Reviewer’s report

Title: Functional serotonin transporter gene polymorphisms and anxiety personality traits: new study and meta-analysis on a psychiatrically healthy population.

Version: 1 Date: 3 September 2010

Reviewer: Scott Stoltenberg

Reviewer’s report:

In this manuscript, Minelli, et al., report the results of two studies. The first is a candidate gene association study with two functional polymorphisms in the serotonin transporter promoter (5-HTTLPR and rs25531) and anxiety related personality traits as measured by the Harm avoidance (HA) scale of the TCI in 287 Italian adults (59% women). The results of this study suggest that the association between the 5-HTTLPR S allele and increased HA is observed only in individuals with lifetime Axis I disorders, but not in healthy individuals without such diagnosis. The manuscript then reports a meta-analysis of 35 studies that examined associations between 5-HTTLPR and either HA or the personality trait of neuroticism (N). This meta-analysis was intended to either confirm or disconfirm the finding of their earlier analysis that the association of 5-HTTLPR S and elevated HA or N would only be found in samples that did not screen for psychiatric disorders. The results of the meta-analysis confirmed that the 5-HTTLPR association with HA or N was not observed when only studies that screened for psychiatric disorders.

The interpretation of these results was that psychiatric screening is needed in genetic association studies of personality traits to eliminate the potential confound of diagnosis. The study results were also interpreted to support that the S allele of 5-HTTLPR is a risk factor for depression/anxiety spectrum disorders, but not for HA or N in healthy populations.

I found the manuscript to be quite interesting, but I also found that it was not very user friendly, but required significant effort. I am not qualified to provide a detailed critique of the meta-analysis, so I will confine my comments to the association testing. Specific issues are raised below.

Major compulsory revisions:

1. The quality of the written English throughout the manuscript needs to be improved. For example, in the results section of the abstract there are two errors:
"we loosed" should read "we lost" and "whatever" should read "whenever". Mistakes like these are found throughout the manuscript.

2. Although I am supportive of brief papers, but it seems that this story is too complicated to present in brief. I found it difficult to follow the arc of the narrative at times. In addition, there are opportunities missed for this manuscript to make explicit connections with the empirical literature and to address important issues in the role of 5-HTTLPR in normal and disordered behavior. How do these findings fit with the understanding of the function of S and L alleles? How do these findings contribute to our understanding of the nature of personality traits and mental illness? Are depression and anxiety disorders qualitatively different from normal variation in anxiety and neuroticism?

3. Issues regarding the statistical power to detect effects need to be explicitly addressed. The authors need to demonstrate conclusively that the loss of the association when the disordered subjects are removed is not a function of reduced statistical power.

4. The potential impact of gender needs to be addressed. Gender was included as an independent variable in the analyses, but no gender results are reported.

5. In general, the Discussion section needs to be more thorough in its efforts to interpret these results and put them in to context.

Minor Essential Revisions:
1. The title should be more informative as to the specific markers assessed and to the results.

2. Essentially, the reported effect can be discussed as a case of moderation. In other words, Axis I diagnosis moderates the association between 5-HTTLPR and HA. Such an interpretation needs to be more thoroughly explored in the discussion. What does this study contribute to knowledge about the relations among 5-HTTLPR, HA and diagnosis?

3. How do these findings fit in with the literature on GxE interactions (5-HTTLPR x life stress) in the etiology of depression?

4. It is not clear to me that all of the statistical analyses are necessary for the 5-HTTLPR HA association test. Why not just a single ANOVA and post-hoc test of interaction effects? Why do the subsequent ANCOVA reported in the 2nd paragraph of the results?

5. Error bars (s.e.) should be included on figure 1.

6. What do these results say about the influence of rs25531?

7. It would be useful to see the ANOVA tables and the effect sizes (i.e. proportion of variance explained) should be provided.

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:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**

I declare that I have no competing interests.