Reviewer's report

Title: Evidence for Synergistic Effects of PRNP and ATP7B Mutations in Severe Neuropsychiatric Deterioration.

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Reviewer: Carsten Korth

Reviewer's report:

In this paper, an interesting case is reported with both mutations in the ATP7B and PrP genes. Even though the case is interesting and should be published, there are some shortcomings of the paper as it stands: in general, there is a certain sloppiness when it comes to correctly citing the literature and there are some generalized conclusions that cannot be based on this case.

The following major compulsory revisions should be performed:

- no page numbers, not all references are converted into numbers
- the literature in general is not well referenced. For example, in the introduction the authors should cite the paper where the mutation was first described Nat Genet. 1993 Dec;5(4):344-50. Early papers connecting Wilson's disease with the prion protein are omitted for example Grubenbecher et al. Neuroreport. 2006 Apr 3;17(5):549-52, Merle et al. Arch Neurol. 2006 Jul;63(7):982-5. These papers should be cited.

First paper demonstrating prion protein binding to copper has been cited wrongly.

For psychiatric symptoms in CJD, the authors should, for example cite Ann Neurol. 2005 Oct;58(4):533-43 or similar publications.

- In the conclusion the authors state that "...current findings... point more compellingly toward synergistic interaction between the biochemical and/or cellular effects of the proteins ..., with an unknown mechanism but perhaps mediated by effects on copper metabolism." These kind of statements cannot be made based on just one case report and therefore should not be done. The authors should neither jump to conclusion nor hand-wave their case but just present is soberly.

- Conclusion paragraphs 3-5 are entirely speculative and should be deleted. For example, the idea that PrP G54S would indirectly affect copper binding via a remote structural effect is wild and entirely unproven.

- In the conclusion, it is uncorrect that only ref 22 reports on the PrP G54S mutation, so does ref. 18. The authors should expand on this.

Level of interest: An article of importance in its field

Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.