Author’s response to reviews

Title: Identification of a Novel CTCF Mutation Responsible for Syndromic Intellectual Disability - A Case Report

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Author’s response to reviews:

Dear Editor,

We would like to thank you for providing us with the decision letter and reviewers' comments. We have studied each of the points raised in the decision letter and we either made the requested changes or responded clearly. Below is a detailed list of these changes/responses. We hope that the latter are satisfactory and we are ready to make further changes if need be.

Best regards,

Comments and [Responses]:
Reviewer 1:

1. Case presentation. Can the authors comment more on ...figure 1 could be helpful for clarification. [A detailed family history was taken. However, no similarly affected relatives were found. This detail has been added to the text. Pedigree added as Fig. 1a]

2. Case presentation. Did the patient display any behavioral anomalies and/or autistic features? ... the previously reported cases. [Apart from generalized developmental delay, no specific behavioral anomalies could be detected. Comparison of phenotypic features to patients in previous case reports is provided in Conclusions]

3. Molecular results. Was the de novo CTCF mutation the only variant that passed their filtering criteria in WES ... listing all variants passing filtering criteria. [The CTCF variant was the only most probable candidate causal variant detected in this patient. However, one heterozygous missense variant in the gene SETD5 and another heterozygous, missense variant in SH3PXD2B survived many filtration rounds but evidence of causality was deemed weak based on the limited phenotypic overlap and incompatibility with expected mode of inheritance. WES was mistakenly mentioned in Molecular results as the method that uncovered the CTCF mutation in the parents, this is now corrected. Only CTCF was sequenced in parents and hence we stated that our reported mutation is de novo]

4. Molecular results. The authors should add ... genomic, cDNA as well as protein level. [Done as required by Reviewer]

5. In Figure 1, the authors should organize the electropherograms ... position for all three samples for easier viewing. [Done as required by Reviewer]

6. Conclusions. Lines 11-18. The authors focus their discussion a lot on the role of a potential truncated protein resulting from their frameshift mutation. ... This paragraph should be rephrased in the conclusions section to reflect this. [Done as recommended by Reviewer]
Reviewer 2:

Title: « Autosomal dominant mental retardation … syndromic intellectual deficiency. [Title is changed as recommended by Reviewer]

Abstract: 1. Page 2, line 3 « varied … associated with this phenotype? [Phenotype specified as recommended by Reviewer]

2. It would be interesting to precise the aims of the … you perform exome sequencing on this particular patient? [WES was performed for diagnostic purposes and it is usually done for similar cases of intellectual disability in children born to consanguineous parents]

3. Line 8, regarding the whole exome … that it was a trio-based approach, as it is important in the variant filtering. [Clarification made as recommended by Reviewer; kindly see response to question#2 in Results]

4. Line 11. « The clinical picture … It could probably be improved to be more accurate. [Sentence modified as recommended]

Introduction: 1. Page 3, line 18 « However, the first germline … which goes along with the results reported here. [Text modified as recommended by Reviewer]

2. Line 19 « Numerous lines of evidence support that CTCF … evidence? [This point is elaborated on in the penultimate paragraph of Conclusions; therefore, it was necessary to avoid repetition in the Introduction]

3. You mention that three CTCF mutations have previoulsy been reported. … by Gregor et al? [Information added to Conclusions as recommended by Reviewer]
4. Line 24 « Patients also display minor facial … order to avoid redundancy with the word « display »? Could you be more precise about the dysmorphism? [Done as recommended by Reviewer]

5. Are there other genes involved in chromatin structure and epigenetic regulation associated with syndromic intellectual disability? [Yes, there are many, however the benefit of listing them in the manuscript is doubtful]

Case presentation:

1. Your index case presents with growth retardation, which is a cardinal feature of her phenotype. … features in this condition? Has osteodensitometry been performed to assess the osteopenia? [Patient’s height upon two subsequent follow-ups remained under the 3rd centile. This data has been added to the text. X-rays depicting the generalized diffuse osteopenia have been added as Fig 1c and 1d. Osteodensitometry data is not available, as it is not generally perfumed on children in our facility]

2. Could you please mention shortly the reason why your patient was referred to genetics? That would be interesting to understand about the diagnostic approach. [Details added to the text as recommended]

3. I would suggest to be more …, by describing first the clinical picture, then the imaging data such as echographs and X-rays. [Modifications made as recommended by Reviewer]

4. You mention that the patient had a head circumference below the third centile. How severe is this microcephaly? … and what were the results? [Microcephaly was severe (> 3 SD below mean). This is now mentioned in the report. Only a USS Brain was performed for the patient]

Results: 1. The identified mutation is …to the other evidences you describe, represents a strong evidence for the pathogenicity of your variant. [This very important point was alas missed, and now it is added to Conclusions as was thankfully recommended by Reviewer]
2. Were there other candidate genes that could account for the patient's ... the number of de novo variants. [The CTCF variant was the only most probable candidate causal variant detected in this patient. However, one heterozygous missense variant in the gene SETD5 and another heterozygous, missense variant in SH3PXD2B survived many filtration rounds but evidence of causality was deemed week based on the limited phenotypic overlap and incompatibility with expected mode of inheritance. WES was mistakenly mentioned in Molecular results as the method that uncovered the CTCF mutation in the parents, this is now corrected. Only CTCF was sequenced in parents and hence we stated that our reported mutation is de novo]

Conclusions: 1.

Some interesting reference ... (Rao et al, 2014). [the link between CTCF function and memory formation is highlighted in Conclusions with reference to Sams et al, 2016 as recommended by Reviewer]