Author’s response to reviews

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

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Author’s response to reviews:

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Matteo Pasini, PhD
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To the Editors:

Re: Manuscript MGNM-D-18-00166

Please find the additional revisions requested for our manuscript entitled “Familial inheritance of the 3q29 microdeletion syndrome: case report and review” by Khan et al. The comments and suggestions of the Reviewers and Editor are detailed below, including our responses and manuscript revisions. Please note that changes in the revised Case Report are identifiable by the ‘track changes’ feature of MS Word. We again thank the Reviewers for their valuable feedback and believe the manuscript has been improved by these changes. We look forward to a favorable decision from BMC Medical Genomics.

Editor Comments:

1. Please clarify in the Ethics approval and consent to participate section whether the consent is written or verbal.

- The consent for participation in this Case Report was in written form. This has been updated to the ‘Ethics approval and consent to participate’ section of the manuscript.
Reviewer Comments:

Jill Anne Rosenfeld (Reviewer 2): Most of my previous concerns have been addressed. A few remain that could benefit from additional clarification:

1. Review of previously reported smaller deletions: The citations in the discussion appear to cite the paper with the first author of Coe instead of Cox. Additionally, the previously mentioned paper (Mulle et al. 2014, PMID 23871472 describes the characterization of a de novo smaller 3q29 deletion in the supplement; this is the same case from Mulle et al. 2010 PMID 20691406. Additionally, the authors could consider including a statement about conclusions that could be made from the smaller deletions in the paragraph in the discussion. For example, do these smaller deletions provide support for the role of the candidate genes in this syndrome?

   - Thank you for this helpful comment. In the third paragraph of the Discussion, the Coe et al. reference has been replaced with the Cox et al. citation as the Reviewer correctly points out. The Cox et al. reference mentions a 1.24 Mb deletion that would be in keeping with the concept described here of nested smaller deletions within the recurrent 1.6 Mb deletion. The other instance of the Coe et al. reference, in the opening of the Discussion, is deliberate and was not changed.

   The original reference from Mulle et al. 2010 (ref #33 in this Revised Manuscript), as suggested, has been updated to the third paragraph of the Discussion. It is provided in the same sentence in which the Cox et al. citation was amended. The more recent reference by the same author from 2014 which back-references the 2010 paper was not added as this is primarily about Williams syndrome. Regarding conclusions drawn from examining the smaller deletions, we had commented on some aspects of this in the previously revised manuscript, specifically in the third paragraph of the Discussion. This was done on two levels, common clinical findings among the smaller deletion cohort were broadly provided and a comparison of affected gene content was described.

   In response to this comment, a comparison of the relevant overlapping gene(s) of interest for additional nested deletions relative to the one reported in this index case, and the recurrent deletion, has also been updated to the third paragraph of the Discussion in our Revised Manuscript.

2. Possibility of underascertainment: This is a relevant concern, when it comes to identifying deletion carriers through clinical testing, as some individuals will likely not raise sufficient suspicion to lead to clinical genetic testing. However, it might be misleading to only tie the underascertainment to a population-based incidence. True, ethnicity stratification has not been accounted for, but there is no evidence whether this would lead to under- or over-estimation of incidence. The background may, therefore, benefit from further separation of estimation of incidence from the problem of underascertainment.

   - We agree with the Reviewer that the 3q29 microdeletion syndrome likely is associated with under-ascertainment, and our original Introduction that discussed this did not necessarily
conclude that the incidence is therefore higher than currently reported. Rather, our language was intended to suggest that the true incidence of the microdeletion could be higher than has been previously reported. However, in response to this comment we have modified the text in our Introduction to soften the suggestion of under-ascertainment and incidence/prevalence. We feel that further discussion of disease incidence and ancestry-based population frequencies are outside the scope of this Case Report.

Additional points:

1. Background, first sentence: the addition of the clause about detection of relevant CNVs from sequencing studies could be rephrased, as the beginning of the sentence is focused on the use of CMA.

   - Thank you for this suggestion. We have revised the Background by separating this single sentence into two, one that describes previous CMA based CNV detection and the second that highlights the increasing accessibility of identifying CNVs by sequencing.

2. Discussion, last paragraph, second sentence: "given" is misspelled.

   - We thank the reviewer for pointing this out. It has been corrected and another round of spell check was performed on the Revised Manuscript.

3. Figure 2 legend:
   a. Green & blue dots are mentioned - should be red & blue?

   - Thank you, this oversight has been corrected in the Revised figure legend.

   b. 3rd sentence: the authors could consider rephrasing, as the mention of the dotted lines makes one think it may be referring to the bottom panel, but then it mentions the values on the y-axis, which references the top panel. Additionally, the "2" in log base 2 should be in subscript.

   - Aspects of the third sentence have been incorporated earlier into the second sentence, especially regarding the X/Y axis information. This is followed by the mention of the dotted line and subsequent zoom-in views are described. In addition, the number ‘2’ depicted in the log base value has been converted to a subscript.

   c. 4th sentence: "user-defined" is missing the final 'd'.

   - This typographical error has been fixed

   d. Panel D description: the same FISH probe name is mentioned for both probes.
- The FISH probe name provided by Abbott Molecular for the 3qTEL STS maker has been amended in the figure legend and we thank the Reviewer for this careful observation.

4. Table 1, footnotes: the mention of a transmitting grandmother as "patient 11" may benefit from clarification - the mother represents the 11th case of parental transmission.

- This was rephrased in the footnotes of the Revised Table 1 to indicate the grandmaternal deletion is a parental transmission in a multi-generation family, rather than denoting the grandmother as ‘patient 11’.

Thank you again for the opportunity to improve our manuscript through peer review. We strongly believe that this Case Report will be of interest to your readership and we hope that it is now acceptable for publication in BMC Medical Genomics.