Author's response to reviews

Title: No association between polymorphisms in the brain-derived neurotrophic factor gene and age at onset in Huntington disease

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Author's response to reviews:

Dear Editor,

thank you for your e-mail.
We went through the comments and improved the manuscript according to the reviewer's suggestions.
We hope that you will find everything in order for rapid acceptance and publication.
Enclosed please find the revised manuscript and the comments, addressing the comments of the reviewers point by point. We look forward to learning about your decision.

Kind regards,

Larissa Arning

Referee no 2:

Ad referees' comments: Major Compulsory Revisions

Ad comment 1: Place a table of allele frequencies and undertake Hardy Weinberg analysis.

We included a table with allele and genotype frequencies and stated in the manuscript that all observed frequencies were in Hardy-Weinberg equilibrium.

Referee no 3:

Ad referees' comments:

Ad comment 1: Being a replication study, the presentation of the hypothesis should have highlighted the prior evidence of val/met polymorphism in AO and in possible role in protein's intracellular trafficking. Instead, it highlights the BDNF's role in various neurological and psychiatric disorders and describes the prior evidence in passing.

Upon rereading of the introduction section and the comments we came to the conclusion that it is adequate.

Ad comment 2: In study design, it is not clear why SNPs other than val/met were chosen. The authors may possibly scored them in view of the evidence that HTT regulates BDNF transcription. But then this is not mentioned in clear terms. Also not mentioned is the genomic regions of the SNPs other than val/met.
All SNPs are indicated with their rs number.

Ad comment 3: It is mentioned in the Methods section that all the five markers were tagging SNPs. The next section however points out strong LD between all neighboring markers. This seems contradictory and needs further elaboration.

The selection of the "tag SNPs" has been supported by data provided from the HapMap Project. This information has been added in the manuscript. It is not surprisingly that the precise LD patterns are likely to differ between population groups.

Ad comment 4: Further, results have not been provided for the various markers and the haplotypes -only val/met box plot shown in Figure 1. I wonder why the spread of age of onset is much higher in Val/Val and Val/Met patients compared to Met/Met individual. Authors should explore this and provide some explanation.

The boxplot is exactly described: For each genotype, the median AO is represented as a black bar, the quartile is shown as a solid box, and the range is indicated by the margins. Since there are only eight individuals representing the genotype Met/Met a minor range in AO needs no further exploration and explanation respectively.

Ad comment 5: It is necessary that the manuscript is revised in view of the above comments. Recently, two papers (Di Maria et al PMID 16905325 and Metzger et al PMID 16847693) have appeared on association BDNF in AO. Both of them provide negative evidence. Mai et al's manuscript needs to discuss their results in light of these new findings which are corroborative.

While this manuscript was under review two other independent reports have been published by two different groups leading to the same conclusion as we. We added this information in the manuscript.