Reviewer's report

Title: The T1048I mutation in ATP7A gene causes an unusual Menkes disease presentation

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Reviewer: Byung-Eun Kim

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COMMENTS FOR THE AUTHOR

The authors have identified a novel mutation in the copper transporting P-type ATPase encoded by the ATP7A gene. This missense mutation (T1048I) occurs within a conserved phosphorylation motif that is required for the catalytic activity of ATP7A. The moderate presentation of Menkes disease (MD) in the patient suggested that partial copper-transport activity was preserved, and copper-histidinate treatment led to an arrest of developmental regression and an improvement of neurological and cognitive function.

Beyond the initial identification of the mutation by sequencing and RFLP analysis, the authors clearly document the importance of the residues preceding the mutation site and hypothesize that T1048 may not be directly involved in formation of the acylphosphate. This seems plausible in light of the patient's moderate presentation. Instead, they propose T1048 may form hydrogen bonds with residues in the N- and A-domains of ATP7A. They go on to suggest that the mutation could result in mis-folding of the cytoplasmic domains, which could further disrupt copper-induced trafficking to the plasma membrane. It would be interesting to see this hypothesis tested directly, perhaps by assessing the cellular localization of ATP7A in the patient's cultured fibroblasts, although such experiments seem beyond the scope of this paper.

Figure 1B is somewhat difficult to interpret. It could be more intuitive by reformatting the data (age, copper, ceruloplasmin) into a table and moving the labels from the center to one side. In the Table, please also provide specific values for urine beta 2 microglobulin during treatment, since increased excretion of this metabolite is mentioned in the text.

The proposal to apply copper-histidinate treatment immediately after diagnosis of MD seems plausible, but the authors do not address the question of achieving an early diagnosis, except for a mention of newborn screening. It would be interesting for the authors to speculate about the effect of early copper-histidinate treatment on mitigating neurodegeneration in the context of the T1048I mutation. In general, the authors make their case that a better understanding of the relationship between genotype and phenotype of MD could lead to improved prognosis and treatment response in this difficult illness.

Some minor changes would improve the paper:
1. Include additional references to occipital horn syndrome (e.g., a family with mutation in the nucleotide binding domain of ATP7A - see Tang et al. reference below), the spectrum of epilepsy in Menkes disease (White et al.), and the issues to consider in copper treatment of older symptomatic subjects with Menkes disease, such as this patient (Sheela et al.)


2. Please provide the patient’s age at time of diagnosis, the total duration of copper histidine treatment, and source of the copper. These elements are not clear in the current version of the manuscript.

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.

Declaration of competing interests:

I declare that I have no competing interests.