### Manuscript Details

<table>
<thead>
<tr>
<th>Manuscript ID:</th>
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<tbody>
<tr>
<td>Wiley - Letter to Editor:</td>
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<tr>
<td>Manuscript Title:</td>
<td>Distinct de novo deletions in a brother-sister pair with RTT: A case report</td>
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</tbody>
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| Authors: | Mittal, Kirti  
E-Mail: kirtiwiz@yahoo.com  
Gupta, Neerja  
E-Mail: neerja17@gmail.com  
Kabra, Madhulika  
E-Mail: mkabra_alims@yahoo.co.in  
Juyal, Ramesh  
E-Mail: ramesh@nii.res.in  
BK, Thelma  
E-Mail: bkttlab@gmail.com |

### Instructions

**Please provide an editorial review that evaluates the scientific contribution made by the investigator.**

An acceptable paper should ask questions and provide some answers to significant problems related to the scope of the journal. Please give explicit judgment in this regard. Also, please suggest modifications, if revision of the manuscript is recommended, and provide specific criticisms that will be helpful to the authors when revising the manuscript.

### Questionnaire:

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
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<tr>
<td>1. Does the manuscript contain new and significant information to justify publication?</td>
<td>Yes</td>
<td></td>
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<td>2. Is the problem significant and concisely stated?</td>
<td>Yes</td>
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<td>3. Are the experimental and/or theoretical methods described comprehensively?</td>
<td>Yes</td>
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<td>4. Are the interpretations and conclusions justified by the results?</td>
<td>Yes</td>
<td></td>
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<td>5. Is the abstract concise?</td>
<td>Yes</td>
<td></td>
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<td>6. Is the language acceptable?</td>
<td>Yes</td>
<td></td>
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</tbody>
</table>

### Paper Size is:

- **Adequate**
- Too Long
- Too Short

### Tables and Figures are:

- Adequate
Comments

- The event that is described in this paper is unique to my knowledge i.e. the occurrence of male and female siblings with different Mecp2 gene deletions.

- They have correctly stated that the male sibling must have his deletion on the maternal chromosome (minor comment - they have not shown whether the female sibling has inherited on the same chromosome or maternally as well).

- They have not adequately explained why a deletion of the Mecp2 gene in a male, can give rise to such a mild phenotype (they correctly state that mutated males have shown varied phenotype, but not that this could be related to the mutation type e.g. missense mutations - mild). A deletion would suggest a more severe phenotype.

- The results suggest that the male sibling may actually be mosaic for the deletion (a male will have half dosage of a non deleted female, but a deleted male will not be half dosage of a normal male, there would not be dosage at that locus and this would explain his mild phenotype). Therefore, the deletion has likely occurred de novo in him and the mother is not gonadally mosaic for this deletion.

- The authors have not fully detailed their reaction methods e.g. cycling conditions for the dosage analysis.

- There are a small number of grammatical errors in the abstract - "in the MECP2" - needs addition of "gene" and The non-shared de novo deletion" - "non identical de novo deletions"

Recommendation

- Requests for the submission of the paper and the corresponding editor have been submitted.

- The priority for publication is high, and the paper will be published if space is available.

- The recommendation is to accept after minor revision (without re-review).

- The comments are confidential to the editor.

- The comments to editor include:
  - The event described in this paper is unique to my knowledge i.e. the occurrence of male and female siblings with different Mecp2 gene deletions.
  - The authors have correctly stated that the male sibling must have his deletion on the maternal chromosome (minor comment - they have not shown whether the female sibling has inherited on the same chromosome or maternally as well).
  - They have not adequately explained why a deletion of the Mecp2 gene in a male can give rise to such a mild phenotype (they correctly state that mutated males have shown varied phenotype, but not that this could be related to the mutation type e.g. missense mutations - mild). A deletion would suggest a more severe phenotype.
  - The results suggest that the male sibling may actually be mosaic for the deletion (a male will have half dosage of a non deleted female, but a deleted male will not be half dosage of a normal male, there would not be dosage at that locus and this would explain his mild phenotype). Therefore, the deletion has likely occurred de novo in him and the mother is not gonadally mosaic for this deletion.
  - The authors have not fully detailed their reaction methods e.g. cycling conditions for the dosage analysis.
  - There are a small number of grammatical errors in the abstract - "in the MECP2" - needs addition of "gene" and The non-shared de novo deletion" - "non identical de novo deletions"
- The event that is described in this paper is unique to my knowledge.

- My interpretation of your results suggest that the male sib may actually be mosaic for the deletion (A male will have half dosage of a non deleted female, but a deleted male will not be half dosage of a normal male, there would not be dosage at that locus and this would explain his mild phenotype). Therefore, the deletion has likely occurred de novo in him and the mother is not gonadally mosaic for this deletion. Do you agree or have I misinterpreted your results?

- Have you any evidence to show whether the female sib has inherited on the same chromosome or maternally as well?

Files attached

- No files have been uploaded.