Reviewer’s report

Title: Familial inheritance of the 3q29 microdeletion syndrome: case report and review

Version: 0 Date: 27 Oct 2018

Reviewer: Jill Anne Rosenfeld

Reviewer’s report:

Khan et al. report a family with a 3q29 microdeletion, slightly smaller than the recurrent microdeletion and present in a child and his affected mother. This report highlights implications of identifying genetic changes that may lead to milder phenotypes - and variable expressivity of phenotypes - in the setting of familial inheritance.

The presentation and review of the literature is currently imprecise and could use clarification. Major points:

1. Clearer discussion of the "3q29 microdeletion syndrome" as being defined by the recurrent, 1.6-Mb deletion caused by non-allelic homologous recombination. This should be explicitly stated in the background. While most of the literature cited is about the recurrent microdeletion, there are some reports of other atypical deletions mixed in. The use of the "3q29 microdeletion syndrome" term should be carefully defined/applied, perhaps being limited to cases with the recurrent deletion.

2. Inheritance. Table 1 reportedly reviews reports of inherited 3q29 microdeletion cases, but it is incomplete. For example, the paper by Clayton-Smith et al. (reference #8) is not included in the table.

3. Coordinates. In table 1, there is a mixture of genome builds in the reported coordinates of the deletions. These should all be converted to the same build and reported as such. Additionally, the coordinates are marked as unknown - for example, the inherited deletion from the Baliff et al. is shown in the paper to be the standard, recurrent deletion. (Also, it is not clear where the phenotype data for this report comes from, as patient-level data doesn't seem to have been included in the paper. The mother was also reported as "mildly affected" but is not shown as having any symptoms.)

4. Atypical deletions. The reported patient and his mother have a slightly smaller deletion than is recurrent. This should be stated earlier when the testing results are presented; it is currently not stated until the discussion or through examination of figure 2. The authors could also consider specifically stating what is the difference between their patient's deletion and the recurrent deletion - what are the genes that are normally deleted that have been spared in this patient? As these are relatively few genes and not the proposed critical genes, perhaps this family would be expected to have similar manifestations of the recurrent microdeletion syndrome? Additionally, the paper could benefit from a more explicit review of other cases with smaller, atypical deletions within the recurrently
deleted region. For example (not necessarily an exhaustive list): Mulle et al. 2014 (PMID 23871472), Cox & Butler (Ref. 9), Dasouki et al. (Ref. 10), and Ballif et al. (Ref. 13 - although detailed clinical information is not provided) all include smaller deletions, several of which seem similar to the deletion in this proband. And while the paper by Cobb et al. refers to a "1.3-Mb" deletion, this was found by BAC array, and not enough information is available to confirm if this is the recurrent deletion or atypical - so it should not be included among cases with smaller, atypical deletions.

Minor points:

1. Abstract, case presentation, and discussion: Missing hyphen in "3-year-old".
2. Background, 2nd paragraph: The authors mention that the 1 in 30,00-40,000 frequency may be an underestimate, but this number is derived from a population-based screening so wouldn't be subject to an underascertainment bias.
3. Case report, CMA results: What are the refined coordinates of the deletion, based on the higher-resolution CytoScan testing?
4. Discussion & Conclusions, 1st paragraph: "structural variation" is referred to in the first sentence, but it may be clearer to state chromosomal or genomic structural variation.
5. Discussion & Conclusions, 1st paragraph: it may also make sense to cite a paper like Ref. 3 that attempts to catalog CNVs associated with human disease?
6. Discussion & Conclusions, 1st paragraph: The authors cite a study about penetrance/interpretation of SNVs, but there are additional studies that could be cited that are specific to CNVs. For example, Ref. 24 & PMID 23258348 about penetrance; there is also literature more focused on counseling difficulties (for example, PMID 29146387).
7. Discussion & Conclusions, 2nd paragraph: this paragraph is mostly re-stating much of the information from the background and could be further streamlined.
8. Discussion & Conclusions, last paragraph: The authors note anemia as an uncommon finding in the 3q29 deletion. Because it is uncommon, it is possible this is finding unrelated to the deletion, and that possibility should be stated.
9. Figure 2 legend: Description of panel A could be clarified. The top panel has all of chromosome 3 showing, and the bottom has a "zoomed-in" (as opposed to "zoom-in") view.
10. Figure 2 legend: Mentions an arrow in figure 2D, but there is no arrow showing.

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.

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:

Acceptable

**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 receive salary support from a genetic testing laboratory that offers clinical genetic testing (including CMA analysis) on a fee-for-service basis.

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