

ORIGINAL ARTICLE

Multicenter retrospective study of patients with PCDH19-related epilepsy: The first Hungarian cohort

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Abstract

Objective: PCDH19-related epilepsy occurs predominantly in girls and is caused by pathogenic variant of the protocadherin-19 gene. The initial seizures usually develop in association with fever, begin on average at 15 months of age, and often occur in clusters. Autistic symptoms, intellectual disability, and sleep disturbance are often associated.

Methods: In our retrospective, multicenter study, we reviewed clinical data of nine children with epilepsy genetically confirmed to be associated with PCDH19.

Results: In the Hungarian patient population aged 0–18 years, the prevalence of PCDH19-related epilepsy was found to be lower (1/100000 live births in females) than the reported international data (4–5/100000 live births in females). Four of our nine patients had positive family history of epilepsy (cousins, sister, and mother). We assessed brain anomalies in three patients (in one patient focal cortical dysplasia and left anterior cingulate dysgenesis, and in two children right or left hippocampal sclerosis) and in another three cases incidentally identified benign alterations on brain MRI were found. The first seizure presented as a cluster in seven out of nine children. In seven out of nine cases occurred status epilepticus. Six out of nine children had autistic symptoms and only one child had normal intellectual development. Seven of our patients were seizure free with combined antiseizure medication (ASM). The most effective ASMs were levetiracetam, valproate, and clobazam.

Significance: The prevalence of PCDH19-related epilepsy is presumably underestimated because of the lack of widely performed molecular genetic evaluations. Molecular genetic testing including PCDH19 pathogenic variants is recommended for female patients with an onset of seizures before the age of 3 years.

KEYWORDS

autistic features, epilepsy, genetics, intellectual disability, PCDH19 gene, protocadherin-19

Abbreviations: ASM, antiseizure medication; EEG, electroencephalogram; MRI, magnetic brain imaging; PCDH19, protocadherin-19.

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1 | INTRODUCTION

PCDH19-related epilepsy is caused by mutations in the protocadherin-19 gene, more than 150 different pathogenic variants have been identified.¹ The PCDH19 gene pathogenic variant was described in 2008 by Dibbens et al.² Kolc et al.¹ confirmed de novo mutation in half (50.2%) of their 271 patients. The protocadherin-19 gene is located on chromosome Xq22.1; therefore, the disease is mostly found in girls. First Depienne et al.³ reported PCDH19 gene pathogenic variant in a male patient. There are about 20 reported cases of males, usually with predominant psychiatric symptoms.⁴ The PCDH19 gene is currently in the top 10 list of epilepsy genes.⁵ According to Symonds et al.,⁴ this is the sixth most common gene regarding the etiology of epilepsy that begins before the age of 3 years.

PCDH19-related epilepsy is a rare syndrome, the estimated prevalence is 4–5/100000 live births of girls.

The protocadherin-19 protein is a member of the cadherin superfamily, the δ 2-protocadherin family, it is a transmembrane glycoprotein and its main role is to produce calcium-dependent cell–cell adhesion. Protocadherin is expressed in 19 different tissues, mainly in the limbic system (amygdala, hippocampus) and cortex of the central nervous system. The gene plays a crucial role in the formation of neuronal and synaptic connections, cell adhesion, and cell migration during brain development.⁵

Researchers have identified pathogenic variants in the PCDH19 gene in conditions such as Dravet syndrome, Febrile Seizure Plus syndrome, Early Infantile Epileptic Encephalopathy, Migrating focal seizures, West syndrome, and Lennox–Gastaut syndrome.^{6–8} They have also described pathogenic variants of the PCDH19 gene in non-epileptic disorders such as Asperger syndrome, autism spectrum disorder, and schizophrenia.^{9,10}

Dravet syndrome is due to the pathogenic variants of the sodium channel gene in 70%–80% of cases, but pathogenic variant of PCDH19 gene was found in nearly half of SCN1A-negative cases.¹¹

The clinical symptoms of PCDH19-related epilepsy and Dravet syndrome overlap. Table 1 shows the characteristics of these two diseases. The table was created on published data of original articles and reviews.^{11–15}

2 | PATIENTS AND METHODS

In our retrospective study, we reviewed data on patients diagnosed with and treated for PCDH19-related epilepsy in Hungary. Data collection was conducted during 2022. We included patients in whom the pathogenic variant of the PCDH19 gene was confirmed by molecular genetic testing. We collected gender, age, familial and perinatal

Key points

- PCDH19-related epilepsy is attributed to a pathogenic variant in the protocadherin-19 gene, predominantly affecting females.
- In our retrospective study, we gathered data from all Hungarian patients diagnosed with genetically confirmed PCDH19-related epilepsy, encompassing a total of nine patients.
- We observed a higher prevalence of epileptic family history and structural brain abnormalities in these patients compared to previous publications.
- The prevalence of PCDH19-related epilepsy is likely underestimated due to the limited availability of widely conducted molecular genetic evaluations.
- Molecular genetic testing, including screening for PCDH19 pathogenic variants, is recommended for female patients who experience seizure onset before the age of 3 years.

history, psychomotor development (motor, speech and intellectual development, autistic symptoms, sleep disturbance) before and after the diagnosis of epilepsy, history of epilepsy (age at the time of the first seizure and its type, cluster and/or status epilepticus, presence of possible provoking factors, frequency of convulsions), neurological status, EEG and brain MRI findings, antiseizure medication (ASM), and its efficacy.

3 | RESULTS

A total of nine girls with PCDH19-related epilepsy are being followed up by Hungarian pediatric neurologists in seven neuro-pediatric centers.

3.1 | Perinatal history

The nine children had a mean birth weight of 2942 g (2140–3340 g), a mean gestational age of 38 weeks (34–40 weeks), and an Apgar score of 9/10. One girl was born premature (week 34), and perinatal adaptation was normal.

3.2 | Family history

In five of nine patients, the family history showed positive for seizures or epilepsy. Patients 7 and 8 were first cousins;

TABLE 1 Clinical presentation of Dravet syndrome and PCDH19-related epilepsy (+ slightly, ++ moderately, +++ very characteristic).

	Dravet syndrome	PCDH19-related epilepsy
Prevalence	1/16000	4–5/100000 (female)
Gender (female)	+	+++
Epilepsy in family history	+	+
Normal psychomotor development before the onset of seizures	+++	+++
Age at the first seizure (months)	2–16	6–36
Cluster seizures	+	+++
Prolonged seizures (>5 min)	+++	+
Status epilepticus	+++	++
Myoclonic, clonic, atonic, absence seizures	+++	+
Photosensitivity	+++	+
Provoking role of fever	+++	+++
Abnormality on first brain MRI	+	+
Intellectual disability after the onset of seizures	+++	++
Motor development delay after the onset of seizures	+++	+

their fathers were brothers and both tested positive for PCDH19. Their paternal grandmother had benign epilepsy in her childhood, but she was not tested for the PCDH19 gene. The mother of patient 2 had been treated for epilepsy since toddlerhood, and her molecular genetic testing also confirmed a pathogenic variant of the PCDH19 gene. The brother and maternal grandparents were also tested and found negative for PCDH19. The cousin of patient 5 also received ASM in her childhood for an unknown type of epilepsy (not tested for PCDH19). The sister of patient 6 had a secondarily generalized seizure of focal origin associated with febrile enteritis at the age of 6. EEG examination showed focal interictal epileptiform abnormalities. She was 13 years old during data collection and had been seizure free since then. She had special educational needs but was not tested for PCDH19.

3.3 | History of epilepsy

The average age of the patients at the time of the study was 9.9 years (range 4.1–24.2 ± 7.1 SD). The average age at the onset of seizures was 15 months (range 5–22 ± 6.6 SD). The first convulsions occurred in clusters in seven of nine children. The first seizure began focally in five of nine cases and became secondarily generalized in four cases. Four patients had fever and two had subfebrility at the onset of the first convulsion. One child received a meningitis B vaccine on the day of the first convulsion. The second convulsion/cluster recurred after an average of 2.1 months (range 0–10), and one child had a recurrent episode after a few hours. In three children, convulsions

occurred in clusters each time. Seven of the nine children developed status epilepticus at least once (Table 2).

3.4 | Results of EEG examination

The first EEG examination found bilateral paroxysmal epileptiform discharges with frontal dominance in six patients. The first EEG showed no abnormalities in three cases. Repeated EEGs in two patients with initially normal results remained negative. In the third child with initial normal brain activity, the EEG became positive after 2 months, showing a left posterior ictal pattern.

3.5 | Results of brain MRI

The first brain MRI was performed at an average age of 20 months (range 5–48 months). In three of the nine cases, the following abnormalities were detected: (1) focal cortical dysplasia and left anterior cingulate dysgenesis, (2) right hippocampal sclerosis, and (3) left hippocampal sclerosis. In another three cases, the MRI revealed ventricular asymmetry, widened extracerebral liquor space, and septum pellucidum cyst/cavum vergae (Table 2).

3.6 | Psychomotor development after the onset of epilepsy

The intellectual development was age-appropriate only in one patient, and the speech development was adequate

TABLE 2 Age at the time of the first and second seizures, clinical description of seizures, and brain MRI results of nine children with PCDH19-related epilepsy.

Patient no	Age at the time of first seizure (month)	Age at the time of second seizure (month)	Type of first seizure	First seizure in clusters	First seizure with fever	Brain MRI
1	20	22	Focal, secondarily generalized	No	Yes	Septum pellucidum cyst + cavum vergae
2	22	23	Focal, secondarily generalized	Yes	Yes	Ventricular asymmetry
3	13	16	Focal, secondarily generalized	Yes	Yes	Right HS
4	6	6	Focal	Yes	No	Left HS
5	22	22	Generalized	Yes	Subfebrility	FCD + left anterior cingular dysgenesis
6	18	18	Generalized	Yes	Yes	Negative
7	5	15	Focal, secondarily generalized	Yes	No	Widened extracerebral liquor space
8	11	11	Generalized	No	Subfebrility	Negative
9	18	21	Generalized	Yes	No	Negative

Abbreviations: FCD, Focal cortical dysplasia; HS, Hippocampal sclerosis.

only in three patients. Autistic symptoms were observed in two thirds of our patients (Table 3).

3.7 | PCDH19 pathogenic variants and genotype–phenotype correlations

Five of our nine patients had a missense mutation; all of them had delayed intellectual development, and four also had delayed speech development. Two girls with frameshift mutations had delayed intellectual and speech development along with autistic symptoms. Only the patient with a stop-gain mutation had normal motor, intellectual and speech development, and no autistic symptoms.

Among the five patients with missense mutations, three girls had a confirmed proline–leucine amino acid change. All of them experienced delayed speech and intellectual development. Patients 7 and 8, who were cousins, shared the same pathogenic variant (c.1031C>T (p.Pro344Leu)). The father of patient 8 had the same pathogenic variant (the father of patient 7 was not genetically tested). Patient 2 and her mother both had the same pathogenic variant (c.208_209insG, (p.His70Argfs*19)).

3.8 | Antiseizure medication and its effectiveness

Seven patients were seizure free on ASM. The average seizure-free period was 21months (range: 4months–7years). At the time of the data collection, two girls had frequent epileptic seizures (Table 4).

Only one child was receiving monotherapy (topiramate), and she had been seizure free for 10months. Both patients on bitherapy (LEV+VPA or LEV+CBZ) remained seizure free for at least 1year. Six children were taking three ASMs, and four of them were seizure free.

The first ASM in none of the cases resulted prolonged seizure-free periods, and the ineffectiveness of the therapy necessitated multiple changes in the treatment of all children. Patients received three to nine different antiepileptic drugs. The first choice of ASM was VPA in five cases. Ketogenic diet was not initiated in any of these children.

4 | DISCUSSION

4.1 | Prevalence

PCDH19-related epilepsy constitutes a rare genetic epilepsy syndrome. Its prevalence remains uncertain, with

TABLE 3 The psychomotor development of our patients at the last developmental follow-up (dev. – development, dist. – disturbance) and the results of their molecular genetic testing.

Patient no	Age at the time of the study (year)	Age at the time of first seizure (month)	Motor dev.	Intellectual dev.	Speech dev.	Autistic symptoms	Sleep dist.	PCDH19 pathogenic variant	Type of mutation
1	4	20	Normal	Delayed	Normal	No	No	c.1671 C>G (p.Asn557Lys)	Missense
2	5	22	Delayed	Delayed	Delayed	Yes	No	c.208_209insG, p.(His704Argfs*19)	Frameshift
3	24	13	Normal	Delayed	Delayed	Yes	–	c.1019A>G (p.Asn340Ser)	Missense
4	16	6	Normal	Delayed	Normal	Yes	No	c.1022A>G (p.Asp341Gly)	Splicing
5	12	22	Normal	Delayed	Delayed	Yes	No	c.1152_1180del (p.Gln385Serfs*6)	Frameshift
6	11	18	Normal	Delayed	Delayed	Yes	No	c.1682C>T (p.Pro561Ileu)	Missense
7	4	5	Normal	Delayed	Delayed	Yes	Yes	c.1031C>T (p.Pro344Leu)	Missense
8	5	11	Delayed	Delayed	Delayed	No	No	c.1031C>T (p.Pro344Leu)	Missense
9	4	18	Normal	Normal	Normal	No	No	c.949C>T, (p.Gln317*)	Stop gained

TABLE 4 Antiseizure medication therapy (ASM) of the nine females with PCDH19-related epilepsy.

Patient no	Age at the time of the study (year)	First choice of ASM	Other ASMs	Current ASM therapy	Effectiveness of ASM therapy	Seizure-free periods (months)
1	4	VPA	LEV, LTG, CLB	LEV + VPA + LTG	Not seizure free	–
2	5	PB	LEV, VPA, CLB, CZP, LTG, TPM	TPM	Seizure free	10
3	24	VPA	CBZ, TPM, LTG, PHT, VGB, CZP, CLB	VPA + CZP + CLB	Seizure free	24
4	16	LEV	VPA, TPM, CBZ, CZP, NZP, LCM, PHT, BRV	BRV + PHT + LCM	Seizure free	6
5	12	VPA	CBZ, CLB, LEV	LEV+CBZ	Seizure free	84
6	11	VPA	CBZ, CLB, LEV, LTG, TPM, ZNS	LEV+CBZ + TPM	Not seizure free	–
7	4	LEV	CBZ, VPA, CLB, LTG, PB, CZP, BRV	VPA+BRV + CZP	Seizure free	4
8	5	VPA	LEV, CLB	LEV+VPA	Seizure free	12
9	4	LEV	VPA, TPM, CLB, STP	CLB + TPM + STP	Seizure free	8

Abbreviations: BRV, Brivaracetam; CBZ, Carbamazepine; CLB, Clobazam; CZP, Clonazepam; LCM, Lacosamide; LEV, Levetiracetam; LTG, Lamotrigine; NZP, Nitrazepam; PB, Phenobarbital; PHT, Phenytoin; STP, Stiripentol; TPM, Topiramate; VGB, Vigabatrin; VPA, Valproic acid; ZNS, Zonisamide.

predominantly case reports published. The most extensive study, comprising 271 patients analyzed across 38 publications, revealed a prevalence of 4–5 per 100 000 female live births.⁴ However, based on the current study and considering Hungarian epidemiological data, we estimated the prevalence of PCDH19-related epilepsy to be 1 in 100 000 female live births, lower than previously reported.

4.2 | Family history

Similar to previous reports, all children in our study were girls. Although the number of our cases is low, regarding the presence of epilepsy in the family members we have found a slightly higher rate of positive family history in our patients (4/9; 44%) than in Smith et al. (3/38; 8%).¹⁶

4.3 | Family relationships

Patients 7 and 8 were first cousins on the paternal side, and father of patient 8 carried the pathogenic gene variant (father of patient 7 was not tested). The paternal grandmother had epilepsy of an unknown type during her childhood (no molecular genetic test was conducted). Juberg and Hellmann,¹⁷ who described the clinical presentation of PCDH19-related epilepsy syndrome in 1971, studied 15 females from four generations of a family. They also found first cousins among the family members with PCDH19-related epilepsy. The mother of patient 2 was confirmed to carry the PCDH19 pathogenic variant. Our results are similar to the data of Smith et al.¹⁶ who found PCDH19 pathogenic variant in 5/38 fathers and 7/38 mothers. Marini et al.¹⁸ reported that only one mother of their 35 patients had PCDH19 pathogenic variant and one girl inherited the pathogenic variant from her father.

4.4 | Epilepsy

The mean age of the patients at the time of the first seizure was 15 months (range 5–22 months), consistent with the observations of Scheffer et al.¹⁹ In the study by Marini et al.,¹⁸ seizures began at an average age of 10 months.

In more than half of our patients, the first seizure was focal (5/9). Seizures occurred in clusters in seven out of nine cases. Smith et al.¹⁶ also noted a predominance of focal (58%) and cluster (92%) seizures. Only one case in our study population exhibited screaming at the onset of seizure, whereas Trivisano²⁰ observed it in 82% (50/61) of the girls. In six of our nine patients, higher body temperature was noted at the onset of the first seizure. In addition

to fever, other triggering factors such as infection, emotional stress, vaccination, or even bathing in warm water were observed by other authors.²¹ One of nine of our seizing patients also had a history of vaccination administered on the same day. In our study, we found a higher prevalence of status epilepticus (7/9) than Marini et al.¹⁸ (10/35; 28%) or Trivisano et al.²⁰ (19/60; 31%).

4.5 | EEG

In one third of our patients, the first EEG examination revealed no abnormalities; bilateral epileptiform discharges were observed in six children. Dell'Isola et al.²² reported the absence of typical interictal EEG abnormalities in PCDH19-related epilepsy. Seizures typically initiate in the frontotemporal or temporooccipital regions and frequently propagate to the other hemisphere.²³

4.6 | Brain MRI

We found higher prevalence of brain anomalies in our patients than in Lotte.²⁴ In three of our patients, structural anomalies were revealed by MRI: focal cortical dysplasia and left anterior cingulate dysgenesis in one patient and right or left hippocampal sclerosis in another two children. Lotte et al.²⁴ found brain abnormalities such as focal cortical dysplasia, hippocampal sclerosis, or arachnoid cysts in nine of their 48 (19%) patients. In three of our patients, incidentally identified benign ventricular asymmetry, dilated extracerebral liquor space, and septum pellucidum cyst/cavum vergae were confirmed.

4.7 | Treatment of epilepsy

Considering the ASM treatment of children with PCDH19-related epilepsy, our data are consistent with those reported previously. The ASM treatment of patients with PCDH19 epilepsy is difficult, children frequently need a combination of drugs. According to studies by Lotte et al.,²⁴ 98% of children with PCDH19-related epilepsy were at least on bitherapy.

Lotte et al.²⁴ identified clobazam, bromide, and valproic acid as the most appropriate antiepileptic drugs, whereas Higurashi et al.²⁵ reported that phenytoin, bromide, and clobazam are the most effective medications. We found clobazam to be less effective, as only two out of eight girls on clobazam became seizure free. Three girls on add-on VPA were seizure free. We lack experience with bromide. We generally concur with Higurashi et al.'s²⁵ assessment that carbamazepine is not effective in treating PCDH19-related

epilepsy, although one of our patients who was seizure free while on a combination of levetiracetam and carbamazepine had been seizure free for 7 years. One of our patients experienced seizure aggravation while on carbamazepine.

Lotte et al.²⁴ observed an aggravation of seizures with lamotrigine. Five of our patients were on lamotrigine and only one girl became seizure free. Regarding the efficacy of levetiracetam, our experience is similar to Sadleir et al.²⁶ Stiripentol is also considered an adjuvant treatment option. The one child among our patients who received stiripentol had been seizure free since the introduction of this drug. A placebo-controlled study is currently in progress to investigate the effectiveness of ganaxolone in PCDH19 epilepsy.²⁷

Due to the small number of our patients and the varied effectiveness of different antiepileptic drugs, we cannot definitively recommend a specific first-line or add-on ASM for children with PCDH19 epilepsy.

The frequency of seizures decreased after the age of 10 years, while spontaneous remission could occur. Our data also support these observations, the frequency of initially difficult-to-treat seizures decreased with increasing age, and remission may occur. Seven out of nine girls became seizure free with the prescribed antiepileptic drug therapy and 4/7 seizure-free patients were younger than 5 years.

4.8 | Associated symptoms

According to the published data, most patients with PCDH19-related epilepsy had associated symptoms: autism spectrum disorder, hyperactivity, varying degrees of intellectual disability, and sleep disturbance. The psychomotor development of the children was typically found to be normal before the onset of seizures. In eight of the nine children we studied, intellectual development showed mild/moderate delay. Our observations regarding the psychomotor development of the patients closely align with those of Lotte.²⁴ They noticed in a multicenter study that 86% of children had normal psychomotor development before the onset of seizures, but after the epilepsy onset, 82% of children were found to be developmentally delayed.

Marini et al.¹⁸ observed a delay of intellectual development in 68% of their patients and Scheffer et al.¹⁹ in 67% of their studied children. In our study, only one child exhibited normal intelligence. It is well known that the cognitive outcome is significantly influenced by the age of the child at the onset of epilepsy; the earlier the onset of seizures, the poorer the prognosis tends to be. All three of our patients who experienced the onset of seizures before the age of 1 year exhibited delayed intellectual development. However, we did not find any association between the age of the child at seizure onset and epilepsy outcomes.¹²

The type of pathogenic variant does not seem to affect later cognitive outcome of the patients.¹

Autism spectrum disorder was diagnosed in two third of the girls (6/9).

Consistent with the investigations conducted by Smith et al.,¹⁶ we also observed a notable prevalence of speech developmental delay among our patient cohort (76% vs. 78%).

4.9 | Genotype–phenotype correlation

Due to the limited number of cases in our study, we were unable to confirm any genotype–phenotype correlation.

Similar to the data of Liu (9/18)²⁸ and Marini (16/33),¹⁸ we also identified missense mutations in half of our patients. The only child who had normal motor, intellectual, and speech development had stopped gaining mutation.

Kolc et al.¹ found that milder phenotype may be associated with the p.Asn340Ser variant. We had one patient with this variant who remained seizure free, although she experienced delayed speech and intellectual development. We did not find any correlation between the genotype and effectiveness of the ASM therapy.

5 | SUMMARY, CONCLUSIONS

Compared to the reported data, we found a lower prevalence of PCDH19-related epilepsy (approximately 1/100.000 female live births) in the Hungarian population of children. In our study, almost half of our patients had a positive family history of epilepsy. We identified two cases of first-cousin relationships among our patients, and one patient had a mother with confirmed PCDH19-related epilepsy. In comparison to the published data, we observed a higher proportion of status epilepticus in our patients. In contrast to what has been reported so far, brain MRI revealed more frequent structural brain anomalies associated with epilepsy or incidental cerebral abnormalities in our patient population. More than two third of our patients were seizure free with ASM therapy.

We conclude that molecular genetic testing for PCDH19 pathogenic variants is strongly recommended for girls whose seizures begin before the age of 3 years.

6 | STRENGTHS AND LIMITATIONS

The strength of our study lies in its multicenter design, allowing for the assessment of the entire population of children within a country for the prevalence of

PCDH19-related epilepsy. However, a limitation of our study is the small number of cases. Nonetheless, it is worth noting that the available data on this topic are also limited, primarily consisting of case reports or multinational studies. It can be anticipated that the widespread use of molecular genetic testing will lead to an increase in the incidence of PCDH19 gene pathogenic variant-related disorders worldwide.

AUTHOR CONTRIBUTIONS

All authors have unanimously agreed to submit this final version of the paper to the journal and all contributed equally. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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CONFLICT OF INTEREST STATEMENT

None of the authors have any conflict of interest to declare.

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REFERENCES

1. Kolc KL, Sadleir LG, Scheffer IE, Ivancevic A, Roberts R, Pham DH, et al. A systematic review and meta-analysis of 271 PCDH19-variant individuals identifies psychiatric comorbidities, and association of seizure onset and disease severity. *Mol Psychiatry*. 2019;24(2):241–51.
2. Dibbens LM, Tarpey PS, Hynes K, Bayly MA, Scheffer IE, Smith R, et al. X-linked protocadherin 19 mutations cause female-limited epilepsy and cognitive impairment. *Nat Genet*. 2008;40(6):776–81.
3. Depienne C, LeGuern E. PCDH19-related infantile epileptic encephalopathy: an unusual X-linked inheritance disorder. *Hum Mutat*. 2012;33(4):627–34.
4. Symonds JD, Zuberi SM, Stewart K, McLellan A, O'Regan M, MacLeod S, et al. Incidence and phenotypes of childhood-onset genetic epilepsies: a prospective population-based national cohort. *Brain*. 2019;142(8):2303–18.
5. Gerosa L, Francolini M, Bassani S, Passafaro M. The role of protocadherin 19 (PCDH19) in neurodevelopment and in the pathophysiology of early infantile epileptic Encephalopathy-9 (EIEE9). *Dev Neurobiol*. 2019;79(1):75–84.
6. Yang L, Liu J, Su O, Yufen L, Yang X, Xu L, et al. Novel and de novo mutation of PCDH19 in girls clustering epilepsy. *Brain Behav*. 2019;9(12):e01455.
7. Carvill LG, Heavin SB, Yendle SC, McMahon JM, O'Roak BJ, Cook F, et al. Targeted resequencing in epileptic encephalopathies identifies de novo mutations in CHD2 and SYNGAP1. *Nat Genet*. 2013;45(7):825–30.
8. Specchio N, Micco VD, Trivisano M, Ferretti A, Curatolo P. The epilepsy-autism spectrum disorder phenotype in the era of molecular genetics and precision therapy. *Epilepsia*. 2022;63(1):6–21.
9. Harssel JJT, Weckhuysen S, Kempen MJA, Hardies K, Verbeek NE, Kovel CGF, et al. Clinical and genetic aspects of PCDH19-related epilepsy syndromes and the possible role of PCDH19 mutations in males with autism spectrum disorders. *Neurogenetics*. 2013;14(1):23–34.
10. Johannessen M, Kjellsen IM, Malt E. Behavioral and neuropsychological profile of a male patient with mosaic PCDH19 mutation. *Epilepsy Behav Rep*. 2022;19:100559.
11. Ding J, Wang L, Jin Z, Qiang Y, Li W, Wang Y, et al. Do all roads lead to Rome? Genes causing Dravet syndrome and Dravet syndrome-like phenotypes. *Front Neurol*. 2022;13:832380.
12. Trivisano M, Pietrafusa N, Ciommo V, Cappelletti S, Palma L, Terracciano A, et al. PCDH19-related epilepsy and Dravet syndrome: face-off between two early-onset epilepsies with fever sensitivity. *Epilepsy Res*. 2016;125:32–6.
13. Depienne C, Bouteiller D, Keren B, Cheuret E, Poirier K, Trouillard O, et al. Sporadic infantile epileptic encephalopathy caused by mutations in PCDH19 resembles Dravet syndrome but mainly affects females. *PLoS Genet*. 2009;5(2):e1000381.
14. Cardenal-Muñoz E, Auvin S, Villanueva V, Cross JH, Zuberi SM, Lagae L, et al. Guidance on Dravet syndrome from infant to adult care: road map for treatment planning in Europe. *Epilepsia Open*. 2022;7(1):11–26.
15. Lagae L. Dravetsyndrome. *Curr Opin Neurol*. 2021;34(2):213–8.
16. Smith L, Singhal N, Achkar CME, Truglio G, Sheidley BR, Sullivan J, et al. PCDH19-related epilepsy is associated with a broad neurodevelopmental spectrum. *Epilepsia*. 2018;59(3):679–89.
17. Juberg RC, Hellman CD. A new familial form of convulsive disorder and mental retardation limited to females. *J Pediatr*. 1971;79(5):726–32.
18. Marini C, Darra F, Specchio N, Mei D, Terracciano A, Parmeggiani L, et al. Focal seizures with affective symptoms are a major feature of PCDH19 gene-related epilepsy. *Epilepsia*. 2012;53(12):2111–9.
19. Scheffer IE, Turner SJ, Dibbens LM, Bayly MA, Friend K, Hodgson B, et al. Epilepsy and mental retardation limited to females: an under-recognized disorder. *Brain*. 2008;131(Pt 4):918–27.
20. Trivisano M, Pietrafusa N, Terracciano A, Marini C, Mei D, Darra F, et al. Defining the electroclinical phenotype and outcome of PCDH19-related epilepsy: a multicenter study. *Epilepsia*. 2018;59(12):2260–71.
21. Samanta D. PCDH19-related epilepsy syndrome: a comprehensive clinical review. *Pediatr Neurol*. 2020;105:3–9.
22. Dell'Isola GB, Vinti V, Fattorusso A, Tascini G, Mencaroni E, Cara GD, et al. The broad clinical Spectrum of epilepsies associated with protocadherin 19 gene mutation. *Front Neurol*. 2022;12:780053.
23. Chemaly N, Losito E, Pinard JM, Gautier A, Villeneuve N, Arbues AS, et al. Early and long-term electroclinical features of patients with epilepsy and PCDH19 mutation. *Epileptic Disord*. 2018;20(6):457–67.

24. Lotte J, Bast T, Borusiak P, Coppola A, Cross JH, Dimova P, et al. Effectiveness of antiepileptic therapy in patients with PCDH19 mutations. *Seizure*. 2016;35:106–10.
25. Higurashi N, Nakamura M, Sugai M, Ohfu M, Sakauchi M, Sugawara Y, et al. PCDH19-related female-limited epilepsy: further details regarding early clinical features and therapeutic efficacy. *Epilepsy Res*. 2013;106(1–2):191–9.
26. Sadleir LG, Kolc KL, King C, Mefford HC, Dale RC, Gecz J, et al. Levetiracetam efficacy in PCDH19 girls clustering epilepsy. *Eur J Paediatr Neurol*. 2020;24:142–7.
27. Moncayo JA, Vargas MN, Castillo I, Granda PV, Duque AM, Argudo JM, et al. Adjuvant treatment for protocadherin 19 (PCDH19) syndrome. *Cureus*. 2022;14(7):e27154.
28. Liu A, Xu X, Yang X, Jiang Y, Yang Z, Liu X, et al. The clinical spectrum of female epilepsy patients with PCDH19 mutations in a Chinese population. *Clin Genet*. 2017;91(1):54–62.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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Test yourself

1. Which of the following is not a characteristic feature of PCDH19 epilepsy?
 - A. Seizures usually occur in clusters
 - B. It affects mainly boys
 - C. Psychomotor development of the patient is usually normal before the onset of seizures
 - D. Status epilepticus is common
 - E. Infection, fever, and emotional stress can provoke the seizures
2. The first seizure usually starts at the age of
 - A. <2 years
 - B. 2–6 years
 - C. 7–10 years
 - D. 11–14 years
 - E. 15–18 years
3. Children with PCDH19 epilepsy usually do not have
 - A. Sleep disturbance
 - B. Delayed intellectual development
 - C. Delayed speech development
 - D. Autistic features
 - E. Hearing disturbance

Answers may be found in the [Supporting information](#).