Reviewer’s report

Title: HDR Syndrome with a Novel Mutation in GATA3 Mimicking a Congenital X-linked Stapes Gusher: a case report

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Reviewer: Chuan-Jen Hsu

Reviewer’s report:

Yang and colleagues reported a 14-month-old male of HDR syndrome mimicking an X-linked stapes gusher. According to the patient’s phenotype, the author performed Sanger sequencing of two related genes, POU3F4 and GATA3. A de novo variant GATA3 c.1201_1202delAT was detected in a heterozygous state, which was predicted to cause a frameshift (p.Met401Valfs*106). This finding expanded the genotypic and phenotypic spectrum of HDR syndrome. In general, the manuscript is well written and the study is thoroughly conducted. However, this article will benefit from some revisions and some points remain to be clarified.

Major Comments:

1. Page 8, the authors concluded that the wide clinical spectrum and severity of HDR syndrome poses a great challenge to arrive at a molecular diagnosis. However, with the advent of next generation sequencing (NGS), designed NGS-based panels can achieve molecular diagnosis in advance of complete clinical evaluation. Genetic diagnosis of HDR syndrome before the clinical diagnosis has been reported in the literature (Mutat Res. 2015 Jan;771:1-5).

2. Figure 1. Can the authors provide other axial HRCT sections? Although there is bulbous dilatation at the distal end of IAC, the fusion between the cochlear basal turn and the IAC is not obvious. Please refer to the literature (e.g. Laryngoscope. 2016;126:E123-8) for a typical image of incomplete partition type III inner ear malformation.

3. Although GATA3 c.1201_1202delAT has not been reported, the predicted protein p.Met401Valfs*106 was the same as another variant c.1200_1201delCA reported in a Japanese girl (Endocr J. 2010;57:171-4). It would be interesting to compare the phenotypes of these two patients.

4. Instead of losing the two zinc fingers domains of GATA3, p.Met401Valfs*106 preserves the ZnF1 and ZnF2 and extends the protein length. It should be mentioned that this variant was different from other reported GATA3 frameshift mutations which damaged the ZnF1 and ZnF2.

Minor Comments:
1. Page 3, line 1. There are no Fig. 1A, 1B, 1C. It should be Fig. 1.

2. Figure 2A, the electropherogram is in reverse order. Please use forward primer for Sanger sequencing. Besides, the label of the 2-bp deletion variant should be AT instead of A.

3. Figure 2B, for readers to understand better about the consequence of the frameshift, it will be better to show the full amino acid sequence of GATA3 and indicate the location of two transactivating domains (TA1 and TA2) and two zinc fingers domains (ZnF1 and ZnF2).

**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.

Unable to assess

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

Yes

**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

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Acceptable

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