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: M. Andrew Nesbit

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The authors have not addressed the comments in my original review of this paper. While it is stated that neither parent had the GATA3 mutation, neither the sequencing traces from the parents nor a restriction digest of a GATA3 exon 6 PCR products spanning the mutation site from parents and proband were shown. One cannot state definitively that the mutation is de novo without presenting these data.

In addition to the mutation reported by Muroya et al (2010), Ali et al (2007) reported a frameshifting mutation in codon 407 that is predicted to result in a 98 amino acid C-terminal extension. Stapes gusher was not reported in either of these patients. This should be added to the discussion. These mutations do not affect the zinc fingers because they occur downstream of them. The wide spectrum of GATA3 mutations that cause HDR (missense, nonsense, frameshifting indels, whole gene deletions) underline the fact that it is likely that functional GATA3 protein dosage is the important factor here - all mutations result in the loss of functional GATA3 whether that is total or partial loss of function.

Interestingly, frameshifting insertions that result in C-terminal extensions are the most common GATA3 mutations found in breast cancer.(Gaynor et al, 2010; Mair et al, 2016)

On line 141 it is stated that the mutation occurs at codon 1758 and 1759. As GATA3 has only 444 amino acids this needs to be corrected, especially as the mutation is given as p.Met401Valfs*106. i.e. at codon 401.

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

Yes

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

No

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

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