Author's response to reviews

Title: Failure to confirm influence of Methyltetrahydrofolate reductase (MTHFR) polymorphisms on age at onset of Huntington disease

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Author's response to reviews:

Dear Editor,

We went through the comments of reviewer 2 again and improved the manuscript according to the reviewer's original suggestions. The once-again revised manuscript with a cover letter has already been resubmitted to BioMed Central.

We hope that you will find everything in order for rapid acceptance and publication.

Enclosed please find the revised manuscript and the comments, addressing points of the referee point by point. We look forward to learning about your decision.

Thank you for your time, valuable suggestions and patience.

Kind regards,
Larissa Arning

Ad referees' comments: Major Compulsory Revisions

Ad comment 1:

In the present analysis, only 1 person from each HD family was included. However, it is not stated, according to which criteria additional relatives were excluded. (Who was taken as propositus?) This reduced series was replenished with 23 HD patients, but criteria for inclusion are not given. (All new referrals to the Hospital since the first paper appeared?)

The initially diagnosed family member remained in this study. Replenishment of the new study is indeed based on the recruitment of new patients referred to our clinics.

We added this information to the manuscript.

Ad comment 2 and 3:

The Methods Section is vague, and it appears that the multiple linear regression has no power to detect any possible interaction between the overwhelming influence of CAG repeat number and expectedly weaker influences of MHTFR polymorphisms. This even more so, as the authors code the polymorphisms as '0,1' which implies a pathogenic hypothesis (no influence of one of the homozygous genotypes) that could be wrong.

May I suggest that the authors first take an descriptive statistics approach: They may take the residuals of
the CAG-AO regression and calculate for each polymorphism the mean of the residuals. If all 6 genotypes have mean residuals of about zero I would believe their present conclusion. If one or more of the six genotypes (or their combinations) would show significant negative or positive means, they should ask a statistician for the correct method of proving the difference.

In order to clarify these open questions we reformulated the method's section more precisely