Reviewer's report

Title: Co-expression network of neural-differentiation genes shows specific pattern in schizophrenia

Version: 3 Date: 24 November 2014

Reviewer: Simone de Jong

Reviewer's report:

This paper by Maschietto et al. describes an effort to characterize genes differentially expressed during neuronal development exclusively in schizophrenia. I appreciate the approach of integrating several datasets and making use of publically available data. I feel that the results of different analyses (expression in cells, expression in brain bulk, methylation) could be tied together a bit better.

Major Compulsory Revisions

1. My biggest concern is sample size for the cell lines with only one patient and one control, and no replicates for each cell line. I am sure the authors are aware of this, however, I don’t see this issue in the discussion.

2. Abstract & Introduction: state the exact aim more clearly.

3. Methods/Results: clearly state how many probes (for each assay) are left for analysis after quality control.

4. Methods: the description of WGCNA branch cutting, preservation and module eigengene is a little bit confusing. Try to clarify a bit more.

5. Methods/Results: clearly state whether you’ve built the WGCNA network on all samples, or on CTRLs and you’ve tested preservation in SCZ.

6. Results: Why are so many genes upregulated in SCZ vs CTRL brain bulks, and so little downregulated? Additionally, would it make a difference to correct for technical variables (RIN, PMD etc).

7. Results: hiPSC vs NPC comparision, why are there so many more genes differentially expressed for controls than SCZ?

8. Results/Discussion: WGCNA results could be discussed in more detail by pinpointing hub genes and discussing their possible role.

9. Results/Discussion: The fact you are not finding much overlap between cell results and brain bulk results might stem from the fact that the genes you are testing are related to neurodevelopment, exclusive to SCZ but still neurodevelopment. This might not be reflected (anymore) in adulthood.
Minor Essential Revisions

1. Abstract ‘background’ section: remains uncovered? I think you mean the opposite.
2. Introduction, line 1: world-wild = world-wide?
3. Methods: sex chromosomes instead of sexual chromosomes
4. Methods: hyper-methylated (there is a d missing)
5. Methods: some occurrences of cortex have an ‘ on the o
6. Results: brain samples instead of brains samples
7. Results: the ranges, I am assuming they are log fold changes?
8. Discussion: use of SCZP, SZP, SZCP is confusing.
9. Discussion: First line is a strange statement.

Discretionary Revisions

1. I have not seen the use of hyper-represented before, in the field we mostly use overrepresented.
2. Keep in mind that even though the structural variation you’ve found in your cells doesn’t contain any of your genes of interest, it might still contain regulatory variants for important genes.
3. Consider making a diagram containing the different analysis steps you’ve performed and how they tie together.

Level of interest: An article of limited interest

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