Reviewer's report

Title: No Relationship between 2',3'-Cyclic Nucleotide 3'-Phosphodiesterase and Schizophrenia in the Chinese Han Population: an Expression Study and Meta-analysis

Version: 1 Date: 3 January 2009

Reviewer: Albert Wong

Reviewer's report:

The authors describe a genetic association analysis of five SNPs in the CNP gene in a relatively small schizophrenia case-control sample of Han Chinese, and a comparison of CNP mRNA levels in PBLs from the same subjects. The results basically show no differences in either dataset between schizophrenia patients and controls.

Major Compulsory Revisions:

1) There should be a brief review of the known function of the CNP gene and protein in relation to oligodendrocyte function and schizophrenia. In particular, the authors should present support for their hypothesis that genetic variation or altered expression levels of this gene can produce the clinical features of the disease. I.e. More mechanistic consideration of how changes at the genetic or transcription level for CNP are involved in the pathophysiology or etiology of schizophrenia.

2) I do not agree that the literature cited by the authors supports the notion that the CNP gene is "one of the most promising candidate genes for schizophrenia [abstract line 1 and background paragraph 2]." While the quoted statement is not precise (how many genes would be considered "most promising": 10 or 100?), the subjective tone is certainly strong, but in my opinion, overstated. For example, only one genetic linkage study pointing to the genomic region in which CNP is located is cited, without mention of the many other linkage studies that highlight other chromosomal regions being linked to schizophrenia. There are four cited post-mortem studies of altered CNP expression in schizophrenia, but no mention of the large body of post-mortem work on other altered transcript or protein levels in schizophrenia, nor a discussion of how prominent or obscure CNP is in genome-wide transcriptomic or proteomic screens (i.e. how does the change in CNP gene product compare with other genes?).

3) There is no power calculation. Especially with the small sample size, it is important to know the threshold at which this study might show statistically significant genetic associations. The failure to replicate previous genetic association results could stem from the low power of this study. In addition, there is only a cursory mention of the three papers considered for the meta-analysis, even though this current paper represents an attempt to replicate those results. Again, there is little discussion of what the genetic association data means in
terms of disease mechanisms.

4) The relationship between PBL and postmortem brain CNP mRNA levels is unclear, and not carefully discussed. Obviously PBLs are not myelinated, so what is the relevance of CNP mRNA measurements to brain disease?

5) The meta-analysis does not consider publication bias (e.g. funnel plot).

6) Given that the small number of previous genetic association reports of CNP and schizophrenia are negative in East Asian sample populations, what is the rationale for this study?

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Needs some language corrections before being published

**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.