Reviewer's report

Title: A Case Report of Chinese Brothers with Inherited MECP2-containing Duplication: Autism and Intellectual Disability, but not Seizures or Respiratory Infections

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Reviewer: Luigi Boccuto

Reviewer's report:

• Overall Comment

The paper by Xu et al. represents an interesting report of the first case of MECP2 duplication in the Chinese Han population. The phenotype caused by CNVs of variable size is always subjected to some degree of variability and new case reports provide more information to better define such phenotype.

The case described in the manuscript is also peculiar because it involves two brothers, the deletion is inherited by the mother, who shows some borderline behavioral features, and the family pedigree is suggestive of further potential carriers, although unfortunately deceased.

Moreover, the clinical presentation of the two patients lacks some of the typical features of the MECP2 duplication syndrome, such as recurrent infections and epilepsy.

For all the aforementioned reasons, I believe the paper constitutes an important contribution to the medical genetic field, but there are two major areas of the work that need some improvement: the authors should provide more detailed clinical information about the family members (i.e. for the patients percentiles of birth parameters, body measurements at the time of clinical evaluation, medical records; for the deceased relatives reason of death, medical history) and should further discuss the implications of the genes involved in the chromosomal rearrangements identified in the family members. In fact, the presence of multiple CNVs, even if inherited, can be responsible for the atypical clinical presentation and for the minor phenotypical differences between the two affected brothers.

• Major Compulsory Revisions

Abstract

1. Page 2: the authors should mention the other CNVs detected in the patients, even if they are less likely to be pathogenic than the duplication involving MECP2.

Background

2. Page 3, line 3: “behavior phenotypes including” should be eliminated because the three main features of autism spectrum disorders are not just related to behavior.
3. Page 3, line 4: “reciprocal” should be eliminated because it is redundant.

4. Page 3, lines 8-11: there is no reference #6 in the text and in the References List #4 and #6 are referred to the same paper. The authors should correct the list and update the numbers in the text.

5. Page 3, line 8: “led” should be “leads”.

6. Page 3, line 9: “progress” should be “progressive”.

7. Page 3, lines 9-11 and lines 19-21: the sentences “neurodevelopmental disorder….1:10,000 girls” and “Similarly, …. Autistic features” are redundant, the second sentence should be eliminated.

8. Page 4, line 3: why the authors cite only reference #22 if they intend to refer to all the previously reported cases with MECP2 duplication? References #9-27 should all be cited in this case, as well as in Conclusions section (page 10, line 3).

Case Presentation

9. Page 4-6, Clinical Summary: the authors should clarify if they have access to any medical record regarding the members of the family and should provide a more detailed report. Important missing information about the patients include birth parameters (only patient P01A’s birth weight is reported) and percentiles, body measurements at the time of the evaluation and percentiles, vaccinations, hospitalizations. Important missing information about other family members include parents’ medical history (developmental milestones, school, hospitalizations), reason of death for the deceased relatives and their medical history.

10. Page 4, lines 22-23: the sentence “Both the boy…the mother (P01D)” should be eliminated because it is just repeating what assessed at the end of the previous paragraph and is not pertinent with the context of the clinical summary.

11. Page 7, lines 2-12: the authors should provide more details about the genes involved in the reported CNVs: function, pathway, tissue expression pattern, possible interaction with MECP2 or other genes associated with autism and/or intellectual disability.

12. Page 7, lines 12-14: the statements “the other CNVs… can be ruled out as disease causing” is too strong, considering that the authors based their assessment only on the literature. Also, the patients, especially P01B, carry multiple CNVs, that may have a cumulative effect not observable in the parents carrying just one (father) or two (mother) of such rearrangements. The authors should thoroughly discuss the implications of multiple CNVs in the patients and the potential role in determining the phenotype differences between the two brothers.

Discussion

13. Page 8, line 14: the word “patient” should be eliminated because redundant and the author should provide at the end of the sentence the size range for the deletions reported in the literature and the corresponding references.
14. Page 9, lines 17-27: the whole paragraph just repeats the results and presents no discussion. Since the clinical features are already repeated at the beginning of the Discussion section, and in the following Conclusions, the authors should either discuss the findings or eliminate the paragraph (except for lines 15-17).

Supplemental Table
The genes must be in italics.

- Minor Essential Revisions

Abstract
1. Page 2, lines 2-3: “developmental neurological” should be replaced with “neurodevelopmental”, as well as in the Background section (page 3, line 2).
2. Page 2, line 4: “this disorder” should be replaced with “these disorders”, since the spectrum includes more than one condition.
3. Page 2, line 5: “loss-of-function” should be replaced with either “loss of function” or “loss-of-function mutations”, as well as in the Background section (page 3, line 8 and line 19).

Background
4. Page 4, line 1: “duplication in MECP2” should be replaced with “a duplication encompassing the MECP2 gene”.

Case Presentation
5. Page 4, lines 9-10: can the authors provide further information about this cohort of 53 ASD patients? For example, age range, number of males and females, tools used to make the diagnosis. In Table 1 and later in the text the authors mention the ADOS questionnaire: they should clarify if that was used in all these 53 patients.
6. Page 4, line 10: after “boy” the authors should add “(P01A)”, since later in the section they start address the other members of the family with similar codes. In order to be consistent, the author should also replace “Patient 1A” and “Patient 1B” with “Patient P01A” and “Patient P01B”, respectively on page 5 (lines 3, 23, and 24) and 7 (lines 2, 6, and 11).
7. Page 6, lines 16-17: the sentence “mother more apparently so” is not very clear, the authors should rephrase it and explain if the mother is closer to a pathologic score than the father.
8. Page 6, line 28 and page 7, line 1: “between the brothers and with the mother” should be replaced with “in the brothers and the mother”.
9. Page 7, line 28: the authors use the words “very approximate”, implying the analysis is not very precise. How actually reliable is the analysis?

Discussion
10. Page 8, lines 15-16: the sentence “making it likely…duplicated” is not very
clear and should be re-phrased. A possible alternative is “suggesting a potential duplication of a functional copy of the GABRA3 gene”.

Supplemental Methods
11. Page 1, line 3: the authors should provide the web address for the Primer3 software.

• Discretionary Revisions

Background
1. Page 3, line 16: “whose that have found” is not very clear, it should be re-phrased.
2. Page 3, line 22: “deletion or duplication can both result in autistic phenotypes in patients” could be replaced with “both deletion and duplication can generate autistic phenotypes”.

Case Presentation
3. Page 7, lines 6-7: the sentence “that contained no known genes” should be between commas, like the following sentence “containing GDLD4”, in order to avoid confusion.

Discussion
4. Page 8, line 2: the authors should add “Han” after “Chinese” to better specify the ethnicity of the reported family.
5. Page 8, line 4: the authors should add “in size” after “2.22 Mb”.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
I declare that I have no competing interests.