Dear Editors/Reviewers

Thank you for your letter and for the reviewers' comments concerning our manuscript entitled "CNKSR2 mutation causes the X-linked epilepsy-aphasia syndrome：A case report" (ID: 40627). Those comments are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our researches. We have studied comments carefully and have made correction which we hope meet with approval. Revised portion are marked in red in the paper. The main corrections in the paper and the responds to the reviewer's comments are as flowing:

Responds to the reviewer's comments:

Reviewer #1:（00722239）

1. Response to comment: In Figure 1, the table is written in Chinese. Please correct it to English.

Response: Figure 1 has been changed to Figure 2, and the table in the figure has been described in English.

2. Response to comment: The image resolution of Figure 3 is too poor to understand by readers. Please revise Figure 3.

Response: Figure 3 is replaced with the original image to improve the resolution.

Reviewer #2:（00646452）

1. Response to comment: Brief description on the process of genetic analysis is necessary. Maybe authors isolated genomic DNA from whole blood and PCR method was performed to analyze CNKSR2 gene. Description on the brief method should be added. Information on PCR primers used would be better provided.

Response：We briefly describe the genetic analysis process. {2 ml of peripheral venous blood was extracted from the patient and her parents. Genomic DNA from the patient was extracted from blood using standard methods for whole exome sequencing. Mutation of CNKSR2 gene was found in the children. Primers were designed based on the gene tested (chrX:21627228). The parents used Sanger sequencing after PCR to analyze the coding exons and flanking introns of the CNKSR2 gene (NM_014927). The established variant was sequenced in both forward (AGTCCCCAAGCCCAAGCTAC) and reverse directions (ACTGGCTGTCTTGCGAATGG).}

2. Response to comment: In Figure 1, many readers cannot read Chinese characters. Translation into English is necessary.

Response: Figure 1 has been changed to Figure 2, and the table in the figure has been described in English.

Reviewer #3:(00646357)

1. Response to comment: Add more on the basic of this disease in the introduction and the unique of this study compared to other studies discuss the same issue.

Response: We have increased the discussion, including the basic of the disease and our further understanding of the disease. {GRIN2A mutations reduce NMDA receptor trafficking and agonist potency–molecular profiling as well as functional rescue [15]. GRIN2A gene is a rare causative gene in Chinese patients with EAS, suggesting the possibility of other genes being involved in the pathogenesis [16]. The underlying mechanism for EAS disorders occurrence remains unknown, although environmental factors such as thalamic injury [18] and immunity disorders [19], with evidence of onconeural antibodies that can cause the EEG phenotype, have been reported. Studies have shown that the antibodies of brain endothelial cells and nuclei in children were elevated [20]. Additionally, inflammatory markers of children with electrical status epilepticus in

sleep (ESES) may be increased [21]. Some researchers have proposed a potential autoimmune reaction secondary to blood-brain-barrier disruption from a thalamocortical uncoupling secondary to the spike-wave activation seen in slow-wave sleep [22]. Furthermore, few genetic causes of ESESS/CSWSS/epilepsy aphasia spectrum have been reported, where the common underlying pathway is channelopathy [23].}

2. Response to comment: English language correction through the manuscript.

Response: We have sent the paper to the AJE editing company to polish the language.

3. Response to comment: Update of references as most of references are old using these referances.

Response: We have added 10 references, 3 of which are in 2018, 1 in 2017, 1 in 2016, and 1 in 2015.

Reviewer #4:(00646418)

1. Response to comment: kindly provide follow up and treatment details.

Response： We have added follow-up and treatment details to the patient. {After definite diagnosis, patients were given immunoglobulin (400~500 mg/kg/ day, 3~5 days for 1 course) and oral prednisone (from 1~3 mg/kg per day, and after one month, changed to 1 mg/kg/day), with a total course of 6 to 12 months. Meanwhile, lamotrigine (75 mg/qd) and sodium valproate oral solution (6 ml/bid) were continued for antiepileptic treatment. At telephone follow-up one year later, the child had fewer epileptic seizures than before as well as partial improvement in verbal ability and an ability to repeat speech; however, the patient had no improvement in intelligence.}

2. Response to comment: Lesson learned from managing this case would be more interesting.

Response: We consider that the clinical and genetic factors of the case are both important. Because this genetic mutation may be an important cause of morbidity in patient, so we focused on this gene. At the same time, we have also increased the lesson learned from managing this case. {The disease duration was more than 6 years. If diagnosed early and actively treated, the patient's intelligence, seizures, and language may have been better mitigated. The early diagnosis and early use of antiepileptic drugs as well as hormone therapy can recover speech comprehension to different degrees and improve abnormal discharge. Therefore, the overall prognosis of patients is good. Clinical seizures should be treated with antiseizure drugs, and barbiturates, carbamazepine, and phenytoin should be avoided as they can potentiate spike wave discharges during sleep [24-25].}

3. Response to comment: English and grammar are poor.

Response: We have sent the paper to the AJE editing company to polish the language.

Other changes:

1. The reference of “[15]” were changed to “[17].

We tried our best to improve the manuscript and made some changes in the manuscript. AJE editing company has polished our articles. These changes will not influence the content and framework of the paper. And here we did not list the changes but marked in red in revised paper.

We appreciate for Editors/Reviewers’ warm work earnestly, and hope that the correction will meet with approval.

Once again, thank you very much for your comments and suggestions.

Sincerely yours,

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