Reviewer’s report

Title: Identification of a Novel Mutation in MMACHC and Development of a New Prenatal Diagnostic Technique Using Genetic Sequencing

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Reviewer: eirini manoli

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Comments to the authors:
Xiangdong Kong et al. present the molecular confirmation of infantile onset cobalamin C type - combined methylmalonic acidemia and homosystinuria in 6 probands and their parents, as well as 4 additional couples of diseased children affected by the disorder. Moreover they present the results of successful prenatal diagnosis using CVS (chorionic villus sampling) in three at risk pregnancies. In two of the families prenatal diagnosis determined the unaffected status of the fetus resulting in the birth of two normal children. One of the mutations reported was novel, though a different amino acid change was previously reported for that same position in the MMACHC gene.

Major Revisions
1. The manuscript certainly adds to the characterization of cblC disease and mutation spectrum in China, but the methodology and conclusions lack novelty making the title somewhat misleading. The identified mutations are all, but one, previously reported in association with cblC disease, and although the authors report a novel change, p.G155R, they fail to mention the previously described c.464G>A, p.G155E mutation in the same codon (Komhoff et all 2013, Pediatrics). Use of Sanger sequencing for clinical diagnosis, including CVS-chrionic villus sampling-prenatal testing, is the standard of care and if the technology application in the prenatal setting is novel in their center it should be discussed accordingly.

2. Background/introduction includes several mistakes: methylmalonyl-CoA mutase, the enzyme that isomerizes R-methylmalonyl-CoA to succinyl-CoA in the mitochondria is described repeatedly as a “translocase”; the authors report that about 50 mutations have been identified in the MMACHC gene (77 currently listed in HGMD, 76 in the Zhejiang University Center for Genetic and Genomic Medicine (ZJU-CGGM) variant-website; MMA is described as a “treatable” disease, which is not the case, although patients show improvements with current therapies, neurological and eye disease manifestations progress despite treatment.

3. The phenotype information provided is very limited even for those homozygous for the common Chinese mutation, c.609G> p.W203X. It would be helpful to provide clinical information and if possible biochemical values (at diagnosis) in the table with the mutations for each of the patients. The study
though further confirms the association of this mutation with severe early onset disease, given that in both, homozygous or heterozygous form, it led to early demise of the affected infants. The disease progression, eye involvement and causes of death would be important to include, if available, as this would add significantly to the novelty and importance of the manuscript.

Minor Revisions
The term odinopoeia can be replaced by termination of pregnancy (TOP).
Figure 1 legend mentions an arrow that is not inserted in the figure.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Needs some language corrections before being published

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