Reviewer’s report

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

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Reviewer: Helen Leonard

Reviewer's report:

This is a very interesting report on an important topic. I have a few comments.

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.

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.

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

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

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

Comments on Table 1

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

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."

Do you have any information about the age at development of hand stereotypies?

Otherwise the table is very useful.

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?

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.

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.

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.
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.

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.

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.

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.1

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"

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.

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

No

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Unable to assess

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

Yes

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

Not relevant to this manuscript

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Please indicate the quality of language in the manuscript:

Needs some language corrections before being published

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