Reviewer's report

Title: Clinical features and gene mutational spectrum of CDKL5-related diseases in a cohort of Chinese patients

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Reviewer: Alessandra Renieri

Reviewer's report:

Author's report

Authors reported the clinical description of 10 Chinese patients, 9 females and 1 male, with mutations in CDKL5 gene by screening 102 patients with early-onset epileptic encephalopathies and early-onset seizure variant of Rett syndrome. Out of 9 females, six were diagnosed “a priori” as early-seizure variant and three as “non-syndromic epilepsy”. The only male was diagnosed “a priori” as infantile spasms.

The writing should benefit from professional editing.

- Major Compulsory Revisions

The content of the manuscript is of relevance to the sector. Even if it only described 10 patients, we should consider that this is a rare disease and there was the effort of the authors to maximize the clinical description. Therefore, I think that the article is worthy of publication. However, some very important major revisions are needed:

1. The definition of “non-syndromic EP” was incorrectly used throughout the manuscript. In fact, from a technical point of view, “non-syndromic EP” means isolated epilepsy without other signs such as developmental delay or other (stereotypies, etc.). I believe that using this term the authors intended to include patients having a complex clinical phenotype including epilepsy and other signs, in which the clinician did not recognize a known syndrome. Therefore, the term “non-syndromic EP” should be replaced with “unknown epileptic syndrome”.

2. Out of 9 females, six were “a priori” diagnosed as early-seizure variant and three as “non-syndromic epilepsy” (meaning “unknown epileptic syndrome”).

I have analyzed very carefully the phenotype of these last 3 patients (Patient n.1, n.3, and n.10). From the description, these 3 patients seem to have a clinical diagnosis of early-onset seizure variant of Rett syndrome as well. Therefore, the authors should be emphasized in the manuscript that, although the clinician who saw the 3 patients did not think of this diagnosis “a priori”, they can be classified in this type of diagnosis “a posteriori”.

3. Authors should highlight in the abstract and throughout the manuscript the
main results that are:

a) mutations in CDKL5 were found in females with early-onset seizure variant of Rett syndrome diagnosis;

b) mutations in CDKL5 were found in males with early-onset epileptic encephalopathies different from Rett syndrome (this is only one male but the trend is evident).

Additional evidence of this difference is seen in Table 1 in which all females have stereotypes that are instead absent in the only one CDKL5 mutated male.

- Minor Essential Revisions

ABSTRACT

1- paragraph of “Object”: the phrase “have been associated with early-onset epileptic encephalopathies such as infantile spasms, early-onset intractable epilepsy and the Hanefeld variant of Rett syndrome.” should be reworded as follows: “have been associated with early-onset seizure variant of Rett syndrome, also named Hanefeld variant, or early-onset epileptic encephalopathies”.

2- paragraph of “Conclusion”: the phrase “Mutations in CDKL5 gene account for 2.6% of 71 girls and 3.2% of 31 boys with early-onset epileptic encephalopathies or the Hanefeld variant of Rett syndrome.” should be reworded as follows “Mutations in CDKL5 gene is responsible of early-onset seizure variant of Rett syndrome in girls and of early-onset epileptic encephalopathies such as infantile spasms in males.”

3- paragraph of “Methods: authors should replace “MRI” and “EEG” with “magnetic resonance imaging” and “electroencephalogram”. The use of abbreviations in abstract is not appropriate.

INTRODUCTION

1- Reference n.1 should be replace with a paper describing clinical criteria of the variant such as Artuso R. et al. Brain Dev. 2010 Jan;32(1):17-24.

2- Reference n.2 is mentioned in inappropriate manner with respect to the sentence to which it refers, therefore it is recommended replacing it with reference n.15.

3- the phrase “The early-seizure of RTT, initially described by Hanefeld in 1985, showed overlapping phenotype with early-onset epileptic encephalopathies.” should have as reference the Hanefeld’s paper.

4- Please enter appropriate citations to the following sentence “The initial genetic screening of CDKL5 mutations were performed in a cohort of patients with early-onset seizure variant of RTT without MECP2 mutation and infantile spasms with some Rett-like features.”, such as Scala E. et al. J Med Genet. 2005 Feb;42(2):103-7, and Mari F. et al. Hum Mol Genet. 2005 Jul 15;14(14):1935-46.

5- last sentence of first paragraph: “drug-resietant” should be changed in “drug-resistant”.

6- last sentence of first paragraph: add a comma after “months of life”.
METHODS
1- Describe the used sequencing method.

RESULTS
1- In “CDKL5 gene mutations”: “one (2.77 %, 1/36) cases were diagnosed with infantile spasms” should be changed in “one case was diagnosed with infantile spasms.
2- In “Clinical manifestation”, the authors should describe for each female patient what kind of stereotypes is present.
3- In “Clinical manifestation”, add the actual head circumference percentiles for each patient (female or male). This should also be added in Table1.
4- In “Clinical manifestation”: the authors should describe for each patient the mutations found.
5. The authors should collect additional Rett signs such as feeding difficulties, sphincter control, IQ, gastrointestinal disturbances, bruxism, eye pointing capability, and breathing dysfunction. This may help readers in understanding the difference between females and male.
6- In “Patient 6 and Patient 7”, it is not clear to me what means “elder” and “younger” in twin sisters.

DISCUSSION and CONCLUSIONS
1- Discussion and Conclusions should be completely rewrite highlighting the fact that CDKL5 mutations are responsible of a variant of Rett syndrome in females and a slightly different condition in males, where Rett syndrome characteristics are more difficult to recognize.

Level of interest: An article of importance in its field

Quality of written English: Needs some language corrections before being published

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
I declare that I have no competing interests