Reviewer's report

Title: No evidence for association between polymorphisms in GRM3 and schizophrenia.

Version: 1 Date: 31 March 2005

Reviewer: Hiroki Shibata

Reviewer's report:

General
The authors claim the four previous studies reporting significant associations of GRM3 with schizophrenia were not well controlled for multiple tests and for genetic heterogeneity. Therefore they conducted an expanded follow-up study to test the association of GRM3 with schizophrenia by genotyping the same set of 7 SNPs as investigated in previous studies. They did not observed significant associations with the disease in any of the tests on alleles, genotypes and haplotypes. The authors conclude GRM3 should not be viewed as a susceptibility locus for schizophrenia. The question is very hot in the field and properly defined. The methods are sound, however some details in statistics are not clearly described as I pointed below (Minor Essential Revision #3). All the data are sound and well controlled. The discussion is missing an important issue of the discrepancy with one previous study as I pointed below (Major Compulsory Revision #1).

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Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)
1. It is not reasonable to attribute the discrepancy to genetic heterogeneity unless investigating the particular SNP, rs2299225 of which a significant association has been reported with schizophrenia in Chen et al 2005. At least the authors must argue about Chen et al 2005 in the discussion as well as the other three previous studies.
2. It is too much straightforward to make direct comparison of P values obtained by two different types of statistical tests. The current results were obtained by haplotyping of unrelated samples by the E-M algorithm and likelihood tests (probably, since the authors did not clearly state), while the results by Egan et al 2004 have been obtained by TDT through direct haplotyping of familial samples.
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Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)
1. The SNP names are inconsistent. For example, a SNP, "+1193C>T" is written as "snp5" in Table3. For simplicity, all the SNPs should be noted with dbSNP ID (rs number) as follows:
hCV2627921 into rs13242038
hCV11245618 into rs6465084
+1131C>T into rs228595
hCV2536213 into rs7804100
2. Page 4, line 18: "â€¦which has not been not genotypedâ€¦." The second "not" needs to be removed.
3. It is unclear how the authors tested haplotype associations with the disease. For example, while the total number of typed samples differ among the SNPs, the actual number of samples used in haplotyping is not clearly stated.
4. Page 7, line 8: The GOLD software generates graphical image using previously calculated LD values. However, it does not help to calculate D' or r^2. The authors must have used some other software for the calculation itself.
5. Page 8, line 5: Is "312" correct for the number of genotypes?? 46 multiplied by 7 makes 322.
6. Typo: Page 9 line 14: "h1V2627921" -> "hCV2627921". The same typo is also found in Table 1.
7. Typo: Page 10 line 11: "Bonferoni" -> "Bonferroni"
8. Tables must be retouched. Vertical lines in Table 1 and Table 2 should be removed. On the other hand, a few horizontal lines should be added to Table 3 for readers' convenience.
9. All the values in tables must be corrected based on the idea of significant figures. For example in Table 1, 0.06 and 0.6 should be written as 0.058 and 0.60, respectively, because all other values have two significant figures.
10. Table 1: The frequency of allele 1 of the last SNP, hCV2536213 should be 0.76, not 0.75.

Discretionary Revisions (which the author can choose to ignore)
While the PCP psychosis has been known from 1950's, I understand the first paper hypothesized "global" glutamate transmission dysfunction is Kim, Kornhuber, Schmid-Burgk and Hozmuller, NeuroscLett 20: 379-382 (1980).

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory 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

Declaration of competing interests:
I declare that I have no competing interests.