Reviewer's report

Title: Association and Interaction of the MAOA Promoter uVNTR Polymorphism with Suicide Attempts in Patients with Major Depressive Disorder

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Reviewer: Hiroshi Kunugi

Reviewer's report:

This study examined the possible association of the MAOA uVNTR polymorphism and suicide behavior. The authors obtained some significant differences in the frequency of genotype groups defined by them. The data are valuable; however, I had several concerns in the study, in particular, the statistical analysis and conclusions drawn by the methods.

Comments

1. Is there any evidence in terms of transcriptional activity showing that the 2 repeat (R) allele and the 5 R allele should be grouped together with the 3 R allele and the 4 R allele, respectively in the analysis? If there is no such evidence, the authors should exclude individuals who carried either the 2R or 5R allele from the analysis because they were very rare. (Major Compulsory Revision)

2. In table 1, allele frequencies of female and total subjects should also be described.
   (Minor Essential Revision)

3. In table 1, numbers of recruited subjects (N) were different from the numbers of genotyped subjects (n). I feel that the authors should describe only individuals with genotype from the Sample collection part on page 6 to avoid confusion.
   (Minor Essential Revision)

4. A possibly major problem of the statistical analysis is the dichotomization of genotypes L7-9P10), i.e., the authors defined the “high activity group” as male carriers of the long form variants and female homozygotes for the long-form variants and the low activity as their counterparts. I feel skeptical about the validity of such dichotomization. Is there any scientific rationale and evidence for such dichotomization? The authors analyzed the data based on the dichotomization and obtained peculiar results; only female community suicide attempters showed smaller frequency (62.3%) of carriers of short-form alleles, yielding “significant” differences between the group and the other groups. Consequently, the main results were such that the MAOA long-form variant was associated with increased vulnerability to suicide in the general population, whilst in MDD subjects, suicidal behavior was associated with the MAOA short-form variant. I think such conclusions are incoherent and invalid as well because they were derived from the genotype data that may have happened to be unusually low in the female suicide attempters from the community (N=only 38; the smallest
group). In modern behavioral genetics, one should not draw any conclusion from such a small sample size. (Major Compulsory Revision)

5. According to my calculation, there seems to be a significant difference between female comm-suic group and female MDD group (p=0.002 instead of p=0.854) (Table 2). (Major Compulsory Revision)

6. Concerning MAOA gene on the X chromosome, the gene dose is different between males and females. And there are several sex differences in clinical depression and suicide behavior. Therefore, to be robust, the authors should analyze the data men and women separately. If the authors do so, there appear clear and simple results; the R4 allele was significantly more common in MDD and suicide attempters in men while there was no such association in women. This might be the main conclusion of the study. Since the R4 allele is associated with increased transcriptional activity, this result is biologically reasonable. (Major Compulsory Revision)

7. It is unlikely that individuals who had less anxiety are at risk for suicide attempt, suggesting that the model used in the study was something unfit with the reality. (Major Compulsory Revision)

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

Quality of written English: Needs some language corrections before being published

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.