Author's response to reviews

Title: Glutathione S-Transferase omega 1 variation does not influence age at onset of Huntington's disease

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PDF covering letter
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Dear Editor:

Herewith we resubmit the completely revised version of our manuscript: 
Glutathione S-Transferase omega 1 variation does not influence age at onset of Huntington's disease (MS: 1969901163278017). All comments of the referees and your editorial remarks have been taken into account as far as possible (see accompanying page). We guarantee the accuracy of our bibliographic references. We hope that you will find everything in order for rapid acceptance and publication. Enclosed please find the comments addressing the points of the referees and your editorial statements point by point.

Thank you and your referees for reviewing the manuscript. We look forward to learning about your decision as soon as possible.

Best regards
Sincerely

Larissa Arning
Jörg T. Epplen
Major Compulsory Revisions

Ad comment 1:

Statistical analyses: The authors present crude analyses relating glutathione S-transferase polymorphisms to age of onset (AO) of HD. It is established that AO is influenced by the size of CAG repeat and we have recently demonstrated normal and expanded CAG repeats interact to influence AO. Thus, it is important in any association study of AO to account for repeat size. One way of achieving this is to use analysis of covariance to estimate adjusted means of age of onset (adjusted for CAG repeat size and perhaps normal repeat and their interaction) and evaluate whether these means differ by GSTO genotypes. The statistical methods utilized in the manuscript should be clearly indicated in the text.

We complemented the statistical analyses as suggested and indicated the methods used in the text.

Ad comment 2:

The best fit of association between AO and repeat size is log-linear. I would recommend the use of log-transformed AO in the regression model instead of crude AO and present geometric means.

Since the relationship between CAG repeat number on the HD causing chromosome (in our case the small range of CAG repeat lengths between 41 – 45) and age of onset of disease is linear, the use of log-transformed AO is not mandatory.

Ad comment 3:

The number of HD patients described in the methods (n=232) is different from that reported on the figure 1a/b (n=143) and no explanation is provided. The authors should explain what happens to the other 89 HD subjects not included in the graph.

From the total number of 232 HD patients, the AO is only ascertained for 143 as indicated in the text.

Add comment 4:
The conclusion is missing. After the discussion, a brief conclusion should reiterate the lack of an association between GSTO and AO.

A conclusion has been added.

Minor Essential Revisions

Ad comment 1:

Figure 1: label used on the x-axis is not defined in the text. It is unclear what these numbers are referring to.

We changed the labels on the x-axis, they now correspond to the nomenclature used in table 2.

Ad comment 2:

In the study design, the authors used 228 controls. What is the role of controls since they did not play a role in the main analysis? Evaluation of AO of HD according to GSTO genotypes presumes that subjects have been diagnosed with HD.

The controls have been used to determine if the distributions of the allele frequencies of the rs4925 GSTO1 and rs2297235 GSTO2 polymorphisms are the same in the population of HD patients and in a healthy control group. Since we accept that the inclusion of the controls is not essential, we leave the decision to delete this information to the discretion of the editor.

Ad comment 3:

Table 1: the way genotypes for GSTO1 and GSTO2 are presented is a bit confusing. One might think that haplotypes are presented.

We tried to improve the presentation by replacing the hyphens with slashes.
Reviewer: Alexis Brice

Ad reviewer’s comments:

Minor Essential Revisions

Ad comment 1:

Concerning the first part of the study, which is not really justified given that the cause of the disease is known, the authors do not indicate whether controls were matched with patients in terms of sex, age and geographical origin.

Controls were matched with respect to sex and geographical origin.

Ad comment 2:

The authors over interpret their results when they state that the “chromosomal region of GSTO1 and GSTO2 flanked by the investigated SNPs is not a candidate region for a major susceptibility allele influencing the age at onset in HD”. In fact, the authors have only excluded the responsibility of the two SNPs tested (for a given statistical power). They cannot exclude the possible influence of other polymorphisms in these genes, which would not be in linkage disequilibrium with those tested.

The reviewer has a point here and we corrected the text accordingly.