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CNKSR2 mutation causes the X-linked epilepsy-aphasia syndrome: A case report and review of literature

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Abstract

The mutation in *CNKSR2* leads to a broad spectrum of phenotypic variability and manifests as an X-linked intellectual disability. However, we reported that the male patient in this study not only had intellectual disability but also epileptic seizures. In addition, there were progressive language impairment, attention deficit hyperactivity disorder and autism. Electroencephalograms showed continuous spike-and-wave during sleep. Genetic testing revealed a *de novo* mutation of the *CNKSR2* gene (*c.2185C>T, p.Arg729Ter*) in the child that was not detected in the parents. Therefore, the child was diagnosed with X-linked epilepsy aphasia syndrome. Deletion of the *CNKSR2* gene has been rarely reported in epilepsy aphasia syndrome, but no *de novo* mutation has been found in this gene. This report not only adds to the spectrum of epilepsy aphasia syndrome but also helps clinicians in diagnosis and genetic counseling.

Key words: Epilepsy; Language impairment; Mental retardation; *De novo* mutation of *CNKSR2*; X-linked epilepsy-aphasia syndrome

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Core tip: Patient with epileptic seizures and progressive language impairment. Genetic testing revealed a *de novo* mutation of the *CNKSR2* gene in the child and was not detected in the parents. Therefore, the gene may lead to X-linked epilepsy aphasia syndrome.

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INTRODUCTION

Atypical epilepsy-aphasia syndrome is caused by Landau-Kleffner syndrome (LKS) and epileptic encephalopathy, with a continuous spike-and-wave pattern during sleep^[1]. The synapse is the core component of brain operations and executive functions, and its function plays an important role in brain neuron function^[2]. *CNKSR2* is located on the X chromosome, and as a synaptic protein, it is involved in RAS/MAPK signal transduction^[3]. It is highly expressed in the brain^[4], and its mutation or deletion causes a wide range of neurodevelopmental defects^[5]. Currently, *CNKSR2* deletion or mutation has been shown to induce symptoms that are part of the EAS spectrum^[6-9]. In this paper, we review clinical data and genetic test results of a child with epilepsy and aphasia and have identified a *de novo* mutation: *CNKSR2* (*c.2185C>T*, *p.Arg729Ter*). We reviewed the literature and analyzed the clinical features of X-linked epilepsy-aphasia syndrome in order to assist clinicians in their diagnosis of this condition and to help provide genetic counseling.

CASE REPORT

An 8-year and 8-mo-old boy from China was admitted to the hospital due to paroxysmal unconsciousness for more than 6 years. The performance of paroxysmal loss of consciousness was associated with brief jerks of the limbs, eye staring, lip bruising, spitting foam from the mouth, and sometimes with urinary incontinence; however, fever was absent. Each episode lasted 2-3 min and resolved on its own. The episodes of epileptic seizures occurred in varying lengths of times; sometimes, the episodes occurred once every six months, and sometimes only once a month. The form of each seizure was similar.

During the clinical examination, the child did not have any abnormal physical signs. There was no abnormal language expression before epileptic episodes. After the onset of a seizure, he gradually showed signs of poor language expression, repeated speech, unanswerable questions, uncooperative actions, and attention deficit hyperactivity disorder (ADHD). The child had intellectual

disability, childish behavior, poor communication skills with the outside world, and autism performance. Parents were healthy and involved in a nonconsanguineous marriage, and family history was not significantly abnormal. Maternal pregnancy was normal, and perinatal history of hypoxia and asphyxia was denied. The Apgar score was unknown.

Auxiliary check: There were no abnormalities in routine laboratory examinations, ultrasonography or craniocerebral MRI. His video-electroencephalogram (EEG) (Figure 1) results showed an abnormal EEG and supported the diagnosis of epilepsy.

Gene detection

Two milliliter 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 (AGTCCCAAGCCCAAGCTAC) and reverse directions (ACTGGCTGTCTTGCGAATGG). A nucleotide variation of *c.2185C>T* (code no. 2185 nucleotides changed from C to T) was identified in the patient's *CNKSR2* gene. The mutation altered the codon sequence of the amino acid Arg into a termination codon (*p.Arg729Ter*). No abnormalities were identified at this site in the parents. The mutation was *de novo* (Figure 2). The child was eventually diagnosed with X-Linked EAS, and was treated with hormone and anti-epileptic drugs (Sodium valproate, Levetiracetan). After these treatments, his seizures had eased.

To highlight changes in the secondary structure of the *CNKSR2* gene, we used the more popular PSIPRED (<http://bioinf.cs.ucl.ac.uk/psipred/>)^[10] for structural prediction. The codon of no. 729 amino acid Arg was altered into a termination codon (*p.Arg729Ter*), resulting in the inability to express the 729-1034 sequence of amino acids (Figure 3). RaptorX (<http://raptorx.uchicago.edu>)^[11-13] can predict protein tertiary structures. After inputting the sequence, the 3D structure of the protein sequence can be predicted from the protein database (PDB) (Figure 4). Compared with the wild type, the patient's *CNKSR2* gene did not fold completely in its spatial structure, thus affecting protein function.

DISCUSSION

CNKSR2 (also known as *CNK2*, *KSR2*, *MAGUIN*)^[8] interacts with synaptic scaffold molecules (*S-SCAM*) and the postsynaptic density (*PSD*)-95/synaptic-associated protein (*SAP*) 90 to form a complex^[14]. The complex is involved in RAS/MAPK signaling and mediates neuronal proliferation, migration, differentiation and death, as well as RAS-mediated synapse formation^[5-9]. It also connects



Figure 1 Electroencephalogram of the patient. It showed generalized continuous spike-and-wave patterns in the bitemporal and frontal lobes, noticeable on the left side. Abnormal discharge was more pronounced during the sleep-electroencephalogram. Slower on background activity.

ts N-methyl-D-aspartate (NMDA) receptors to neuronal cell adhesion molecules^[14]. The NMDA subunit encoded by *GRIN2A* is the first gene associated with EAS^[2]. *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]. Hence, we speculate that a mutation or deletion of *CNKS2* may result in changes to the NMDA receptor activity and might affect downstream signaling cascades. Abnormal NMDA receptor will potentially damage the cortical thalamus network during sleep^[17]. *CNKS2* is highly expressed in the brain (especially in the hippocampus, amygdala, and cerebellum), and mutations result in loss of specificity and might also affect brain function^[7], leading to seizures and neurodevelopmental disorders that especially affect the patient's speech expression^[2]. *CNKS2* is a gene located on the X chromosome, and its mutations or deletions lead to X linkage intelligence disorder (XLID)^[8]. The main features of XLID are: (1) intellectual disability; (2) highly restrictive speech (especially expression of language); (3) ADHD; (4) transient childhood epilepsy; and (5) epilepsy with continuous spike waves of slow-wave sleep (CSWS) in early childhood^[5].

Before experiencing seizures, our patient suffered from developmental delays and ADHD, which is consistent with the performance of X-linked intellectual disability. After seizure occurrence, the patients' speech expression gradually decreased, the EEG continued to show abnormal wave patterns during sleep, and a *de novo* mutation of the *CNKS2* gene was identified. Therefore, we diagnosed this patient as X-linked epilepsy-aphasia syndrome. After definite diagnosis, patients were given immunoglobulin (400-500 mg/kg per day, 3-5 d for

1 course) and oral prednisone (from 1-3 mg/kg per day, and after one month, changed to 1 mg/kg per day), with a total course of 6 to 12 mo. 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. 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 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 ESES/CSWS/epilepsy aphasia spectrum have been reported, where the common underlying pathway is channelopathy^[23]. The different forms of seizures in EAS include partial seizure, generalized tonic-clonic seizure, atypical absence seizure, myoclonic seizure, atonic seizure, *etc.* Aphasia can occur before or after epilepsy. Moreover, 70% of patients with epilepsy-aphasia syndrome have epileptic seizures with EEG features that reveal spike-and-wave patterns in the unilateral or bitemporal lobes during the waking period.

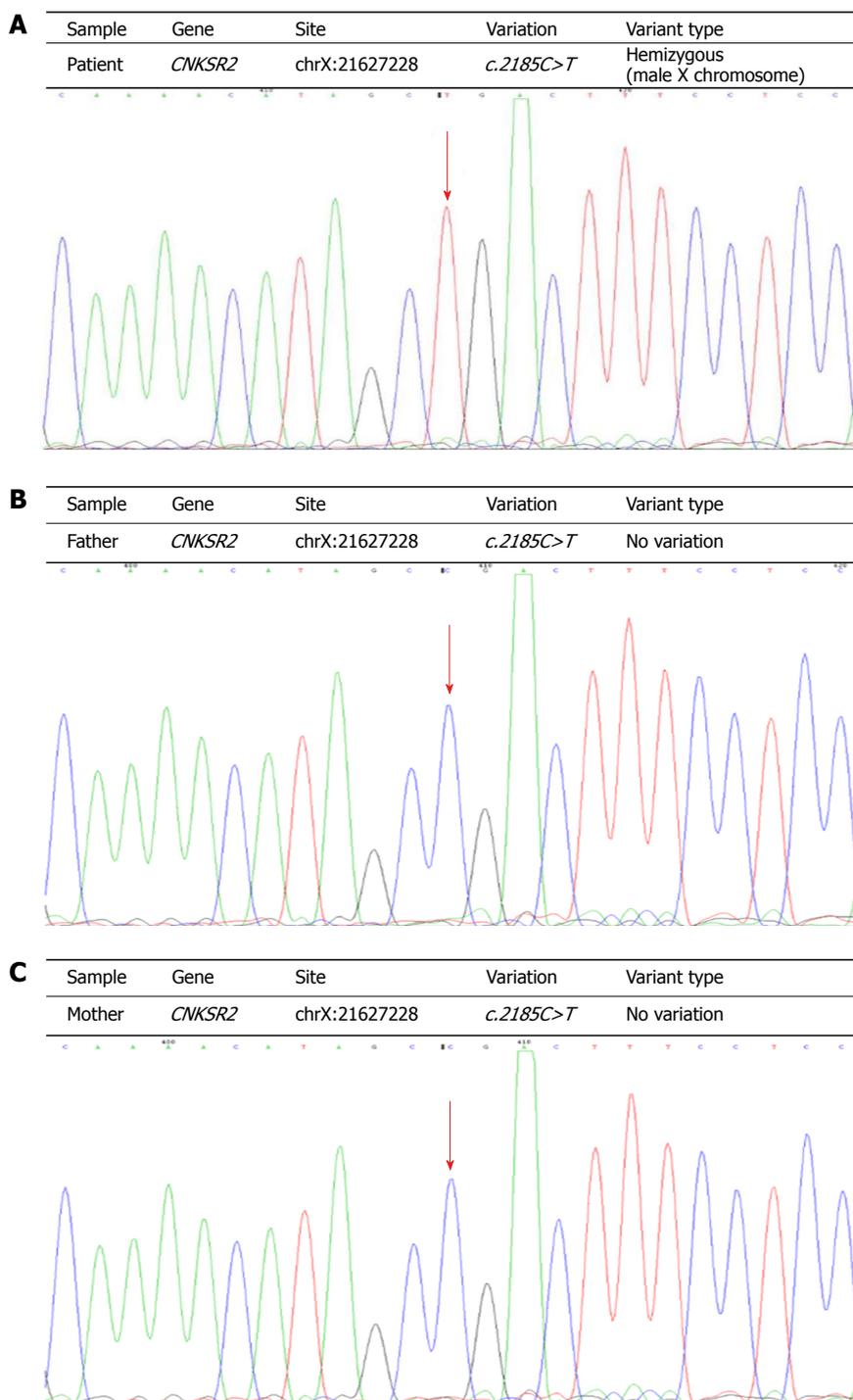


Figure 2 Gene sequences of three members in the family. A: *De novo* mutation of the *CNKSR2* gene (*c. 2185C>T, p.Arg729Ter*) in the patient; B, C: No mutation was observed at the same locus in the parents (arrows).

Generalized continuous spike-and-wave is seen in all leads during sleep, and bilateral synchronous discharge accounts for more than 85% of stage in abnormal discharge^[1]. The other 30% of children do not seizures, but show EEG abnormalities (which does not meet the EEG standards of CSWS). Their EEG's showed the following during sleep: Induced focal epileptiform discharges were identified mainly at the center (but may also might be involved in other areas); or there was no bilateral synchronous

activity; or synchronous activity accounted for less than 85% of NREM (non-rapid eye movement) sleep. These cases are all called intermediate epilepsy aphasia (IEADs). The speech recovery ability of IEADs patients is better than that of EAS.

Patients with epilepsy and speech disorders should be advised to undergo EEG monitoring and genetic testing to confirm the diagnosis. Currently, there are no specific medications for the treatment of X-linked epile-



Figure 3 Secondary structures of wild-type and mutated *CNKS2* proteins predicted by PSIPRED. A: The wild-type *CNKS2* gene encodes an intact peptide chain of 1034 amino acids; B: The mutated *CNKS2* gene leads to an early termination of the synthesis of the peptide chain and only No.1-728 amino acids are expressed.

psy-aphasia syndrome. 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]. Although there is evidence that mutations or deletions of *CNKS2* lead to neurological development defects, such as epilepsy and intellectual disability, the pathogenesis remains unclear. Therefore, the next step is to screen a large number of epileptic encephalopathy individuals to

delineate the phenotypic spectrum of the *CNKS2* mutation. Second-generation gene sequencing can assist in the identification of hereditary etiology and discovery of new mutations while expanding on the early epilepsy encephalopathy clinical phenotype and genetic spectrum. Simultaneously, the pathogenesis of X-linked epilepsy-aphasia syndrome should be studied to assist clinicians in diagnosis and genetic counseling.

ARTICLE HIGHLIGHTS

Case characteristics

Before experiencing seizures, our patient suffered from developmental de-

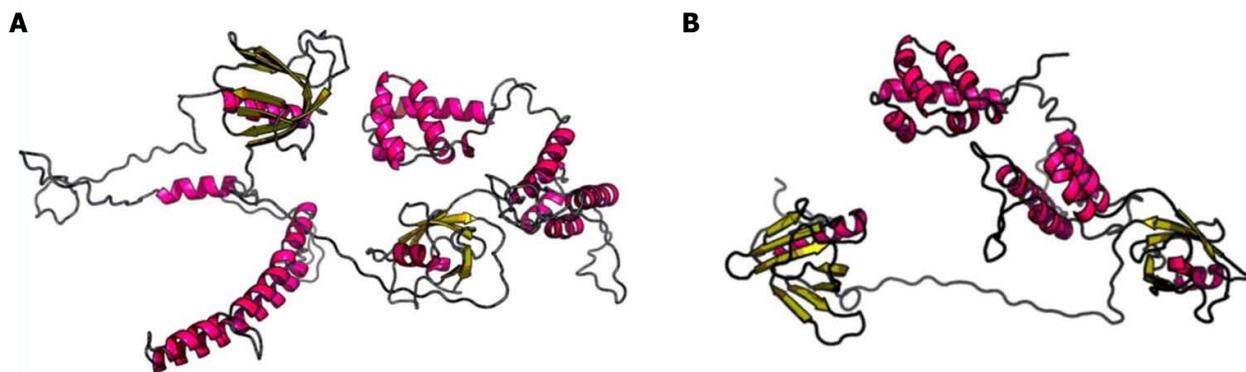


Figure 4 Tertiary structures of wild-type and mutated *CNKSR2* proteins predicted by RaptorX. The spatial structures of *CNKSR2* proteins are significantly different between the wild-type (A) and the patient (B).

lays and attention deficit hyperactivity disorder, which is consistent with the performance of X-linked intellectual disability. After seizure occurrence, the patients' speech expression gradually decreased, the electroencephalogram (EEG) continued to show abnormal wave patterns during sleep, and a *de novo* mutation of the *CNKSR2* gene was identified.

Clinical diagnosis

X-linked epilepsy-aphasia syndrome.

Differential diagnosis

Hysteria and childhood autism.

Laboratory diagnosis

A de novo mutation of the *CNKSR2* gene.

Imaging diagnosis

EEG continued to show abnormal wave patterns during sleep.

Treatment

Immunoglobulin, oral prednisone, lamotrigine and sodium valproate oral solution.

Related reports

Frequency of *CNKSR2* mutation in the X-linked epilepsy-aphasia spectrum has been reported in the journal of Epilepsia.

Term explanation

Epileptic encephalopathy with continuous spike-and-wave during sleep.

Experiences and lessons

This case will contribute to improvements in our understanding of X-linked epilepsy-aphasia syndrome. Patients with epilepsy and speech disorders should be advised to undergo EEG monitoring and genetic testing to confirm the diagnosis. 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.

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