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

Version: 0 Date: 06 Jan 2017

Reviewer: Anne Gregor

Reviewer's report:

In this manuscript Bastaki et al. report a new de novo frameshifting mutation in CTCF in an Arab patient with MRD21. This is only the fifth patient with a CTCF aberration reported to date. It is also the first de novo CTCF mutation reported in an Arab patient. The study helps to further delineate and expand the phenotype associated with CTCF mutations, adding skeletal anomalies to the phenotypic spectrum. The manuscript is well written, but will benefit from some clarifications both regarding the clinical as well as the molecular characterization.

Specific points:

1. Case presentation. Can the authors comment more on potential family history of any of the phenotypes described, especially the skeletal anomalies that have not previously been associated with CTCF mutations. Are there any other affected family members? Does the patient have any siblings (affected or unaffected)? Additionally, a pedigree in figure 1 could be helpful for clarification.

2. Case presentation. Did the patient display any behavioral anomalies and/or autistic features? For easier comparison of phenotypes, the authors could consider to add a table comparing the phenotypic features of the patient described in this case report with the previously reported cases.

3. Molecular results. Was the de novo CTCF mutation the only variant that passed their filtering criteria in WES analysis (de novo, compound heterozygous or homozygous)? If there were any other variants the authors should add a table listing all variants passing filtering criteria.
4. Molecular results. The authors should add the full mutation description on genomic, cDNA as well as protein level.

5. In Figure 1, the authors should organize the electropherograms so that the mutation is in the same position for all three samples for easier viewing.

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. However, the in silico prediction for the mutation lists nonsense mediated decay (NMD) as the most likely outcome. This is in line with the expression analysis from the 2 frameshift mutations published by Gregor et al., that showed haploinsufficiency probably due to NMD as the most likely pathomechanism. This paragraph should be rephrased in the conclusions section to reflect this.

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

Yes

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

Yes

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
Quality of written English
Please indicate the quality of language in the manuscript:

Needs some language corrections before being published

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