Reviewer’s report

**Title:** Identification of novel L2HGDH mutation in a large consanguineous Pakistani family- a case report.

**Version:** 0  **Date:** 11 Mar 2017

**Reviewer:** Dinesh Rakheja

**Reviewer's report:**

The authors present a large family with six members affected by a neurological disease. Whole genome microarray identified a homozygous region on chromosome 14 that tracked with affected individuals. This region includes L2HGDH, and subsequent sequencing identified that the affected individual harbored a rare (not novel, as stated in the abstract) homozygous mutation in L2HGDH - c.178G>A, p.Gly60Arg.

To assess pathogenicity of the mutation, the authors used standard computational algorithms - PROVEAN score, PolyPhen-2, and MutationTaster - that predict the mutation is likely deleterious. However, the authors should also include the results from other common prediction tools such as SIFT and Align GVGD. SIFT (score 0.11) predicts that this mutation is tolerated and Align GVGD assigns it to class C0, least likely to be deleterious.

The authors need to do metabolic testing of the family to show elevated levels of L-2-hydroxyglutarate in the urine samples of affected individuals; that would be the most convincing data linking the mutation to the neurologic disease in this family. GC/MS-based urine organic acid assay is straightforward and widely available.

**Are the methods appropriate and well described?**
If not, please specify what is required in your comments to the authors.

No

**Does the work include the necessary controls?**
If not, please specify which controls are required in your comments to the authors.

Yes

**Are the conclusions drawn adequately supported by the data shown?**
If not, please explain in your comments to the authors.

No
Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?

If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

Not relevant to this manuscript

**Quality of written English**

Please indicate the quality of language in the manuscript:

Needs some language corrections before being published

**Declaration of competing interests**

Please complete a declaration of competing interests, considering the following questions:

1. Have you in the past five years received reimbursements, fees, funding, or salary from an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

2. Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

3. Do you hold or are you currently applying for any patents relating to the content of the manuscript?

4. Have you received reimbursements, fees, funding, or salary from an organization that holds or has applied for patents relating to the content of the manuscript?

5. Do you have any other financial competing interests?

6. Do you have any non-financial competing interests in relation to this paper?

If you can answer no to all of the above, write 'I declare that I have no competing interests' below. If your reply is yes to any, please give details below.

I declare that I have no competing interests.

I agree to the open peer review policy of the journal. I understand that my name will be included on my report to the authors and, if the manuscript is accepted for publication, my named report including any attachments I upload will be posted on the website along with the authors' responses. I agree for my report to be made available under an Open Access Creative Commons CC-BY license (http://creativecommons.org/licenses/by/4.0/). I understand that any comments which I do not wish to be included in my named report can be included as confidential comments to the editors, which will not be published.

I agree to the open peer review policy of the journal