Reviewer's report

Title: Excess of transmission of the G allele of the -1438A/G polymorphism of the 5-HT2A receptor gene in patients with schizophrenia responsive to antipsychotics.

Version: 1 Date: 29 October 2007

Reviewer: Daniel J. Müller

Reviewer's report:

General
The study is well designed, the paper reads fluently, and the sample size is reasonable. The rationale to analyze the 5-HT2A polymorphism in patients treated with conventional antipsychotics (mainly haloperidol), however, remains weak. One would expect the DRD2 gene to be the target of first choice (see for example Schafer et al., 2001). The authors should perhaps explain as to why they have not targeted the DRD2 at first place or should seek to explain if there is a "biological" link between the 5-HT2A receptor and the DRD2 receptor. Once explained, the authors may come to the simple conclusion, that the 5-HT2A receptor polymorphism (-1438A/G) is (for unknown reasons) associated with a type of schizophrenia that respond differentially to antipsychotics.

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Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

By explaining the limitation of their study the authors must acknowledge that the sub-sample of responders (n = 38) is very small and that only 23 subjects entered the TDT analysis (17 transmitted G-Allele vs. only 6 untransmitted G-Allele). This may well represent a spurious association and the p-value of .02 is not indicative for a 'high' significance.

The "May and Dencker scale" may be explained a in more detail, as this scale is not widely used in clinical practice. This and the fact that the scale appears to represent only a rough estimate of responders as well as for the retrospective nature of assessment, is another limitation that should be addressed.

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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)

The abstract should provide some numbers regarding the TDT (50:38, 17:6 etc.) as well as the p-value (.02)

The authors may wish to mention that the 5-HT2A polymorphism is (if at all) conferring only a small proportion of the variance observed in antipsychotic
response and that the clinical applicability will depend on many other genes.

Discretionary Revisions (which the author can choose to ignore)

The notion that the 5-HT2A is on chromosome 13q14.2 and that this region is linked to schizophrenia may be misleading, if is not mentioned, that case-control studies were predominantly negative for the 5-HT2A gene.

**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, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests.