Reviewer's report

Title: Overlap of Expression Quantitative Trait Loci (eQTL) in Human Brain and Blood

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Reviewer: Eske M Derks

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Review of BPS-D-13-01105

“Overlap of expression Quantitative Trait Loci (eQTL) in human brain and blood”

The authors investigate whether eQTLs (genomic regions which regulate RNA transcript expression levels” overlap in blood and brain tissue. This is an important question, since gene expression studies become increasingly important in the study of neuropsychiatric disorders. Yet little is known on whether gene expression levels assessed in blood is a reliable proxy for gene expression levels in the brain. The authors also compare gene expression levels between different brain areas. The manuscript is well written and the research questions important and well-described. I do have a number of questions/comments.

1) The degree of overlap between blood and brain was calculated by ascertaining if an qQTL identified in one study was also identified in the other study. Why did the authors use this approach, instead of, for example, comparison (correlating) effect sizes. The dichotomous distinction between presence/absence of an effect size may not be the most powerful approach? Can the direction of effect be different between studies? (i.e., the allele associated with increased gene expression levels in one study is associated with decreased gene expression levels in the other study?). The statistical power of the study will have a large influence on the number of eQTLs detected in a single study. Even though the authors controlled for that, would focusing on effect sizes be an alternative?

2) Disease status seems to be an important mediating factor and even though this is described as such in the limitations section I do wonder why the authors used a single sample of healthy controls as a blood comparison sample. The authors should state more explicitly that the lack of overlap between blood and brain may be explained by differences in disease status.

3) The authors may consider to read and cite the following paper: “Cai et al. BMC Genomics 2010, 11:589”. In this paper it is shown that conservation is stronger in “hub genes”, this is also related to my following comments (4)

4) The authors compare the overlap between eQTLs for all genes/probes. I think it would be informative to compare the overlap in brain vs. non-brain expressed genes etc. Also, what if there is no variation in the gene expression levels of a
particular probe in one or both tissue types? If there is no or very little variation, gene expression levels can not be significantly associated with an eQTL. So, if the authors would focus also on those probes which do show variation in both tissue types, would the overlap between blood and brain be higher? A related question, the authors conclude that gene expression levels in blood may in some instances be used as a proxy for gene expression levels in brain, can they provide more insight in the characteristics of a probe that predict whether there is good correspondence between tissue types?

5) The formula’s do not show correctly, probably due to conversion problems. Therefore, I did not understand formula’s 1 and 2

Minor comments
- Page 15, middle of the page, “high give” should be “high given”
- Table 1: one column is duplicated (column 2 and final column)
- Table 1: Header “Number if genes” should be “Number of genes”
- Table 2: Could the author include the total number of genes tested?
- Table 4: second column, fourth row, 16. should be 16.X?
- Supplementary Table 4: Header is placed before Figure 1 while table itself is placed after the Figure

Level of interest: An article of importance in its field

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 that I have no competing interests