Reviewer’s report

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

Version: 3 Date: 20 April 2015

Reviewer: eirini manoli

Reviewer’s report:

The authors made a diligent effort to address the comments of the reviewers, yet many inaccuracies still remain in the manuscript in its current form.

Major compulsory revisions

• Please revise the title to something like: “Prenatal diagnosis using genetic sequencing and identification of a novel mutation in MMACHC” instead of “….Development of a New Prenatal Diagnostic Technique Using Genetic Sequencing”. The authors do not present the development of a new prenatal diagnostic technique, but use standard methodology for CVS –based prenatal diagnosis. If they wish to highlight the novelty of using molecular techniques for prenatal screening in China, this should be described appropriately.

• Clinical information is limited. Unless further clarified the description “some patients also had acidosis, urine ketone positive, elevated lactate and ammonia” would better be removed, as it raises questions to the readers of the manuscript, unless more information can be added on table 2 or else in the paper.

• Given the number of normal controls screened was small, additional information on the frequency of the mutations from whole exome sequencing databases, such as the Exome Variant Server or ExAc browser should be provided.

Minor Essential revisions:

• Subtypes of combined methylmalonic acidemia and homocystinuria include: MMACHC (cblC), MMADHC (cblD combined, cblD-MMA and cblD-HCY), LMBRD1 (cblF), and ABCD4 (cblJ) – please describe appropriately

• Italicize gene names as well as cobalamin subtype (cblC, D, J, F) names throughout the manuscript.

• cblC deficiency should not be referred to as MMA in the document (see conclusion in the abstract etc). Please replace with combined methylmalonic acidemia and homocystinemia or cblC deficiency.

• Rephrase the sentence: “Although partial MMA is a treatable genetic disease, both the high mortality during…”. It is unclear what the authors refer to by “partial MMA”, may want to re-phrase to “MMA is a partially treatable disorder”.

• Indicate amino acid change and numbers in Figure 2.

• Patient 6 is reported as having normal HCY and MMA at follow-up – this would be particularly unusual for patients with cblC disease, please clarify.
• Add age at follow-up before the clinical details
• On patient 7 in table 2, “Recovered well after rehabilitation and taking medicine” – please rephrase or clarify.
• Comment on prenatal treatment of the mothers with B12 in the confirmed MMACHC affected fetuses.

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: Nothing to declare.