Author’s response to reviews

Title: Clinical and Molecular Genetic Characterization of Familial MECP2 Duplication Syndrome in a Chinese Family

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Author’s response to reviews:

Dear Anne Slavotinek,

We are pleased to submit our second revision titled "Clinical and Molecular Genetic Characterization of Familial MECP2 Duplication Syndrome in a Chinese Family" to BMC Medical Genetics.

Here we have provided point-by-point responses to the reviewers’ comments. We have also revised the manuscript accordingly. We hope that you will find the new version much improved and acceptable for publication.
We thank you for your time and effort with this manuscript.

Xiaoli Chen on behalf of coauthors

Responses to the reviewer’s comments

Reviewer #1: authors nicely presented a study reporting a family trio carrying duplication of MECP2 gene in some family members who showed strong autistic symptoms. this work is well designed and convincingly showed the duplication of MECP2 is strongly associated with the autistic symptoms. this work is a nice addition to current publications reporting MECP2 duplication syndromes.

Reviewer #2: This is a very interesting report on an important topic. I have a few comments.

1. In the background it would be good to report the indications for which microarray is requested. It would also be useful to know for how long it has been in regular use in China and if available how many such diagnostic tests would be performed annually. This could provide some idea of how likely children with MECP2 Duplication syndrome would be identified in China.

Response: Thanks for reviewer’s suggestion. We have added some microarray information used in China according to the reviewer’s suggestion in the second paragraph of the background.

2. Methods

The clinical descriptions are provided in the Methods section. I would have considered the clinical descriptions as a component of the Results and equally as important as the genetic findings. In the Methods section as well as a description of the genetic techniques one should provide the setting and the source of patient data and the ethics approvals for the study. Also you should mention if any of the authors were involved in the clinical examinations or whether the information was extracted from medical records.
Response: Accordingly, we have removed the “clinical descriptions” to the Results section. Meanwhile, we have added the information about ethics approval and patients’ informed consent in the last paragraph of the Methods section (page 5).

3. However, I will make my comments on the clinical descriptions here.

(1) P4, line 13 III:16 It seems unusual for a patient to be admitted to hospital at the age of 11 years for language deficits. This may mean for the investigation of intellectual disability. In most countries this might occur earlier.

Response: Thanks for reviewer’s comments. Actually, the patient III:16 had referred to Jiangxi Children’s Hospital for many times before the age of 11 years. In order to clarify our meaning, we have revised these descriptions in the second paragraph of the Results section “He had referred to Jiangxi Children’s Hospital several times due to global developmental delay since he was 6 months old, and then transferred to the Affiliated Children’s Hospital of Capital Institute of Pediatrics at 11 years old for final diagnosis/treatment.”

I would reorder the presentation of findings including the dysmorphic features earlier and perhaps the brain imaging at the end.

Response: Thanks for reviewer’s suggestion. It is a pity that the patient’ guardian did not agreed to publish more photos including earlier facial feature and brain imaging.

P5, line 9 III:6 Are you able to include a clinical description of the dysmorphic features as you have for III:16?

Response: We have described dysmorphic features of III:6 in the legend of Figure 1. Also we have revised the sentence “and similar dysmorphic features as III:16 were also noticed.” in page 7.

P5, line 58 IV:2 This boy is much younger than the others and so he may not yet have developed seizures or recurrent respiratory infections.

Response: Thanks for reviewer’s comments. We have added a sentence “Young age is the possible explanation.” in line 21 of page 8.
Comments on Table 1

Does period of ambulation mean "age learned to walk" If so please change heading.

Response: We have corrected this error in the table 1.

I would be interested to know who assigned the diagnosis of autism spectrum disorder. In many countries to make this diagnosis involves a 1-2 day assessment. If such assessments were not carried out I might replace with the term "autistic features."

Response: Thanks for comments. Yes, it is tough to use the ADOS, ADI-R to diagnose ASD for each patient due to long duration. In China, not too much clinician has this special diagnosis training. So we used DSM-V, which is based on clinician/parent’s queationnaire, as an alternative for ASD diagnosis. Now we added related information in the last paragraph of Methods section “Physical and neurological evaluations were completed by a neurologist and a developmental specialist. IQ was measured by Wechsler Intelligence Scale for Children (WISC), DSM-V was used by the neurologist for ASD diagnosis.” We have clarified that “ASD was diagnosed in four male patients (III:6, III:16, IV:1, IV:2) based on the DMS-V criteria” in the 1st paragraph of Results sections.

Also according to the reviewer’s suggestion, we change “ASD” to “autistic feature” in some places for precise description (such as table 1).

Do you have any information about the age at development of hand stereotypies? Otherwise the table is very useful.

Response: Agree to review’s suggestion. We tried to record it when we reviewed the parents. It is pity that they can not recall the exact age of their children at development of hand stereotypies.
4. Genetic results

P8 line 28 it states female II:11 harbours the duplication but in line 34 it mentions II:3 and II:11. Can you clarify?

Response: Sorry to confuse. Three female family members (II:11, III:2 and III:12) were detected the duplication using the custom 8×60 K array, and another female (II:3) was detected by MLPA. To fully clarify our meaning we revised the sentence “In total, four female carriers (II:3, II:11, III:2 and III:12) and four male patients (III:6, III:16, IV:1 and IV:2) in this pedigree proved that this duplication is inherited maternally.” in last paragraph of page 9.

5. Discussion

P10 line 6 Please explain what you mean by MECP2 duplication is the key pathogenicity for neurodevelopmental disorders? It may be that this has to be reworded.

Response: Thanks to point out this error. We have reworded the sentence “Now it is recognized that the MECP2 duplication is one of the key causation for neurodevelopmental disorders.” in 39 line page 10.

P10 line 11 It is too early to make statements such as "the prevalence of the MECP2 Duplication syndrome in male and female patients with unexplained mental retardation is approximately 1% and 0.3%, respectively." If this were the case, there would be many thousands of cases in China.

Response: We have reviewed the literature again and revised the sentence “The survey from 700 Caucasian patients suggested that the prevalence of the MECP2 duplication syndrome in male and female patients with unexplained mental retardation is approximately 1% and 0.3%, respectively.” in 40 line page 10.

P10, line 17 When one mentions intellectual disability it is not really necessary to also say developmental delay as all patients with intellectual disability will have developmental delay.
Response: In general, “developmental delay” was described for the children under 5 years old because IQ can’t be evaluated exactly for young child, and “intellectual disability” was diagnosed only for the children more than 5 years old. So we would like to keep this word.

P10, line 20 Please remove the statement or word quite differently "Half of the affected patients die before reaching 25 years old." This widely cited information on mortality has actually been derived from six small cross-sectional studies, each including less than 24 cases. There is a need for epidemiological studies before such estimates are provided in these terms.

Response: Accordingly, we have removed this sentence in page 10.

P10, line 49 We reviewed 17 related publications on MECP2 duplication syndrome and analyzed the prevalence of major medical issues from 179 male patients (See table 1). Please check very carefully that these are all unique patients because it is possible that the same patients have been repeated in different studies especially in reviews by Ramocki and Van Esch.

Response: Thanks for reviewer’s comments. We checked the literatures very carefully and confirmed that these patients were all unique and have not been reported repeatedly.

P11, line 11 More Chinese patients with MECP2 duplication are needed to study the prevalence and pathogenesis of generalized tonic-clonic seizures.

We are not at the stage of estimating the prevalence of seizures in this disorder, although likely ~ just under half, when we don't even know the prevalence and incidence of the disorder. This is the first priority.

Response: We have deleted the related sentences “More Chinese patients with MECP2 duplication are needed to study the prevalence and pathogenesis of generalized tonic-colonic seizure” in page 11.

P11, line 13 As already stated this statement "Most patients with MECP2 duplication syndrome die before reaching 25 years old." Is based on limited information and there is an urgent need for epidemiological including natural history studies. These could be undertaken in China if more cases were identified and an adequate mechanism was established as has been done to study Rett syndrome.
Response: Thanks for reviewer’s comments. We agree your view and we have deleted this sentence “Most patients with MECP2 duplication syndrome die before reaching 25 years old” in page 11.

P11, line 38 This is a particularly well written paragraph.

P12, line 1 However again I would be wary of statements such as "but no female patient has been reported to die before 25 years old"

Response: we have deleted this sentence.

In summary it would be good to comment on the research undertaken in other rare disorders where large databases have been established to provide real answers about natural history.1 There is the potential for this especially in the large Chinese population.


Response: Thanks for reviewer’s comments. We have revised the summary according to your suggestion.