Reviewer’s report

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

Version: 1 Date: 1 June 2005

Reviewer number: 1

Reviewer’s report:

General

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Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

The seven authors of the present paper refute with their analysis the conclusions of a 2004 paper which was co-authored by four of them. In this sense, the manuscript could formally be considered a retraction and not a failure to confirm somebody's work.

The main error of the first publication obviously concerned sampling: Inclusion of multiple relatives into the study group of patients would have biased estimates of association e.g. between homozygosity of MTHFR 1298C/C genotype and age of onset (AO) of Huntington Disease (HD). - Beside this sampling error, no unified definition of AO was used in the first publication.

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 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.

Negative results deserve the same rigour of analysis than do the positive ones. - Without major revision, this paper cannot be published in your Journal.

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Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

p.4 line 3 from top:
C1298C should read A1298C.
Discretionary Revisions (which the author can choose to ignore)

**What next?:** Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.