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CASE REPORT

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# A case report of X-linked *CDKL5* gene variant in monozygotic twins associated with developmental and epileptic encephalopathy-2

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## Abstract

**Background** CDKL5 (Cyclin-Dependent Kinase Like-5) deficiency disorder (CDD; Online Mendelian Inheritance in Man database 300203, 300672) is a rare neurologic disorder, which is caused by mutation in *CDKL5* gene, situated on the X chromosome. Therefore, this condition is inherited in an X-linked dominant pattern. In general, this gene provides instruction for making a protein that is essential for normal brain development and plays an important regulatory role in neuronal function.

**Case presentation** We report a case of 2.5-year-old monozygotic twins (female), Twin-1 is found to be affected with CDKL5 deficiency disorder; development and epileptic encephalopathy-2; DEE2. The symptoms started at approximately 4 months of age.

**Conclusion** Current study aims to stratify risk using NGS (next generation sequencing) in both the parents and Twin-2. This case highlights the importance of genetic testing in patients with genetic disorder for proper diagnosis, for better treatment/management and to understand the prognosis of the condition. Together with the clinical and genetic information, genetic counselling of the patient/patient's parents can help them in taking informed decision.

**Keywords** CDKL5, Case report, Monozygotic, Neuronal, Next generation sequencing, X-linked

## Background

Cyclin-dependent kinase-like 5 (CDKL5), also known as STK9 (serine/threonine protein kinase), is a developmental encephalopathy caused by the mutation in *CDKL5* gene that leads to the loss of its activity, are also thought to cause severe neurological diseases to arise. In lives, a number of pathogenic CDKL5 mutations show decreased or no phosphorylation activity, which causes CDKL5 deficiency disease [1, 2]. It was previously classified as an atypical form of Rett syndrome because it has overlapping features with many of the developmental encephalopathy's disorders defined by genetic or presumed genetic etiology, severe seizures and intellectual/cognitive disability. With an incidence of 1 in 40,000 to 60,000 newborns, about 90% of those diagnosed with CDKL5 deficiency disorder are girls than boys, which approximately one-half to one-third as common as Dravet syndrome (1:20,000–50,000) or Rett syndrome (1:10,000 female births). However, CDD also affects several other neurologic domains, with evidence of disrupted sleep, gastrointestinal problems, dysautonomia, and cortical visual impairment [2, 3]. The majority of *CDKL5* gene variations are "de novo", which means they arise on their own and are not inherited from parents. There have been

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a few reported rarely seen families with multiple affected siblings that share the same mutation.

## Case presentation

A 2.5-year-old female twins (Twin-1 and Twin-2), born to the non-consanguineous couple (shown in Fig. 1), presented with low birth weight (2.5 kg) were bought with the chief complaint of seizures started at 4 months (regular episode of fits), developmental delay, speech delay, hypotonia, reduced eye contact, facial dysmorphism, sparse eyebrows, deep-set eye, depressed nasal bridge, thin lower lips, broad forehead, hand wringing, cognitive delay, eeg (electroencephalogram) showing epileptic encephalopathy and has been evaluated for associated disease/disorder as shown in Fig. 2.

## Result

The whole exome sequencing result shows the pathogenic mutation in Twin-1 in *CDKL5* gene at ChrX:18606106 with missense variant c.587C > T/ p.Ser196Leu in heterozygous state with depth 79x, related to CDKL5 DEFICIENCY DISORDER, DEVELOPMENTAL AND EPILEPTIC ENCEPHALOPATHY 2; DEE2.

The Sanger sequencing (NGS) was carried out for Twin-2 and both the parents (image A. father and image B. mother), where Twin-2 (image C) was also found to be affected with the same gene variation (found in Twin-1), whereas the parents result came normal as shown in Fig. 3.

## Discussion

CDKL5 deficiency disorder is characterized by early-onset seizures, global developmental delay, facial dysmorphism and severe motor deficits. CDKL5 is widely expressed in the brain, predominantly in neurons, with roles in cell proliferation, neuronal migration, axonal outgrowth, dendritic morphogenesis and synapse development. It is caused by pathogenic variants in the cyclin-dependent kinase-like 5 (*CDKL5*) gene [3].

According to ACMG (American College of Medical Genetics and Genomics) guidelines, genetic counselling should be offered at all stages of genetic testing.

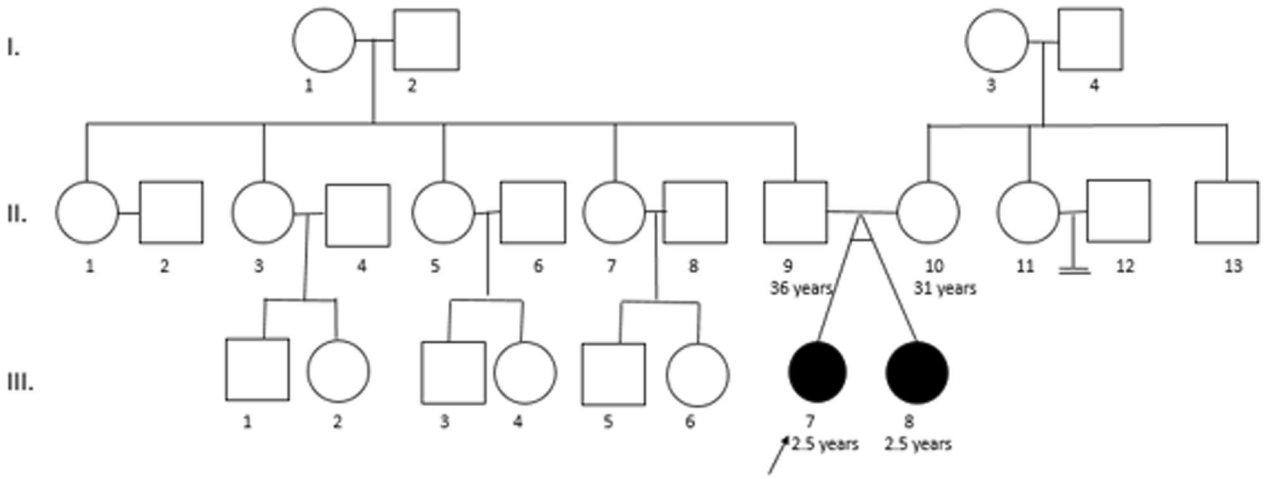


**Fig. 1** Three-generation pedigree with no other family history of genetic diseases

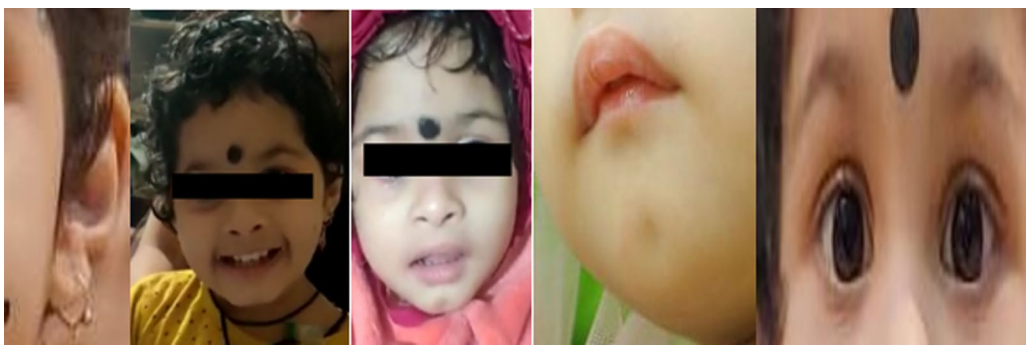

**Fig. 2** Monozygotic twins—Twin-1 (**A**) and Twin-2 (**B**) show dysmorphic facial features

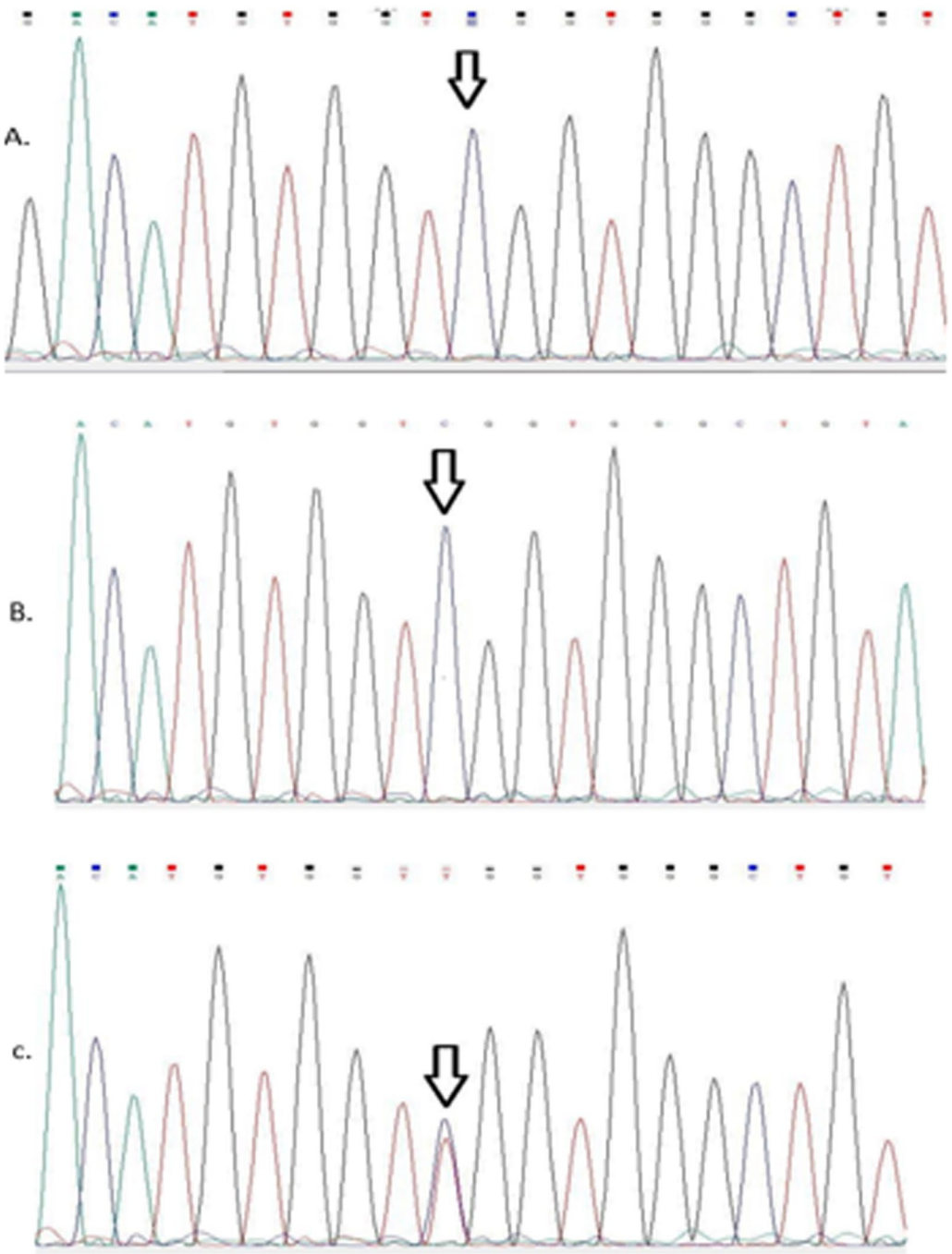


**Fig. 3** The figure shows the chromatogram of unaffected parent **A**. father; parent **B**. mother and affected Twin-2 (**C**)

A study conducted by Sam Amin et al. (2022), using a Delphi method, an anonymous survey was conducted where the Survey Consensus was reached (45 responses, 97.8%) to offer genetic testing to all DEE (Developmental and Epileptic Encephalopathy) patients before confirming the diagnosis. There was no consensus when asked when they offer genetic counselling; and responses were almost equally divided between "before genetic testing" (17 responses, 44.8%) and "after genetic testing" (21 responses, 55.2%), However, the community is motivated to join team as a result of their research, which caused frequent emails between them to debate potential solutions to enhance the collective experience [4]. The previous study of the literature reports are the following cases.

A study conducted by Weaving et al. (2004) reported the case of two affected identical twin girls and an affected brother with X-linked developmental and epileptic encephalopathy-2 (DEE2; 300672), were identified with 1-bp deletion (183delT) in exon 5 of the *CDKL5* gene which lead to a frameshift and premature termination of the protein at amino alkanoic acid 75. One twin and her brother had onset of infantile spasms as 9 weeks old and both developed a mixed seizure disorder. The opposite twin had a diagnosis of autism; at age 19 years, she had no history of seizures whereas the brother died at age 16 years [5].

A study conducted by Tao et al. (2004) reported female monozygotic twins with developmental and epileptic encephalopathy (DEE2; 300672), identified a de novo c.525A-T transversion in exon 8 of the *CDKL5* gene which ends up in an arg175-to-ser (R175S) substitution. The phenotype included onset of infantile spasms between 2 and 6 weeks of life, severe psychomotor retardation, stereotypic hand movements, mood swings, and episodes of hyperventilation. One twin developed absence seizures later in life [3].

In the present study (2022) we report a case of affected monozygotic twin girls with X-linked developmental and epileptic encephalopathy-2 in chromosome X with mutation c.587C > T/p.Ser196Leu. They both are presented with seizures, developmental delay, speech delay, hypotonia, reduced eye contact, facial dysmorphism, sparse eyebrows, deep-set eye, depressed nasal bridge, thin lower lips, broad forehead, hand wringing, and cognitive delay. The parents are normal for the found variation in the twins. As both the parents are healthy in these instances so they were counselled that the chance of recurrence in their future children is probably low (About 1%). However, they were also explained that there is a chance that anyone of the parent may have a mutation confined to some cells including testicular or ovarian cells (confined gonadal mosaicism). While rare, confined gonadal mosaicism may significantly change the chance of recurrence in future offspring, with implications for genetic counselling. The failure of Sanger sequencing to detect germline mosaicism may be its most clinically significant flaw.

Even though CDD-specific clinical studies are beginning to emerge, treatment for the neurologic characteristics of CDD is currently symptom-based and empiric rather than CDD-specific.

## Conclusion

This case highlights the importance of genetic testing in patients with genetic disorder for proper diagnosis, for better treatment/management and to understand the prognosis of the condition. Because of overlapping symptoms, it becomes difficult for the clinician to come to a final diagnosis which in turn affects the treatment/management course. Genetic testing helps in confirming the diagnosis based on which further treatment/management can be decided. Together with the clinical and genetic information, genetic counselling of the patient/patient's parents can also help them in taking informed reproductive decision.

### Abbreviations

| | |
|---|---|
| CDKL5 | Cyclin-dependent kinase like-5 |
| CDD | CDKL5 deficiency disorder |
| DEE2 | Development and epileptic encephalopathy-2 |
| NGS | Next generation sequencing |
| STK9 | Serine/threonine protein kinase |
| EEG | Electroencephalogram |

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### Author contributions

AG wrote, interpreted, and analyzed the manuscript. NA contributed to the data collection and AP workup of the case. PU and APU contributed to the supervision and diagnosis of the case. All authors read and approved the final manuscript.

### Funding

Not applicable.

### Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

## Declarations

### Ethics approval and consent to participate

Since this is a case report, there is no need for ethical approval. Written informed consent was obtained from the patient's parents to publish this case report and accompanying images.

### Consent for publication

The patient's parents had signed an informed consent to allow his data to be published.

### Competing interests

The authors declare that they have no competing interests.

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## Publisher's Note