Author's response to reviews

Title: Age at onset of Huntington disease is not modulated by the R72P variation in TP53 and the R196K variation in the gene coding for the human caspase activated DNase (hCAD)

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June 14, 2005

Dear Editor:

Herewith we resubmit the revised version of our manuscript: MS: 2108230776109933. The mostly unfavourable comments from referee Samir K Brahmachari have been taken into account as far as ever possible (see accompanying page). In this context we would like to draw your attention to our rebuttal of his arguments indicating that the submission obviously received a one-sided judgement, perhaps based on conflicts of interest entertained by this reviewer. Nevertheless, we hope that you will find everything in order for rapid acceptance and publication. Enclosed please find the comments, addressing points of the referee point by point. Thank you and your referees for reviewing the manuscript. We look forward to learning about your decision as soon as possible.

Sincerely

(Larissa Arning) (Jorg T. Epplen)

Ad referees' comments:

Ad comment 1:

This is just a replication study with absolutely no novelty in the question posed by the author as well as the method followed. They report negative results and conclude that age at onset of Huntington disease is not modulated by variations in these genes.

Firstly, essentially new findings need replication and validation. On the other hand, here a second cohort with different ethnicity has been investigated in detail. In complex disease genetics, which concerns also modifier genes in monogenic diseases, replication of results were especially critical.

Ad comment 2:

If the genes have been earlier shown to be associated through two polymorphisms, it is possible that there could be different sets of polymorphisms within the same genes in the studied population which could also modulate the age of onset. The authors have not excluded this possibility as their study only seeks to validate the earlier polymorphisms. Therefore their conclusions of no involvement of these two genes in
modifying age of onset are rather far fetched. It is well documented that similar genes can have different population specific mutations. The authors would have to exhaustively screen for other variations in these genes before they make these conclusions. Not only variation data but also sequence from different genomes are abundantly available. The authors could make use of this information for prioritizing polymorphisms which would enable construction of haplotypes for identification of other mutations which could be modifiers.

Our conclusion says that our study failed to replicate the association between the genotypes at the R72P polymorphism in TP73 and R196K polymorphism in hCAD genes with AO. We do not assume our report as exclusion study. If this would be the case, the remarks of this reviewer should be considered. Since two non-synonymous SNPs are concerned that at least in one case are definitely known to alter the function of the protein, a simple replication analysis appears also quite appropriate.

Ad comment 3:
Since the authors have earlier tested variations in other genes in the same cohort, they could now look at the effect of all of them in conjunction, which might give a more comprehensive picture.

This point is excluded by itself, since not even a tendency towards influence on AO was observed here.

Ad comment 4:
The data presented in the manuscript is very minimal and more rigorous association studies needs to be carried out before these conclusions can be made. The results and discussion section is very poorly written which is also because, there is hardly any result which has been presented.

The comments in the first sentence are in our opinion quite unspecific. Certainly, we would have welcomed improvements as to the criticisms referred to in the last part of this comment.

Ad comment 5:
The title of the manuscript suggests that many variations would have been screened before authors would have made these conclusions.

The title was indeed misleading to some extent and has, therefore, been changed to:
Age at onset of Huntington disease is not modulated by the R72P variation in TP53 and the R196K variation in the gene coding for the human caspase activated DNase (hCAD).
We accept that the initial title was too closely adhering to the one of the paper reporting the association that could not be confirmed in our HD cohort.

Ad comment 6:
The manuscript is not suitable for publication in the current state. More rigorous study needs to be carried out.

In our opinion this notion represents a rather unfocussed remark of this reviewer. In summary, we do not really understand his reservations against the facts of study and, therefore, refrain from speculating about his motivation for this unwarrantedly negative report.

PS: The last author (JTE) has probably met the reviewer once during an invited visit to Bangalore some 10 years ago on the occasion of a DNA fingerprinting conference.