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

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Reviewer: Daphne Lehalle

Reviewer's report:

The authors report the first individual from Arab ethnicity to present with MRD21, the phenotype associated with CTCF haploinsufficiency, identified through whole exome sequencing. If the role of CTCF in chromatin structure and epigenetic regulation has been well studied in recent years, only three individuals with CTCF mutations have been identified so far. This report is therefore very interesting as it provides new insight into a rare disorder. Furthermore, it highlights the power of whole exome sequencing in the identification of genes responsible for unspecific intellectual disability. However, it could be improved by minor changes.

Title: « Autosomal dominant mental retardation 21 » is a quite long and not very suggestive disorder denomination. I would therefore suggest to change the title to highlight the main point of this report: the identification of a novel CTCF mutation responsible for syndromic intellectual deficiency.

Abstract:

1. Page 2, line 3 « varied intellectual disability ». Please could you be more specific regarding the degree of intellectual disability that is usually associated with this phenotype?

2. It would be interesting to precise the aims of the study, or the diagnostic approach. Was the whole exome sequencing performed as part of a research study - then, how many individuals were screened and what were the inclusion criteria? Or was it for diagnostic purposes - then, what is the patient's phenotype, what was the initial diagnosis? Why did you perform exome sequencing on this particular patient?
3. Line 8, regarding the whole exome sequencing methods, you should precise that it was a trio-based approach, as it is important in the variant filtering.

4. Line 11. « The clinical picture of this novel mutation is mostly concordant with previously reported cases of MRD21, albeit with more symptoms that were not observed before » As you do not mention in the abstract the clinical picture of your patient, neither what was observed in the previous reports, this sentence does not add any value to the abstract. It could probably be improved to be more accurate.

Introduction:

1. Page 3, line 18 « However, the first germline CTCF mutations and the resulting phenotype/s were presented in [5], in which, one de novo missense mutation and two frameshift ones and were found to be associated with a phenotype of intellectual disability, microcephaly, and growth retardation ». This sentence contains three key points. I would suggest to split it in order to emphasize their importance and to develop it if possible: germline CTCF mutations are responsible for a phenotype in human; this phenotype is syndromic intellectual disability with microcephaly and growth retardation; the reported mutations are frameshift and missense mutations, which goes along with the results reported here.

2. Line 19 « Numerous lines of evidence support that CTCF haploinsufficiency is responsible for this phenotype of perturbed cognition and stunted growth in the affecteds ». Could you please precise what are these lines of evidence?

3. You mention that three CTCF mutations have previously been reported. Could you please precise how many patients were reported in total? Are there any familial cases or recurrent mutations? What about the fourth patient with a deletion involving CTCF, reported by Gregor et al?

4. Line 24 « Patients also display minor facial dysmorphisms and may have heart anomalies, e.g. atrial septal defect (ASD) and patent ductus arteriosus (PDA) in addition to displaying an autistic behavior » Could you please rephrase this sentence in order to avoid redundancy with the word « display »? Could you be more precise about the dysmorphism?
5. Are there other genes involved in chromatin structure and epigenetic regulation associated with syndromic intellectual disability?

Case presentation:

1. Your index case presents with growth retardation, which is a cardinal feature of her phenotype. The mention of parental heights is very accurate. Could you please add to the report the interpretation of these data (standard deviations of the parental heights), as well as the taget size of your patient? Furthermore, I understand that the length of the child was probably not assessed at birth because of the prematurity. However, would it be possible to give more information about the growth kinetics? Is the growth retardation at prenatal or postnatal onset? Could you please precise the exact growth parameters of the patient, or the standard deviations? Would it be possible to add to the X-rays to the report to show the abnormalities, as they are new features in this condition? Has osteodensitometry been performed to assess the osteopenia?

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.

3. I would suggest to be more systematic in the case presentation, by describing first the clinical picture, then the imaging data such as echographs and X-rays.

4. You mention that the patient had a head circumference below the third centile. How severe is this microcephaly? As a cardinal feature of MRD21, affecting the three other individuals with CTCF mutation, it should be more emphasized in the report. Could you please precise if a brain imaging has been performed in this context, and what were the results?

Results

1. The identified mutation is a frameshift variant, leading to CTCF haploinsufficiency. I would suggest that you add to this report that CTCF is a gene highly intolerant to
haploinsufficiency, as shown by the pLi=1 measured by the ExAC database. This data, added to the other evidences you describe, represents a strong evidence for the pathogenicity of your variant.

2. Were there other candidate genes that could account for the patient's phenotype? I would suggest to mention the number of de novo variants.

Conclusions
1. Some interesting reference regarding the link between CTCF mutations and intellectual disability are missing (Sams et al, 2016), as well as regarding the role for CTCF in development (Narendra et al, 2016) or in chromatin regulation (Rao et al, 2014).

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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