Author's response to reviews

Title: A study of two Chinese patients with tetrasomy and pentasomy 15q11q13 including Prader-Willi/Angelman syndrome critical region present with developmental delays and mental impairment

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Author's response to reviews: see over
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Professor Giovanni Neri and Professor Guian Paolo Declaro
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Dear Professor Neri and Professor Declaro:

We would like to thank the reviewers and editor for their thorough review and constructive critiques. The manuscript now has been revised to incorporate the changes recommended by the reviewers. The followings are our point-by-point responses to reviewers’ comments.

Reviewer 1:

Reviewer’s comment:
I would check the nomenclature of rec 15: I think is not much in general use.

Authors responses:
The nomenclature of rec is usually used to describe recombinant chromosomes originated from crossing-over in inversion or insertion heterozygotes that result in duplication and inversion, but not for marker chromosomes that have additional abnormalities such as deletion in the SMC15s in this study. Marker chromosomes 15 similar to the SMC15 in patient 2 are usually expressed as inv dup(15) by others in the literature. As for the SMC15 in patient 1, it contained three copies of 15q11q13 rather than duplication seen in a recombinant chromosome, therefore, we feel it would be appropriate to express it as rea(15q11q13).

Reviewer’s comments:
I would shorten the manuscript in general, but I would add some more details on the behavioural features of these patients.

Authors’ response:
The manuscript has been shortened, mainly in the Discussion section. Additional information about behavioral features of the patients is included (Pages 5-6).

Reviewer’s comments:
Was an EEG performed even in absence of seizures?

Authors’ response:
EEG was normal in both patients (Page 6, lines 7 and 21).

Reviewer 2

Reviewer’s comment:
the authors should provide more detailed information about the behavioral and developmental evaluation of the patients. For example, they mention “autistic behavior” both in the abstract and
the conclusions, but they only describe “outbursts”, “aggressive” behavior or “difficulty in interacting with peers”: were the patients ever evaluated for autism spectrum disorders?

Authors’ response:
Additional information about the behavioral and developmental evaluation of the patients is provided (see Pages 5-6). The severity of psychomotor retardation in both patients was incompatible with a diagnosis of autism although both demonstrated deficits overlapping with some features in patients with autism. In this revision, “behavioral problems” replaces “autistic behavior”.

Reviewer’s comments:
• Major Compulsory Revisions
  Abstract
  1. Case presentation: “Both 15q11q13 aneusomies were resulted”, “were” must be canceled. Towards the end of the page and in other sections of the paper (pages 8 and 11) “mental impairment” or “mental deficits” should be replaced with “intellectual disability” (or disabilities). “Pentasomy patient was more severely affected than tetrasomy patient” should be replaced with “The patient with pentasomy 15q11q13 was more severely affected than the patient with tetrasomy of the same region”.

Authors’ response:
The changes recommended by the reviewer have been adopted.

Reviewer's comments:
2. Conclusions: add “of” after “best”, replace “pentasomy 15q11q13 case” with “case of pentasomy 15q11q13”. Replace “pentasomy and tetrasomy 15q11q13 patients” with “patients with tetrasomy and pentasomy of chromosome 15q11q13”.

Authors’ response:
These changes have been made in the revision.

Reviewer’s comments:
Background
3. Page 4, line 6: replace “particular, those that are maternally inherited” with “particularly on the maternal chromosome”.
4. Page 4, line 9: add reference(s) after “(SCM) in humans” to validate the statement.
5. Page 4, line 12: replace “underlining” with “underlying”.

Authors’ response:
The changes recommended by the reviewer have been adopted.

Reviewer’s comments:
Case Presentation
7. Clinical data. Page 5 line 10: after “non-consanguineous couple.” Add “Family history was unremarkable” and remove “Family history was insignificant” from page 6.

Authors’ response:
The changes suggested by the reviewer have been adopted.

Reviewer’s comments:
8. Page 5, lines 12-13: can the authors provide references in centiles for the birth parameters, related to the Chinese population? It appears the newborn was underweight for his length, but having a centile would give a better comparison with normal values. The same thing applies for patient 2.

Authors’ response:
References in centiles for patients’ birth parameters are provided (Page 5, lines 12-14; page 6, lines 9-10).

Reviewer’s comments:
9. Page 5, line 14: the authors should provide more details about the post-natal period, if possible. Was there a follow-up to the resuscitation? Any sign of asphyxia, jaundice, feeding problems, infections, or other post-natal problems?

Authors’ response:
No signs of problems in the post-natal follow-up check-ups were reported (Page 5, lines 14-16).

Reviewer’s comments:
10. Page 5, lines 16-17: can the authors document at what age the behavioral problems started to occur?

Authors’ response:
The behavioral problems started at 2 years old in both patients (Page 5, line 18; page 6, line 17).

Reviewer’s comments:
11. Page 5, last line: at what age was the Gesell Developmental Observation performed? Was it contemporary to the evaluation (5 years) or previous? It’s important to compare the output with the chronological age.

Authors’ response:
The Gesell Developmental Observation on patient 1 was performed at 5 years (Page 5, line 5).

Reviewer’s comments:
12. Page 7: all the markers should be in italics (i.e. D15S975).
13. Page 8, after line 4: there should be a “Discussion” header.
14. Page 8, line 6: replace “pentasome” with “pentasomy” and replace “ours is” with “the work presents the results of”.
15. Page 8, line 8: replace “overlapped” with “overlap”.


Authors’ response:
The recommendations have been adopted.

Reviewer’s comments:
16. Page 8, line 9: after “West” the authors should list 3-4 features that are common to both the cases reported in the literature and the two patients in the manuscript and then close the sentence after “[2,4,6,10]”. Then replace “but some differences were also noted” with “However, some differences were noted”.

Authors’ response:
Four features that are common to the cases reported in the literature and two patients described in the manuscript are included (Page 8, lines 21-22).

Reviewer’s comments:
17. Page 8, lines 12-13: move “age of 5 and 6, respectively” from line 13 to line 12, after “examination”, then replace “had not been developed” with “were not observed”, and cancel “patients of” after “15q11q13”.
18. Page 8, line 15: cancel “no” before “vision deficits”, the sentence has already a negative in “Neither”.
19. Page 8, line 16: replace “mental deficits” with “intellectual disabilities” (see also note 1 of the abstract).
20. Page 8, line 18: replace “were” with “had”.
21. Page 8, line 20: remove the dot (”.”) after “age of 5”.
22. Page 9, line 1: replace “other tetrasomy 15q11q13 patients in the West” with “Western patients with the same aneusomy”.
23. Page 9, line 4-5: replace “that increases in copy number in high copy number 15q11q13 may not change” with “that the increase in copy number in 15q11q13 aneusomies may not change”.
24. Page 9, line 10: replace “clinical information available, and the presence of a normal cell line or a state of mosaicism” with “available clinical information, and the presence of mosaicism”.
25. Page 9, line 11: replace “to” with “for a”.
26. Page 9, lines 16-17: replace “present the patients described here” with “described in this report”.
27. Page 10, line 3: add “in” after “resulting”.

Authors’ response:
These changes have been made accordingly.

Reviewer’s comments:
28. Page 10, line 6: the authors stated on page 6, line 17 that the array had an “average spatial distance between neighboring markers of 880 bases” but here they report “a precision of 1-kb intervals”. Which figure is correct?

Authors’ response:
The average spatial distance between intragenic neighboring markers on the array is 880 bases. The discrepancy has been resolved (Page 7, line 10; and page 10, line 17).

Reviewer’s comments:
29. Page 10, line 14: add “than” after “recombination”.

Conclusions
30. Page 11, line 6: replace “mental impairment” with “intellectual disability” (see also note 1 of the abstract and note 19 above).

Authors’ response:
The reviewer’s suggested changes have been made in the revision.

Reviewer’s comments:
Figures 1 and 2 need to be much larger. In Figure 1 the authors should use an arrow to point the preauricular fistula.

Authors’ response:
Figures 1 and 2 are enlarged. An arrow is used to point the preauricular fistula in patient 1.

Reviewer’s comments:
In the Figure 2 legend the authors should explain what is depicted in pink and what is in green, and use arrows to point the different probes.

Authors’ response:
The legend in the Figure 2 notes that Orange corresponds to the SNRPN probe and Green to PML probe, and they are annotated with short and long arrows, respectively.

Reviewer’s comments:
For both Figure 3 and 4 the authors should clarify if the represented regions are from chromosome 15 or SCM 15, since they use “chromosome 15q11q13 in the legends, but “SCM 15” in the text.

Authors’ response:
The array data shown in the Figures 3 and 4 represent copy number for chromosome 15q11q13 that include both from normal chromosomes 15 and marker chromosome 15s (SMC15s). For instance, in Figure 3 the array data shows five copies of 15q11q13: two from normal chromosomes 15 and three from the SCM15.

Reviewer’s comments:
Figure 3 legend: replace “Lower portion is array data from proximal chromosome 15q, and upper portion is enlarged part of affected 15q11q13” with “The lower portion of the figure shows array data from proximal chromosome 15q, and the upper portion represents the enlarged part of affected 15q11q13.
Figure 4 legend: add “the” before “upper”.

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Authors’ response:
The changes suggested by the reviewer have been adopted.

Reviewer’s comments:
Table 1 For STS D15S1013 the proband has “2,2”: is this correct? It would imply no contribution from the mother (1,1).

Authors’ response
In the Table 1, the proband alleles for STS D15S1013 should be “1,2”. The error has been corrected.

Reviewer’s comments:
• Minor Essential Revisions
  Background
  1. Page 4, line 14: the authors may add a coma “,” after “far”.
  Genetic analysis
  2. Page 6, line 17: the authors should explain what CEL stands for.
  3. Page 10, line 17: the authors may replace “ones” with “cases”.
  Conclusions
  4. Page 11, line 7: the authors should add “the” after “with”.
  5. Page 11, line 8: the authors should add “the” after “than”.

Authors’ response:
The changes have been made accordingly. CEL is abbreviation for cel intensity (files) (Page 7, line 7).

We hope the revision has appropriately addressed reviewer’s concerns and adopted reviewer’s recommendations. Once again, we are very grateful to the reviewer and editor for the suggestions which have certainly improved the quality of the manuscript.

Please do feel free to let us know if you have any questions.

Yours sincerely,

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