Reviewer's report

Title: Psychosis candidate genes in the prefrontal cortex: Meta-analysis of gene expression microarray studies

Version: 2 Date: 6 October 2008

Reviewer: Lesley Jones

Reviewer's report:

This paper carries out a meta-analysis of a series of gene expression studies carried out on post-mortem brain samples from people with psychosis and controls. This is potentially very interesting. The authors claim that the meta-analysis increases the power of the studies to detect differentially expressed genes. This is likely to be the case but the analysis conducted here cannot be said to be a true meta-analysis and therefore these data are flawed. The problem is that individual samples must have been included more than once in the meta-analysis and no account seems to have been taken of this. The two sources of tissue used for arraying are the Array Consortium (AC) and the Neuropathology consortium (NPC). The AC has 105 individual brains and the NPC 60. Table 2 indicates that studies 1, 3, 5 and 7 used BA46 samples from the AC, and the studies used 81, 86, 73 and 81 samples respectively. Therefore there must be overlap in the samples used so effectively some of these samples are technical rather than biological replicates. In the analysis it appears that all samples have been given the same weight and there is no indication of the overlap between samples. Likewise the NPC has 55 individual brains and studies 2, 4 and 14 have used 55, 26 and 31 samples respectively. Here different brain areas have been
used so these are not
direct technical replicates but they are not direct biological replicates either. The
effect of the
individual in, for instance, genetic variation, is likely to be reflected in all brain
areas, but there will also be an effect of brain area on gene expression. Thus
there are two
levels of
ambiguity in the analysis here and a direct meta-analysis is not appropriate.
Given that the same
biological samples are replicated several times this might increase the
significance of real signals
but will also increase the significance of any false positive signals.
The QPCR has been carried out on the same samples so it is unlikely that it
would reflect anything
other than the results given from the arrays. If we believe the array results are
accurate for each
individual sample then indeed any other results would be unexpected.
It is possible that I have misinterpreted the paper and the samples were
independent but the
information provided indicates that they are.
When assessing the work, please consider the following points:

1. Is the question posed by the authors well defined?
   Yes

2. Are the methods appropriate and well described?
   Yes - the addition of an explanation of the correction factor for the
   non-independence of samples is an improvement

3. Are the data sound?
   Yes

4. Does the manuscript adhere to the relevant standards for reporting and data
deposition?
   N/a

5. Are the discussion and conclusions well balanced and adequately supported
by the data?
   Yes
6. Are limitations of the work clearly stated?
Yes - the amended discussion is much improved and points out a number of limitations not previously mentioned in detail

7. Do the authors clearly acknowledge any work upon which they are building, both published and unpublished?
Yes

8. Do the title and abstract accurately convey what has been found?
Yes

*Quality of written English: Acceptable*