Author's response to reviews

Title: Association of 5HTR2A gene with suicidal behavior: Case-control study and updated meta-analysis.

Authors:

Thelma Gonzalez (thelma.glez.castro@gmail.com)
Carlos Tovilla (alfonso_tovillaz@yahoo.com.mx)
Isela Juarez (iselajua22@yahoo.com.mx)
Sherezada Pool (shepoga70@hotmail.com)
Martha Velazquez (patvel_7@hotmail.com)
Alma Genis (genis76@yahoo.com)
Humberto Nicolini (nicolini_humberto@yahoo.com)
Lilia Lopez (dralilialonar@yahoo.com.mx)

Version: 4 Date: 19 December 2012

Author's response to reviews: see over
Dr. Laura Mandelli  
Editor of BMC Psychiatry

Dear Mandelli

Attached please find the revised version of the manuscript MS: 1707516807818482 entitled: “Association of the 5HTR2A gene with suicidal behavior: Case-control study and updated meta-analysis” by González Thelma et al. that we are re-submitting for publication in BMC Psychiatry.

In addition, we have made the corrections according to the reviewers’ suggestions as follows:

Reviewer #1: (Clement Zai)  
Major Compulsory Revisions

1. Methods page 4 case-control study: Mexican ethnicity itself is heterogeneous with African, Native American, and European admixture, even if the subjects were recruited from one state. The authors must address this point. We agree. In consequence, we have extended the information (page 4, paragraph 1, lines 12-13).

2. Methods page 4 Clinical evaluation: The findings of this study could have been confounded by the underlying psychiatric illness of the case population, especially when the authors are comparing them to healthy controls. The authors must acknowledge this point. We have modified this point in the Methods section to state clearly the clinical evaluation of the study; besides we have rearranged the information to make it easier for the readers. (pages 4, paragraph 4, lines 20-22 and pages 5, paragraph 1, lines 1-2).

3. Methods page 5 Statistical analysis: What are the other parameters for power analysis (minor allele frequency, model, effect size observed here must be specified)? We have added the other parameters to measure the power analysis in the study (page 5, paragraph 3, lines 16-17).

4. I am not sure if there is a problem with file conversion or typographical errors. There are numerous problems with Tables 1 and 2. Please double check.  
We have double checked. Tables 1 and 2 have been corrected.

Minor Essential Revisions:
1. Abstract: The authors should keep the marker ID and comparisons (ex., T versus C) consistent. We coincide. Therefore, we have added the comparisons in the Abstract section. (page 2, paragraph 2, lines 7-9).

2. Introduction: The authors should include references on observed alterations in 5HIAA levels in suicidal subjects. We have included in the Background section the early findings in relation to suicidal behavior (page 3, paragraph 1, lines 3-5).

3. Methods page 5 Genotype assays: What does “FL” stand for? We have corrected this part and added the meaning of FL (page 5, paragraph 2, lines 7-8).

4. The authors should describe briefly the criteria for meta-analysis. Moreover, the authors should attempt to run the meta-analysis on suicide attempt only, or suicide attempt in schizophrenia only to see if a more homogeneous phenotype would give better results. Also, the authors should not be removing studies from the meta-analysis based only on the effect on heterogeneity. We agree. In consequence, we performed an analysis that solely included suicide attempters with schizophrenia (page 9, paragraph 2, lines 11-13).

5. The authors should explore other variants in HTR2A. We agree. This is a possibility for future studies.

Reviewer #2: (Marcus Sokolowski)
Major Compulsory Revision
1. Background: "Recently, several lines of evidence have suggested that altered serotonergic neural transmission is involved in the pathogenesis of suicidal behavior [3, 4]." This suggestion is not "recent", studies have suggested a role for serotonin since at least the 1980s. We have added a part in the Background section dealing with the early findings of suicidal behavior (page 3, paragraph 1, lines 3-5).

2. Background: "more than 200 SNPs along the gene have been identified [10, 12]. However, only a small number of SNPs have so far been investigated as candidates for suicidal behavior." A recent publication "Ben-Efraim YJ, Wasserman D, Wasserman J, Sokolowski M. 2012. Mol Psych." investigated all SNPs HTR2A in relation to suicide attempts, which should be of interest to reference here. We agree. We have included in the Background section this publication that studies all SNPs in 5HTR2A in relation to this point (page 3, paragraph 2, lines 15-17).

3. Methods, Clinical evaluation: "Following the reports in the literature, we defined suicide attempt as a self-harm behavior with at least some intent to end one’s life." Can this definition of the suicide attempt be described more specifically, or is this whole definition that was used? We have extended the
information. We added in the Clinical evaluation section a scale that we used to define suicide attempt (pages 4, paragraph 4, lines 20-22 and pages 5, paragraph 1, lines 1-2).

4. Discussion: Add to the discussion other aspects raised in "Ben-Efraim YJ, Wasserman D, Wasserman J, Sokolowski M. 2012. Mol Psych.", as to why no association is found in meta-analysis, e.g. possible roles of different genetic inheritance models, epigenetics and/or GxEs. We coincide. As a result, we have addressed this point in the Discussion section (page 11, paragraph 2, lines 16-18).

5. For limitations, another one could be that the e.g. cases used in the current study seem not very well defined, neither for their "suicidal behavior" per se or other suicide-related psychopathologies or covariates, e.g. "DSM-IV Axis-I and II diagnoses" mentioned in the Methods section are not described. Also, the drawbacks of case-control designs may be of interest to mention. We agree. In consequence, we have modified the part concerning the limitations in our study (page 11, paragraph 3, line 24).

Editors comment:- As associated Editor, I think that this paper would represent a valuable contribution, but I do agree with the reviewers that major weak points are present. In particular, I stress the point raised by reviewer nr. 1: it is not proper to remove studies from the meta-analysis only on the basis on their effect on heterogeneity. Sub-analysis on alleles or Caucasian/Asian only may be useful, but the approach based on meta-regression (that allow to control for moderators) on study effect size is more consistent. Authors may also control for other potential confounders, such as psychiatric diagnosis, gender/age differences across samples and so on, which could affect heterogeneity across studies. Moreover, I suggest to discuss in more detail the observed low frequency of the TT genotype (around 5% in the whole sample) and T allele (around 27%) in the Mexican sample, which are extremely lower than that observed in other populations (e.g. TT in Caucasians: around 22%, in Asians: around 27%; African: around 12%). This may be a point of interest. We agree. In consequence, we performed an analysis using only studies on suicide attempters with schizophrenia. (page 9, paragraph 2, lines 11-13). We have also added some comments on the frequency of the TT genotype in the Discussion section (page 9, paragraph 1-5).

Sincerely yours,

Dr. Carlos Tovilla Zárate