Author's response to reviews

Title: Serotonin transporter gene polymorphism is associated with functional dyspepsia: a case control study

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Author's response to reviews: see over
March 11, 2011

Dear the Editor,

Thank you for handling our manuscript (MS: 4814861213084556) “Serotonin transporter gene polymorphism is associated with functional dyspepsia: a case control study” and for the opportunity to revise it. We have responded to the reviewers’ comments and criticisms and have provided a point-by-point response. Please find the edited revised points by red ink. We hope that you will now find the manuscript suitable for publication in BMC Medical Genetics. Thank you for your time and attention in the handling of our manuscript.

Sincerely,

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Responses to Comments from Reviewer #1: Beate Niesler

1. My main criticism represents the poor writing style in terms of terminology concerning molecular genetics. Terms are often used incorrectly or are inappropriate. Most importantly, the term ‘SERT’ used as gene name has to be replaced by SLC6A4 which is the actual gene name according to GenBank. The terms for the gene, the protein as well as the analysed polymorphism are mixed up and should be used correctly depending on the respective context. Consequently, the text needs critical proof reading and correction. I strongly recommend revision of the manuscript with the support of experts of the genetics field.

We apologized for the inappropriate usage of the terms. We have now corrected the inappropriate terms as follows throughout the text. “serotonin” to “5-HT”, “SERT gene” to “SLC6A4”, and “44-bp insertion/deletion in the 5'-flanking promoter region” to “5-HT transporter gene linked polymorphic lesion (5-HTTLPR)”.

We have also changed the gene names in italics.

2. In the background section of their abstract the authors state that they ‘clarified’ the relationship between the serotonin receptor gene polymorphism and FD. At best they addressed this topic and report on first preliminary results. This holds true throughout the manuscript. The authors highly overrated their results and should discuss their data more carefully taking also most recent publications in the field into account.

We apologized for the overstatement. We agree with the reviewer’s opinion. We have now deleted the data of PDS exclude EPS subject and correct the overstatement (Page 2, lines 10-11)(Page 10, lines 3-6). We have also added a recent publication which showed that the amount of SERT mRNA was not affected in pediatric age FD patients (Faure C et al. Gastroenterology. 2010;139:249-58.) (Page 9, lines 5-7).

3. The major weakness of the data is caused by the fact that the authors did not correct for multiple testing of their data and did not even address this problematic in the manuscript.

Thank you for your comments. As the reviewer pointed out, there is a possibility of false positive findings by multiple testing. To avoid the risk of false positive findings, we have deleted the data of PDS excluding EPS from the table. We have also addressed the possibility of false positive findings (type I error) in the Discussion section (Page 10, lines 3-6).

4. Taking the small sample size of patients and the number of tests into account, the authors are dealing with a low statistical power and very high risk for false positive findings. Therefore, correction of the p-values for multiple testing is essential. At the end, none of the associations would withstand correction.

Thank you for your comments. As the reviewer pointed out, there is a possibility of false positive findings by multiple testing. Therefore, as mentioned query 3, we have deleted the data of PDS excluding EPS from the table.

5. The authors should therefore state this problematic more clearly in the
manuscript and also discuss this possibility. It is mandatory to call the
association nominally associated and to take the possibility of false
positive findings into account.
Thank you for your comments. We have now clearly stated the limitation of the
present study and the possibility of false positivity (Page 9, lines 2-3) (Page 10,
lines 3-6).

6. In the text as well as in the tables p-values AND odds ratios plus
confidence intervals should be included.
We are sorry for the incomplete statements in the text. We have added the
p-values.(Page 2, lines16,19) (Page 8, lines22,24)

7. In general, the gene names have to be written in italics.
We are sorry for the inappropriate word style. We have corrected the gene
names in italic.

Responses to Comments from Reviewer #2: Takashi Joh

1. page 1, line 4; Matsumoto4 # Matsumoto3 ?
We are sorry for the careless miss labeling. We have corrected the affiliation
number.

2. * should be inserted in Table 2 in the case of significance.
We directly stated $P$-values in Table 2 and it is stated that “$P < 0.05$ was
considered significant.” in the Methods section. Therefore, we think it is not
necessary to put the marks in the Table.

3. It’s better to demonstrate the data of EPS excluding PDS, which
highlight the one of PDS excluding EPS.
Thank you for your comments. We did the calculation as below. However, the
power is very low (21%). Therefore, as suggested by the Reviewer #1, we do not
show the data of EPS excluding PDS in the manuscript and also erased the data
with low power (the data of PDS excluding EPS).
<table>
<thead>
<tr>
<th>5-HTTLPR genotype</th>
<th>OR</th>
<th>(95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>SS</td>
<td>1</td>
<td>reference</td>
<td></td>
</tr>
<tr>
<td>SL</td>
<td>0.37</td>
<td>(0.05-2.96)</td>
<td>0.346</td>
</tr>
<tr>
<td>LL</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recessive model</th>
<th>OR</th>
<th>(95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>SS vs. SL+LL</td>
<td>0.32</td>
<td>(0.04-2.54)</td>
<td>0.278</td>
</tr>
</tbody>
</table>

*Twenty eight subjects are simultaneously classified EPS and PDS phenotype.

FD, functional dyspepsia; EPS, epigastric pain syndrome; PDS, postprandial distress syndrome; OR, sex- and age-adjusted odds ratio, vs. 646 controls, by a multiple logistic regression model; CI, confidence interval.