Reviewer's report

**Title:** No Association Between the Sigma Receptor Type 1 Gene and Schizophrenia, Results of Analysis and Meta-analysis

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**Reviewer:** Erik Jönsson

**Level of interest:** A paper of considerable general medical or scientific interest

**Advice on publication:** Accept after discretionary revisions

The authors have tried to replicate a previous study reporting association between a sigma receptor type I gene (SIGMAR1) haplotype and schizophrenia. The two previous reports analysing this gene variant in schizophrenia were performed in Japanese subjects as was the present study. The authors searched for additional polymorphisms in the 5'-end as well as the exons but could not detect any variants except those previously reported (G-241T/C-240T and Gln2Pro). These two variants were in perfect linkage equilibrium. This result was also in accordance with the previous reports among Japanese subjects. However, in contrast to previous results the present study displayed an almost equal case-control distribution between patients and controls. When schizophrenic subjects were categorised in clinical subgroups (hebephrenia or paranoid schizophrenia) and compared versus control subjects there were still no significant differences. When subjects from all three studies were pooled, there was no longer any formal evidence of genotype or allele differences between patients or controls, although the difference was at a trend level (p=0.06) with regard to allele comparisons.

The gene investigated is a reasonable candidate gene of schizophrenia. The replication effort is performed in the same population and has a reasonable power to detect the previous reported association. The authors also report all previous reports and perform analysis on pooled data. However, the manuscript would benefit from some modifications.

**COMPULSORY REVISIONS**

1. Subheading "DNA Samples" should be changed to "Subjects".
2. The method of mutation screening should be more detailed.
3. In the Statistical Analysis section the authors should write that they used chi square tests (not
Fisher's exact tests) in the genotype and allele comparisons between cases and controls, because they report chi square results in the results section.

4. The meta-analysis was performed by simply pooling the raw results from the three studies. As the subjects are all of Japanese origin, with similar allele frequencies, and as there are roughly equal number of cases and controls, this may be reasonable in this case. (I applied the method of Woolf and obtained similar results; total OR 1.26, 95% CI 0.99-1.36, pooled chi square = 3.41, df=1, p>0.05, no evidence of heterogeneity). One may argue that a more sophisticated approach of performing the meta-analysis, taking unequal case-control numbers in different studies, etc, into account, may be more appropriate. However, as it would end in similar results the matter is of less importance in this particular case. In any case the authors should indicate in the methods section how their meta-analysis was performed.

5. In the Statistical Analysis section the authors should give the methods used for power estimation. It is not possible to evaluate the author's power estimation without the description of the method used. I suggest that the authors should give the power of the present study to detect the allele differences obtained in the first study claiming this association. (Given the authors' tables, using the method of Cohen the effect size (w) for detecting allele differences in the study of Ishiguro et al was about 0.11. This would give the present study a power of about 0.87 when alfa is 0.05 to detect allele differences. However, for a similar low effect size the present study would only have a power of about 0.50 for the genotype comparisons.)

6. As the pooled results of all studies just fell short of formal significance (p=0.06), i.e. a borderline result, the authors should be more careful with their conclusions. A new study, even a small one, may tip the evidence in favour of association again. Thus, the almost significant meta-analysis regarding allele distribution render a softer conclusion. This should be indicated both in the Abstract, Discussion and Conclusion sections.

7. I also suggest that the authors discuss the different results in the present versus the previous studies. Even if the study by Ohara et al (2000) did not report significant differences, their allele distribution was almost identical with the study of Ishiguro et al (1998), suggesting lack of power of tc detect significant differences in the study of Ohara et al (2000). Thus, the present results are different compared to the two other studies, which should be commented upon.

DISCRETIONARY REVISIONS

8. I would suggest that the authors divide the "Results and Discussion" section into two separate sections ("Results" and "Discussion", respectively).

9. Methods section: who were the two psychiatrists that performed the diagnoses? Are they among the authors? If so, it would be reasonable to describe their contributions in the section "Authors' contributions".

10. There are some minor spelling errors, e.g. in table 2, second column, third line is written "Contro", should be "Control". I also suggest that the title should use a colon(;) instead of a comma (,) between the two parts of the sentence.

Competing interests:

None declared.