Reviewer's report

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

**Version:** 1  **Date:** 10 December 2007

**Reviewer:** Frank Dudbridge

**Reviewer's report:**

This paper reports nominal associations of five SNPs in three genes, found in a candidate gene study of ten genes selected for their relationship to the estrogen hypothesis, differential expression and/or genetic linkage to schizophrenia.

None of the associations withstand correction for multiple testing, which is acknowledged by the authors. However the study was well conducted and reported, and these results may prove useful in a future meta-analysis. This report may therefore prove useful, and I have only a few minor questions to raise.

1. Selection of genes: how many genes involved in the estrogen pathway could have been excluded in step 1? I am particularly concerned that the linkage scans have been so inconclusive that step 1(b) is little more than a random filter.

2. Multiple testing: the authors were appropriately modest in their claims. However they might have tried to establish their hypothesis by combining evidence across genes. This could be done for example by counting the number of nominally significant genes, or using the truncated product of P-values methods. As it is, there is little reason to focus on the nominally associated genes rather than the rest. Put another way, why not report the full set of association tests, for future use in meta-analysis?

3. It's unclear why association tests were adjusted for confounding. No stratification was found between populations using Fst, and there is little reason to expect different allele frequencies between males/females. It would have been more powerful to perform a single unadjusted analysis, with secondary analyses looking for effect modification in different populations/genders.

4. Hardy-Weinberg testing: unclear why 8 markers out of (185-21) were excluded for HWE P<0.05, when this is exactly the number that would be expected by chance.

5. Could the authors comment on the power of their study, and otherwise why the sample sizes were what they were.

**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:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

I declare that I have no competing interests