Author’s response to reviews

Title: Array based characterization of a terminal deletion involving chromosome subband 15q26.2: An emerging syndrome associated with growth retardation, cardiac defects and developmental delay

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Author’s response to reviews: see over
Cover Letter

Dear Editor

Please reconsider our manuscript "Array based characterization of a terminal deletion involving chromosome subband 15q26.2: An emerging syndrome associated with growth retardation, cardiac defects and developmental delay" for publication in your journal.

We have now addressed all the changes in the manuscript suggested by the three expert reviewers. We have also expanded the discussion, extensively edited the text for language improvements, read and incorporated suggested scientific reports and also labeled and resized the images for better visualization.

We hope it will be acceptable for publication in its current state.

The questions raised by the reviewers are listed and addressed below.

Yours Sincerely

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Reviewer 1.

1. The pictures that were submitted were resized to fit the uploading in the electronic submission system. The have now been further improved concerning review resolution and 600 dpi images will be available for copy editing if the article becomes accepted. Updated figure legends are submitted with the manuscript.
2. We totally agree with this comment and maternal age, patient’s growth centiles, and the lack of single umbilical vessel have now been incorporated in the text. The patient did not display talipes and it has consequently not been mentioned in the text.
3. We are grateful for the suggestion of related articles and have read them with great interest. We found them very valuable in refining the introduction and extending the discussion part relating the genetic abnormality found in the patient.
4. We have screened the gene content in the deletion resulting from the dic(15) and in the paper by Slavotinek et al. (2005) MEF2A is mentioned as a putative candidate gene for the cardiac defects seen in patients harboring deletions of 15q26.2. This is now discussed in our manuscript and in addition we evaluate two additional genes,
*CHSY1* and *TM2D3* that are included in the deletion and might contribute to the phenotype of the patient.

**Reviewer 2.**
1. Labels have now been added to the figures as suggested by Reviewer 2.
2. We have read the article by Ravnan et al. (2005) and agree with the suggestion of Reviewer 2 to update the detection rate of subtelomeric abnormalities found in the clinic.
3. We agree with this suggestion and have changed “marker chromosome” to “derivative chromosome” throughout the text in the manuscript.
4. In the clinical evaluation of the patient both parents were cytogenetically investigated, displaying normal karyotypes. This is indicative that the derivative chromosome most likely is of de novo origin and, not as in the single report of a similar dic(15), a result of a maternal (or paternal) paracentric inversion. In addition we believe that the phenotype of the patient is a result of the genetic outcome of the inversion - the terminal deletion on chromosome 15 – not the inversion *per se* and the parental origin of the derivative chromosome is of lesser interest. However, we agree that it could be valuable for future studies to investigate this matter, which although is hampered by the fact that we only have cells in fixative from the parents, making microsatellite analysis difficult. And we do not deem the question to be of such crucial interest of the study that it is worth to expose the parents for the emotional stress that an additional blood-sample drawing would constitute.

**Reviewer 3.**
1. Vide have been changed to wide throughout the text.
2. We agree with this suggestion and have changed the sentence on page 10 as suggested for better clarity.
3. We agree with this suggestion and have changed the sentence as suggested on page 3.
4. We have changed the “and” to “an” on page 9.
5. No, neither duplication nor a deletion (in relation to Prader-Willi or Angelman syndrome) of *SNRPN*. Though we have now added this in the text to clarify.
6. The BAC-probe for *SNRPN* was situated on 15q11.2 but the proximal breakpoint of the detected terminal deletion was on 15q26.2 in this case. We are not sure what is asked for in this question…
7. We agree with the reviewer and have enlarged the two chromosomes 15 in Figure 2.