Reviewer’s report

Title: Disruption of chromatin organisation causes MEF2C gene overexpression in intellectual disability: a case report.

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Reviewer: Cheryl Shoubridge

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Disruption of chromatin organisation causes MEF2C gene overexpression in intellectual disability: a case report.

Yauy et al and Gatinois report on a patient with intellectual disability with a balanced cytogenetic abnormality due to a translocation of chromosomes 5 and 3. Mapping of the breakpoints indicates that while no gene sequence is disrupted, the 5q14.3 region containing MEF2C is localized in a novel TAD structure with a long non-coding RNA translocated from chromosome 3. The authors indicate that MEF2C gene expression is increased in patient LCLs, likely due to this altered TAD structure. Despite substantial evidence for a (partial) loss of MEF2C either via direct mutation or via haploinsufficiency due to CNV and microdeletions in this region contributing to pathogenicity of MRAD20 syndrome, there is little evidence for pathology due to increased MEF2C.

Comments to author

1) I believe the term "triplosensitivity" is not correct here as there is simply not a third copy.
2) It would be useful to show that other genes not included in the novel TAD have normal levels of expression in patients vs controls, such as TMEM161B.
3) Although the authors show that MEF2C expression is upregulated in patient but not controls, they do not adequately address what is driving this altered expression.
4) The current figure 1 could be improved. It would be useful to show the region of 5q14.3 prior to translocation above the current Fig1 A, and include such elements as enhancers that are likely to be involved, CTCF sites, and perhaps in relation to other balanced translocations reported in the literature.
5) I believe the report would benefit from a summary (table or figure) of the clinical findings (and genomic) of the other patients with likely pathology due to increased MEF2C.
6) What is the consequence of too much MEF2C and its relation to pathology? Zweier 2010 showed that in cases of 5q14.3 q15 microdeletion, these MEF2C deficient patients also had diminished levels of MECP2 and CDKL5 in the blood, linking the pathology overlapping some aspects of atypical Rett syndrome. Although the pathology here is much milder, common with overexpression / duplications compared to deletions, could the overexpression of MEF2C in the current patient be having an impact on these two related pathway genes?

Minor comments to author

1) In the section headed "Case presentation and results" (line 83) the authors indicate the patient has "no epilepsy syndrome". However, in the discussion (line 116) they mention a "unique febrile
I appreciate these are different things, but it would be better to include all necessary clinical descriptions as part of the case presentations and results section.

2) Fish could be conducted to prove that the proposed MEF2C and linc01266 are indeed located in the same TAD on the translocated chr5 derivative.

3) (line 93) - should spell out the abbreviation "AP" in full.

4) (Line 98) - This sentence is incomplete - "Visualization of 3D conformation in 7 different cell types suggests that either the MEF2C gene and LINC01226 IncRNA exists in one TAD." Should there be an "or" explanation given that the sentence contained an "either".

5) Data described in Figure 1 legend is potentially misleading. In "Case presentation and results" (line 101) the authors indicate the expression of MEF2C in patient LCLs is compared to 3 controls - with each sample repeated 3 times. However, in the legend for Figure 1 the data is indicated as n=3 samples for patient and 9 for controls.

6) Does the gender of the controls matter?

7) Figure 1 legend (line 228) "…from GM12878 cell lines experiments" Only one of these needs to be plural.

8) Supplementary Figure 1 - A more descriptive figure legend is required. As Figure 1 shows the IncRNA as names, this should be consistent in this supplementary figure instead of listing as AK and AL accession names.

9) Supplementary Figure 2 - Legend (line 237) states these are chromosome 5 TAD boundaries, but the figure indicates chr3, as does the reference to this figure in the text (line 100). Also, there is no information to relate the location of to the CNTN6 and CETN3 genes from chr3 on this figure.

**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.

No

**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.

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