Author’s response to reviews

Title: SIRT1 (rs3740051) role in pituitary adenoma development

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Author’s response to reviews:

Dear Reviewer,

We kindly appreciate the revision of our manuscript. We have enclosed the original manuscript marked with all the changes made during the revision process (red highlight). We hope that the revised manuscript will be acceptable for publication in your journal. Please find our point-by-point response to the comments raised by the reviewer.

Answers to the reviewer’s comments:

GENERAL COMMENTS: The revised manuscript has been improved and table data and results are more clearly. However, majors issues have not yet been solved. Additional files were not available in the attached file and could not be checked.

• All additional files were attached as supplementary materials.

REQUESTED REVISIONS:

Majors:

1- The association of recurrence and SIRT1 SNPs should be interpreted with caution. The authors referred recurrence in some (n=30) patients that was classified according to re-surgery. However, the majority of cases are PRLomas whose first line of treatment is the medical and not surgical approach (or, in this series, the majority of PRLomas were surgically treated?). In addition, no mention about follow-up is provided and we know that PA recurrence could occur between 1-5 years after surgery. These points need to be clarified (time of follow-up and the criteria for tumor recurrence in active PA) and discussed in the text.

•More information was added:

Activeness and recurrence evaluation
The analysis of all pituitary adenomas was based on histopathological findings of PA and hormone levels in the blood serum before surgery. All 142 subjects were categorized into two groups – active and inactive PA. The active PA group was not divided into smaller subgroups by increase of specific hormone because dominant tumours were prolactinomas, while others would not make sufficient numbers for the study. Since some of the 142 subjects had already had surgery in recent years, we categorized them by recurrence of pituitary adenoma into two groups – PA with and without recurrence.

Patients before medical or surgical treatment who were newly diagnosed with PA or came for follow-up with PAs diagnosis to the Department of Neurosurgery were included in the study which lasted for five years and was financed by the Research Council of Lithuania (grant no. MIP 008/2014). Pituitary adenoma recurrence was diagnosed when enlargement of a residual tumor or a new growth was documented on follow-up MRI after surgical resection during the period of this study. The residual tumor was considered stable if there no signs of tumor progression on follow-up MRI. Most of prolactinomas were surgically treated because of remaining pressure effects of surrounding structures or because of ineffective medical treatment.

2- No data about the risk of recurrence and invasiveness by genotype (hazard ratio) was presented. This evaluation should be performed and the results included in Table 3 and 4.

- Odds ratios were evaluated under the codominant and additive genetic models and included in Tables 3 and 4.

- What is the size effect of the SNP rs3740051-12778366 haplotype in the occurrence of PA since the rs12778366 alone was previously associated with the PA occurrence? (I mean, is the odds ratio greater?).

The odds ratios were greater in the previous analysis of rs12778366 in PA development.

Minors:

- Corrections were made for all these minor comments and highlighted in red in manuscript.

1- Standardize: always use capital (preferred) or lower letter for P value.

2 -P1, Line 41: "6.7 %, 86.7 %, p=0.022)" lack the word respectively "6.7 %, 86.7 %, respectively, P=0.022)".

3- Standardize: use always "G/A" for the heterozygous genotype.

4- P1, Line 75: "Sir2" rather than "SIR2".

5- P5, Line 101. If the difference is no statistically significant, the P is > or = 0.05 and not < was referred.

6- P5 Line 103, the phrase "The detailed methodology about invasiveness evaluation has been described previously (28)." Is not necessary, since a detailed description is provided.

7 - P5 Line 104: Standardize: "MRI" rather than "MR".
8- P8, Line 126. More information about recurrence should be provided. See major concern 1.

9- P11-Line 230: Correct the phrase: "The frequency of genotypes and alleles of rs3740051 in patients with PA and control subjects by PA recurrence", no control subjects was compared in this analysis.

10- P14, Line 293-294. Table 6 is unnecessary. This results could be easily presented in the text.

Reply to reviewer is attached as supplementary file.