transcriptome

Version: 2 Date: 31 January 2013

Reviewer: Ke Hao

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RE: Pathway-Based Outlier Method Reveals Heterogeneous Genomic Structure of Autism in Blood Transcriptome

Malcolm G. Campbell and colleagues studied the blood gene expression of ASD and compared to controls. The novelty is that the authors looked at the deviation of the gene expression levels, instead of the shift of mean or median.

Major Compulsory Revisions
1. Blood transcriptome is studied, but how relevant is blood mRNA level to ASD. Is it causal or just reactions to the ASD conditions? For example, altered life style, nutrition and pathophysiology?
2. Did the authors quantify the various types of blood cells in the sample specimen? If not, will the difference found in term of mRNA levels simply reflects the cell count differences?

Minor Essential Revisions
1. Beyond the documented pathways in KEGG or other databases, did the authors also look at the co-expression modules defined by the study cohort itself?
2. Which data bases the three significant pathways were from?

Discretionary Revisions
1. Recent exome-seq studies revealed higher de novo mutation rate in ASD patients than normal controls. The authors could examine the genes that affected by such de novo SNVs and see if ASD subjects are enriched for outliers in these genes.

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