

## A Novel Frameshift Mutation in CDKL5 Causes Epilepsy in A Chinese Patient

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### Keywords:

Chinese; Epilepsy; CDKL5 gene

### Abbreviations:

CDKL5: Cyclin-Dependent Kinase-Like 5; DEE2: Developmental and epileptic encephalopathy2; WES: Whole Exome Sequencing; ACMG: American College of Medical Genetics and Genomics; OMIM: Online Mendelian Inheritance in Man; HGMD: Human Gene Mutation Database; EEG: Electroencephalography

## 1. Abstract

**1.1. Objective:** To investigate the genetic causes of a 6-month-old Chinese female patient with infantile epilepsy.

**1.2. Methods:** Clinical diagnosis and next-generation sequencing.

**1.3. Results:** The patient carries a heterozygous frameshift mutation (c.1592dupC p. Thr531fs) in the CDKL5 gene. The mutation was confirmed as a de-novo mutation as it does not exist in either of the parent's DNA. This mutation was evaluated as a pathogenic mutation based on the standards and guidelines of ACMG and clinical research publications.

**1.4. Conclusion:** The de-novo frameshift mutation (c.1592dupC p. Thr531fs) in the CDKL5 gene is the genetic cause of the infantile epilepsy for the 6-month-old Chinese female. So far, this mutation of CDKL5 gene has not been previously reported in the worldwide overall populations.

## 2. Introduction

The X-linked gene Cyclin-Dependent Kinase-Like 5 (CDKL5) is located on the short arm of human chromosome X (Xp22.13). Pathologic mutations in the CDKL5 gene associated with severe epilepsy and cognitive, motor, visual, and autonomic disturbances et al [1]. The aim of the present study was to detect and report genetic causes of a 6-month-old Chinese female with epilepsy. The patient was found to have a frameshift mutation (c.1592dupC p. Thr531fs) in the CDKL5 gene and the mutation does not exist in

either of her healthy mother or father. The de-novo mutation in the CDKL5 gene has not been reported in previous studies.

## 3. Materials and Methods

### 3.1. Clinical diagnosis

A 6-month-old female patient who was born with no family history of seizures or other types of neurological disease, had experienced an onset of seizures since age 5 weeks. The epileptic spasms usually occurred during her sleep period and rarely during daytime. The syndromes lasted approximately 20 to 30 seconds at each occurrence. The patient was carried to our hospital (Chengdu Shengkang Epilepsy Hospital), and diagnosed with infantile and early childhood epileptic syndromes/focal seizure. The following clinical tests were performed for the patient: physical examinations, blood routing, brain MRI, and electroencephalogram.

### 3.2. Molecular Test

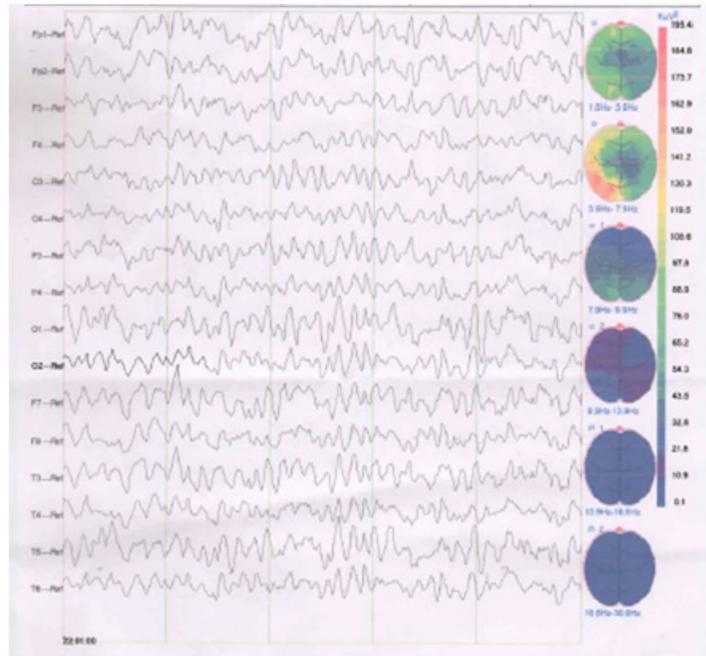
In order to study the cause of the disease, a whole exome sequencing was performed for the patient. Furthermore, Sanger sequencing was used to verify the mutation for the patient and her healthy parents. Sequencing data was analyzed by using numerous bioinformatics' software and careful analysis. The pathogenicity of the mutation was evaluated based on the standards and guidelines of American College of Medical Genetics and Genomics (ACMG), Clinvar database, Online Mendelian Inheritance in Man (OMIM), Human Gene Mutation Database (HGMD), and clinical research papers that were published in scientific journals.

## 4. Results and Analysis

### 4.1. Clinical Data Analysis

The patient was carried to our hospital (Chengdu Shenkang Epilepsy Hospital). The patient cannot walk by herself and has a poor binocular tracking function. The patient also appears to be slow on the growth and development. The patient had no abnormality in her heart, lung and abdomen. Blood routine and hematuria screening were normal. The Brain CT showed no abnormality in the patient's brain parenchyma. As displayed in (Figure 1), Electroencephalography (EEG) showed abnormal discharge during the

awaking and sleeping periods. The patient was diagnosed with infantile and early childhood epileptic syndromes, focal seizure, brain dysplasia, and mental retardation. Antiepileptic drugs of Sodium valproate, Oxcarbazepine, Levetiracetam, Zonisamide, Lacosamide, and Topamax et al. were prescribed, and the improvement of the syndromes of the patient was observed, as the epileptic seizures occurred less than before. Currently, the epilepsy occurs two to three times a week and the episodes are considered refractory epilepsy. The patient is currently taking Phenobarbital, Sodium valproate, and Zonisamide.



neurologic disorder characterized by onset of seizures in the first months of life and severe global developmental delay resulting in impaired intellectual development and poor motor control. Other features include lack of speech development, subtle dysmorphic facial features, sleep disturbances, gastrointestinal problems and stereotypic hand movements et al., and also there are some phenotypic overlaps with Rett syndrome, but DEE2 is considered to be a distinct entity (OMIM#300672).

We report here a 6-month-old patient with the mutation in CDKL5 gene using panels of epilepsy-associated genes and describe the phenotype-genotype correlations in this female patient. The mutation which was identified was a de-novo frameshift mutation (c.1592dupC p. Thr531fs; NM\_001323289) in exon 11 of CDKL5 gene.

More than 1000 mutations of CDKL5 gene were reported and analyzed in the Clinvar database, including deletion, duplication, indel, insertion and single nucleotide types. Around 70% of those mutations were evaluated as pathogenic or likely pathogenic mutations, and about 40% of them responsible for the occurrences of Benign familial infantile seizures or DEE2. The single nucleotide mutation was the most frequently reported mutation type and was about 84% in the total mutations. However, note that there is only about 8.5% of single nucleotide mutations were due to de-novo mutations [2]. Generally, about 28% of women with early-onset epilepsy carried mutations in the CDKL5 gene, and around 81% of these mutations are novo mutations [3].

We evaluated around 360 Chinese patients with epilepsy and did not identify any other patients with this de-novo frameshift mutation in CDKL5 other than in the subject 6-month-old girl. The mutation was evaluated as the cause the disease. The mutation has not been detected in the patient's unaffected maternal father and mother who never had seizures. This mutation of CDKL5 gene related with epilepsy is the first reported in the worldwide overall populations.

In a 6-month-old Chinese girl with epilepsy, we identified a de-novo frameshift mutation c.1592dupC in exon11 of CDKL5 gene, resulting in a p. Thr531 frameshift. This variant was evaluated as a pathogenic mutation based on the ACMG. So far, this mutation of CDKL5 gene related with epilepsy is first reported in the worldwide overall populations.

## 6. Conclusion

In a 6-month-old Chinese girl with epilepsy, we identified a de-novo frameshift mutation c.1592dupC in exon11 of CDKL5 gene, resulting in a p. Thr531 frameshift. This variant was evaluated as a pathogenic mutation based on the ACMG. So far, this mutation of CDKL5 gene related with epilepsy is first reported in the worldwide overall populations.

## References

1. Demarest S, Marsh ED, Amin S, Benke TA, Neul JL, Panzer A, et al. Severity Assessment in CDKL5 Deficiency Disorder. *Pediatr Neurol.* 2019; 97: 38-42.
2. Clinvar
3. Nemos C, Philippe C, Saunier A, Verneau F, Jonveaux P, N'guyen MA, et al. Mutational spectrum of CDKL5 in early-onset encephalopathies: a study of a large collection of French patients and review of the literature. *Clinical genetics.* 2009; 76: 357-371.