Reviewer’s report

Title: The Estrogen Hypothesis of Schizophrenia Implicates Glucose Metabolism: Association study in three independent samples

Version: 1 Date: 14 December 2007

Reviewer: Jubao Duan

Reviewer’s report:

The authors aimed to test the hypothesis of association between estrogen pathway and schizophrenia and they bioinformatically selected a panel of 10 genes relevant to glucose metabolisms. They genotyped 185 SNPs in three independent case-control samples of Scandinavian origin (a total of 765 patients and 1274 control subjects). Among the 156 analyzed SNPs, 5 SNPs in three genes showed nominally significant association with disease (p<0.05). Rare haplotypes (frequency =3% in control) in ENO2 gene were found associated with decreased risk of schizophrenia. These genes have not been previously tested for association with schizophrenia. Overall, the paper is well written and the result has been accurately presented.

Comments for Minor essential revisions:

1. I would suggest that authors change the tone of their conclusion to a negative statement, i.e., no supportive evidence for the association with schizophrenia was found with the ten tested glucose metabolism genes. This is because (1) none of the associations could survive the correction for multiple testing; (2) The number of the SNPs showing p<0.05 (n=5) is even less than expected from testing 156 SNPs; and (3) the more significant haplotype in ENO2 is actually very rare, which may due to unreliable haplotyping.

2. HapMap release # should be mentioned: â##No or limited HapMap data were availableâ## seems not true in Phase II data (release #21a). Also, the most important parameter, r-2, for selecting tag SNP using tagger was not mentioned, is it 0.8 or else?

3. QC: what is call rate cut-off value for SNPs? In particularly the call rate for those SNPs that are nominally significant should be stated. Low genotyping call rate could confound the association in particularly when the association strength is weak.

4. Some QC metrics should be moved to method part, e.g., the part if â##Hardy-Weinberg proportionsâ## in result.

5. In page 5, result of single SNP association analysis: the sentence of â##Also, one SNP in each of the FBP1 and the PCK1 gene (table 3) showed association in the allelic comparisons with elevated risk for schizophrenia of the C alleles of...
both the rs4129219 and rs1040566 loci is not clear, I would change it to The C alleles of both rs4129219 and rs1040566 in each of the FBP1 and the PCK1 gene showed nominal association with elevated risk for schizophrenia (Table 3).

6. The authors aimed to provide a high coverage for the ten selected genes, however, in some of the genes there was only one tag SNP. Can the authors estimate the map coverage of their SNP panel (i.e., how many common HapMap Phase II SNPs can be tagged by the selected SNPs)? This can be done by using Tagger.

7. Page 11, English needs to be corrected in the sentence: Indeed, evidence form a resent study by Bahn and colleagues found elevated glucose levels in cerebrospinal fluid in drug-naïve patients that was normalize upon antipsychotic medication. Form (?) from, Resent? (recent), was (?) were, normalize (?) normalized.

8. Some references (38,39,40) seems redundant and they appeared inconsistent with the description in the main text:


What next?: Accept after minor essential revisions

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