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Variable clinic-EEG trajectories in male patients with *PCDH19* clustering epilepsy

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SUMMARY

Background. The association between the protocadherin-19 (*PCDH19*) gene and epilepsy suggests that the X-linked inherited form of its pathogenic variant affects only women. Recent data has described males with somatic mosaicism, whose clinical picture is similar to the common manifestations in females.

Objective: to report on three new cases of *PCDH19* clustering epilepsy in male patients.

Material and methods. Clinical data were collected from different centers through personal communication between authors, which means that the structured cohort was not tested. For all patients a next generation sequencing-based custom epilepsy gene panel and whole-exome sequencing by NextSeq 500 (Illumina Inc., USA) were performed.

Results. All patients had a previously described mosaic variants in *PCDH19* gene (NM_001184880.1). According to the electroencefalographic data, all patients had a diffuse slowdown of the background rhythm, interictal regional/multiregional epileptiform activity and ictal focal pattern in the frontotemporal regions. Brain magnetic resonance imaging at the age of 3 years showed delayed myelination without focal abnormalities in 2 patients.

Conclusion. Early recognition of the above features should improve early diagnosis and long-term management of patients with epilepsy and *PCDH19* mutations.

KEYWORDS

Clustering epilepsy, *PCDH19*, protocadherin-19, magnetic resonance imaging, MRI, somatic mosaicism.

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Вариабельные клинические и ЭЭГ-кривые у пациентов мужского пола с кластерной эпилепсией, связанной с мутацией в гене *PCDH19*

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РЕЗЮМЕ

Актуальность. Связь между геном протокадгерина-19 (*PCDH19*) и эпилепсией предполагает, что Х-сцепленная наследственная форма его патогенного варианта поражает исключительно женщин. Согласно последним данным описаны мужчины с соматическим мозаицизмом, клиническая картина которого сходна с типичными проявлениями у женщин.

Цель: представить три новых случая кластерной эпилепсии, связанной с мутацией в гене *PCDH19*, у пациентов мужского пола.

Материал и методы. Клинические данные были собраны из разных медицинских центров посредством личного общения между авторами исследования, что подразумевает отсутствие проведения оценки структурированной группы пациентов. Всем больным проводилось исследование индивидуальной панели генов эпилепсии на основе секвенирования нового поколения и полноэкзомного секвенирования с помощью системы NextSeq 500 (Illumina Inc., США).

Результаты. У всех пациентов обнаружены ранее описанные мозаичные варианты гена *PCDH19* (NM_001184880.1). По данным электроэнцефалографии у всех больных в лобно-височных областях отмечались диффузное замедление фонового ритма, межприступная региональная/мультирегиональная эпилептиформная активность и иктально-очаговый паттерн. Задержка миелинизации без очаговых нарушений выявлена на магнитно-резонансной томографии головного мозга у 2 пациентов в возрасте 3 лет.

Заключение. Раннее выявление вышеуказанных особенностей должно улучшить раннюю диагностику и долгосрочное ведение пациентов с эпилепсией и мутациями в гене *PCDH19*.

КЛЮЧЕВЫЕ СЛОВА

Кластерная эпилепсия, *PCDH19*, протокадгерин-19, магнитно-резонансная томография, МРТ, соматический мозаицизм.

ИНФОРМАЦИЯ О СТАТЬЕ

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Дмитренко Д.В., Шарков А.А., Доморацкая Е.А., Усольцева А.А., Волков И.В., Пьянков Д.В. Вариабельные клинические и ЭЭГ-кривые у пациентов мужского пола с кластерной эпилепсией, связанной с мутацией в гене *PCDH19*. *Эпилепсия и пароксизмальные состояния.* 2023; 15 (3): 260–274 (на англ. яз.). https://doi.org/10.17749/2077-8333/epi.par.con.2023.156.

INTRODUCTION / ВВЕДЕНИЕ

The association between the protocadherin-19 (*PCDH19*) gene and epilepsy suggests that its X-linked inherited pathogenic variant is asymptomatic in males and affects solely females causing the syndrome of epilepsy and mental retardation (Epilepsy Limited to Females with Intellectual Disability, EFMR) also identified as Julberg–Hellman syndrome or *PCDH19* clustering epilepsy [1, 2]. However, recent data have described males with mosaic pathogenic variants of the *PCDH19* gene [3], displaying clinical picture similar to the common manifestations of the disease in females.

The *PCDH19* gene is located on the long arm of the X chromosome (Xq22.1) encoding the protein protocadherin-19 (protocadherin-19) [4], a transmembrane protein being involved in neuronal organization and mediating cell migration. It is expressed at high level during neurogenesis in the hippocampus and cortex but found at low amount in the white matter of the brain [3, 5]. Protocadherin is required for calcium-dependent cell-cell communication and adhesion. Total or partial *PCDH19* gene deletion or alternation within the coding region can result in loss of function of the *PCDH19* gene, leading to emergence of cells with impaired intercellular interaction.

PCDH19 expression declines postnatally but remains detectable, with the brain being its predominant site in adulthood. In addition, recent studies have highlighted the role of *PCDH19* in reducing the generation of certain neurosteroid hormones such as cortisol and allopregnalonone followed by potentiated seizure susceptibility [6, 7].

Pathogenic variants of the *PCDH19* gene are associated with early onset of cluster epileptic seizures, often triggered by fever, cognitive impairment of varying severity, as well as behavioral disorders such as autism, attention deficit and hyperactivity disorder, and aggression. Clinical features may mimic Dravet syndrome (OMIM: 300088, MIM phenotype № 300088) [3].

MATERIAL AND METHODS / МАТЕРИАЛ И МЕТОДЫ

We present a report on three new cases of *PCDH19* clustering epilepsy in male patients with developmental delay, drug-resistant cluster seizures, febrile seizure provocation, and early onset. The data on presented male cases were collected at diverse centers through personal communication between authors inferring that the structured patient cohort was not assessed.

For all patients, an NGS-based[1] custom epilepsy gene panel and whole-exome sequencing were performed by using NextSeq 500 (Illumina Inc., USA). An in-house software pipeline was used, designed to detect single-nucleotide variants (SNVs). All gene variants and their *de novo* status were confirmed by Sanger sequencing in blood and buccal epithelium specimens.

Video electroencephalogram (VEEG) was performed in the state of active and passive wakefulness, sleep, as well as during functional tests for standard protocol approved by the International Federation of Clinical Neurophysiology (IFCN) and the International League Against Epilepsy (ILAE) multiple times by using non-shared equipment.

According to the HARNESS-MRI (harmonized neuroimaging of epilepsy structural sequences magnetic resonance imaging) epilepsy protocol, brain MRI was performed multiple times for all patients by using non-shared equipment (1.5 and 3 Tesla).

Detailed clinical data were collected from patient medical records.

Ethical aspects / Этические аспекты

The case report study was conducted according to the guidelines of the Declaration of Helsinki of the World Medical Association (Fortaleza, Brazil, 2013). The patients' parents received a comprehensive information and provided written informed consent.

RESULTS / РЕЗУЛЬТАТЫ

All patients displayed similar clinical picture: onset at age ranging from 5 to 8 months, with disease course including focal attacks in clusters, sensitivity to fever, speech development disorders, neurological and behavioral abnormalities combined with mild to moderate mental retardation. At the time of manuscript preparation, all patients were receiving valproic acid as part of a polytherapy, and one patient was undergoing vagus nerve stimulation. Two patients (at the age of 7 and 11 years old, respectively) were in remission lasting for more than 1 year, and one patient (at the age of 12 years old) suffered from frequent cluster seizures [6].

Whole-exome sequencing / Полноэкзомное секвенирование

Due to the bilateral febrile provoked nature of the cluster seizures, a monogenic etiology was suspected, and an NGS-based custom epilepsy gene panel and whole-exome sequencing were performed by using NextSeq 500 (Illumina, USA). An in-house software pipeline was applied designed to detect gene SNVs. All patients had the following mosaic pattern of *PCDH19* gene (NM_001184880.1) variants: Patient T. – a previously described variant chrX:99663134G>C (p.Tyr154Ter) [PMID: 32425876]; Patient S. – a previously described variant chrX:99661914G>C (p.Pro561Arg) [PMID: 32425876]; Patient K. – a previously described variant chrX:99663003C>G (p.Arg198Pro) [PMID: 23712037, PMID: 26765483, PMID: 19214208]. All variants and their *de novo* status were confirmed by Sanger sequencing in blood and buccal epithelium specimens (**Fig. 1**).

[1] NGS – next generation sequencing.

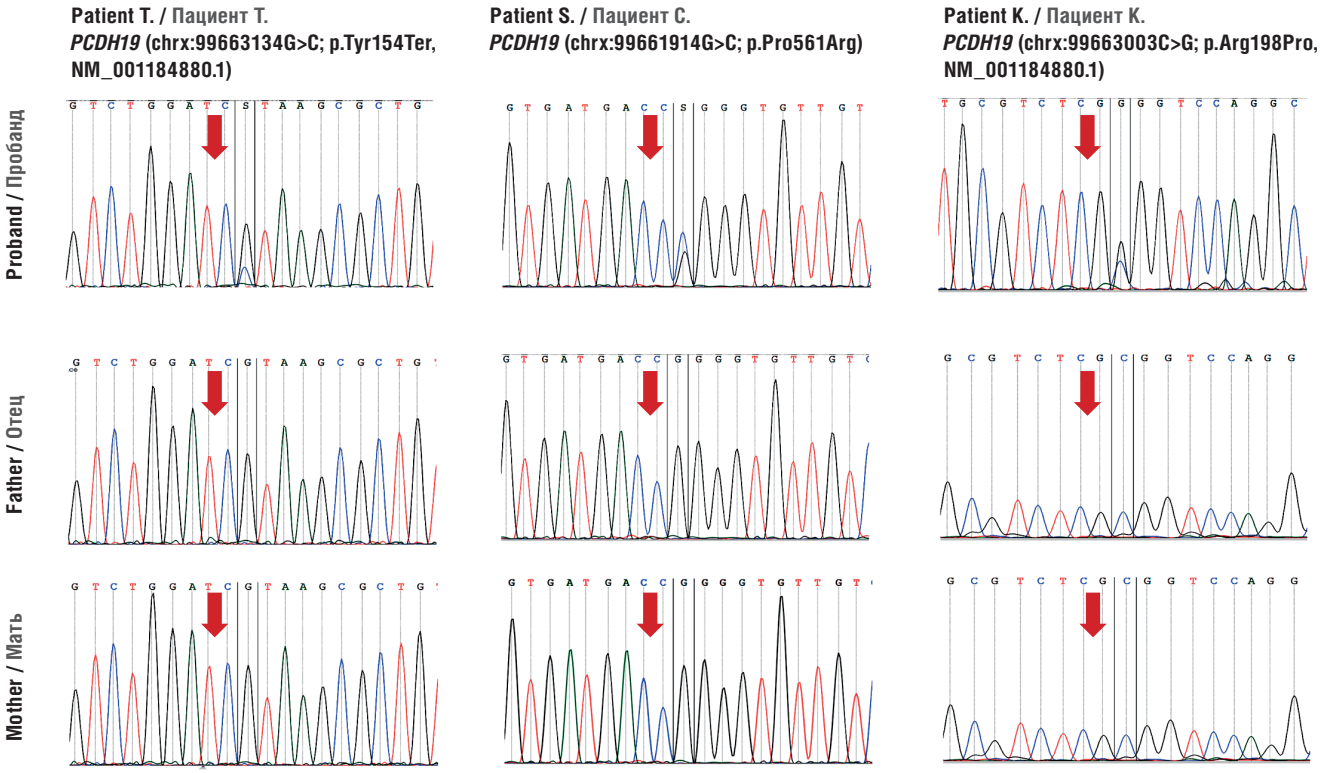
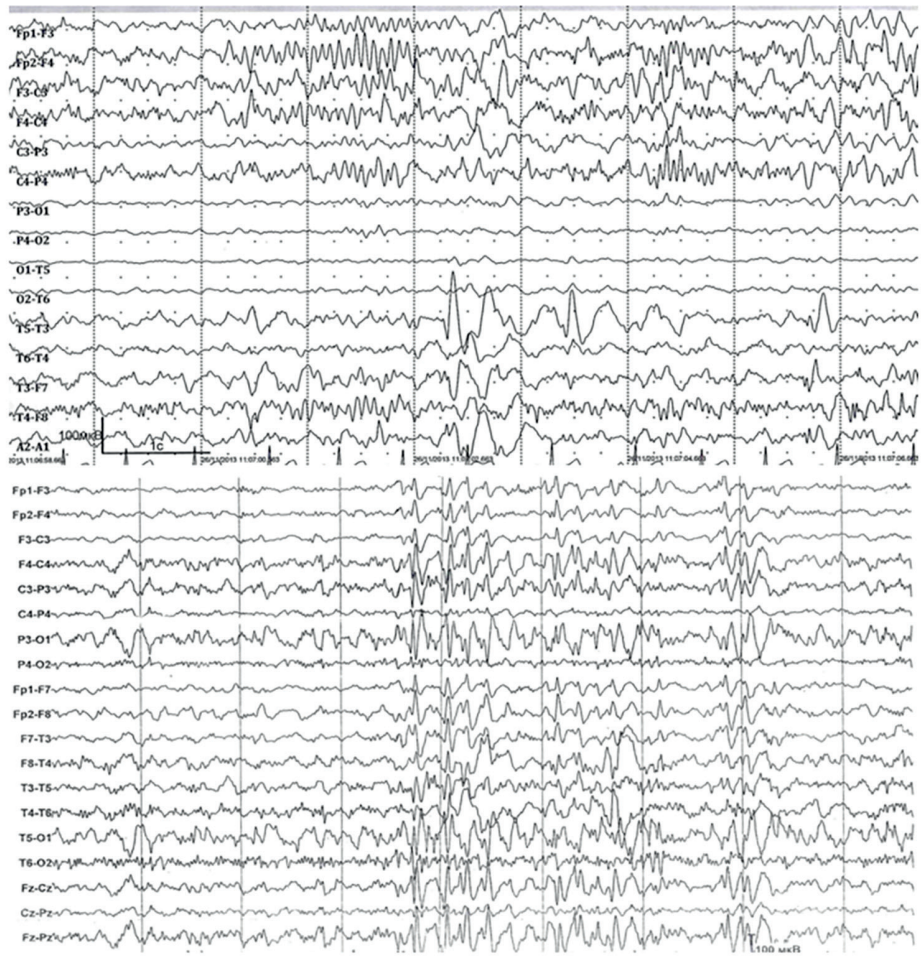
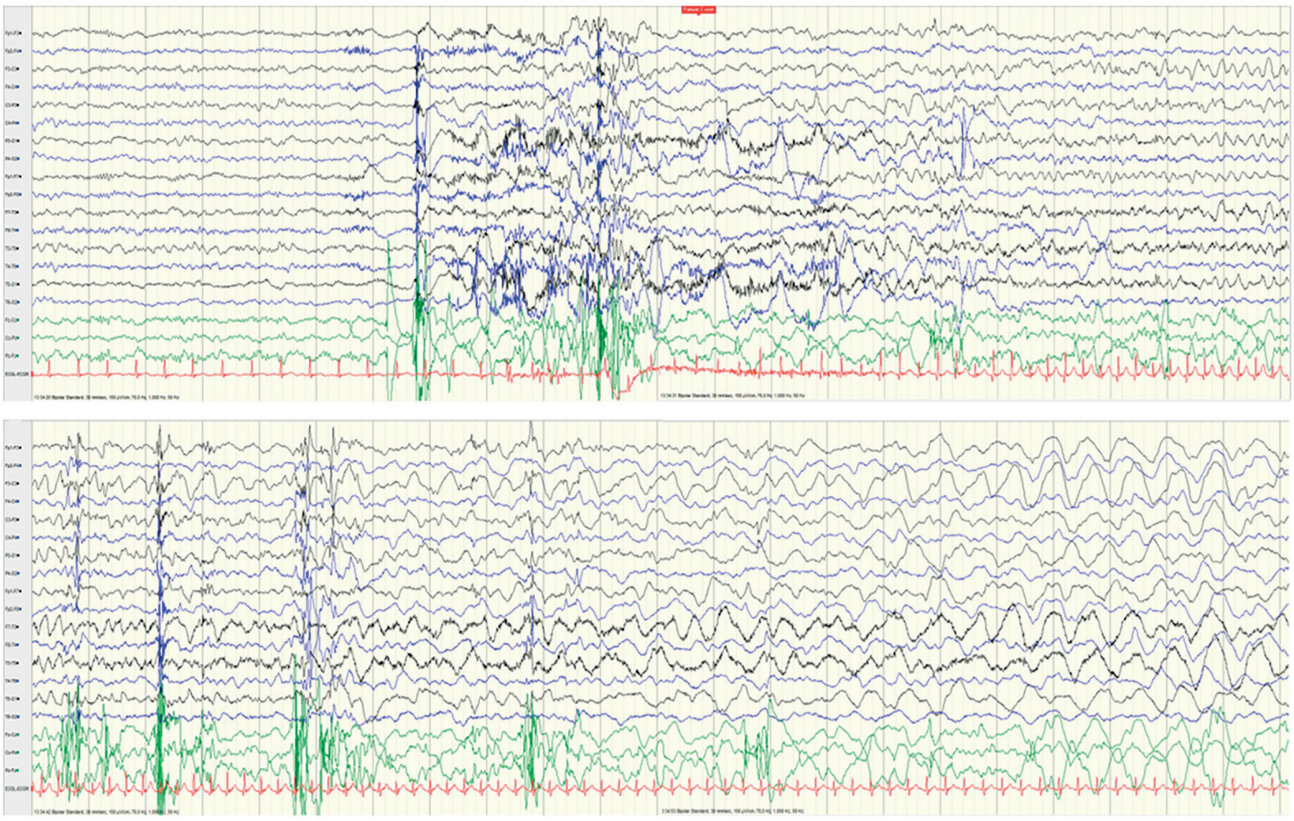


Figure 1. Results of Sanger sequencing (arrows indicate the location of the identified mutation):
a – in blood; b – in buccal epithelium

Рисунок 1. Результаты секвенирования по Сэнгеру (стрелками указано место выявленной мутации):
a – в крови; b – в буккальном эпителии



a



b

Figure 2. Electroencephalography results (interictal regional/multi-regional epileptiform activity and ictal focal pattern in the frontotemporal regions): a – Patient T.; b – Patient K.

Рисунок 2. Результаты электроэнцефалографии (интериктальная регионарная/мультирегиональная эпилептиформная активность и иктальный фокальный паттерн в лобно-височных областях): a – пациент Т.; b – пациент К.

Electroencephalography / Электроэнцефалография

It should be underlined that both at the disease onset and during therapy the electroencephalographic (EEG) data revealed a diffuse slowdown of the background rhythm. All patients showed interictal regional/multiregional epileptiform activity and ictal focal pattern in the frontotemporal regions (**Fig. 2**).

Magnetic resonance imaging / Магнитно-резонансная томография

Brain MRI performed at age of 3 years old showed in two patients delayed myelination without focal abnormalities (**Fig. 3**).

Detailed patients' clinical information is presented in **Table 1**.

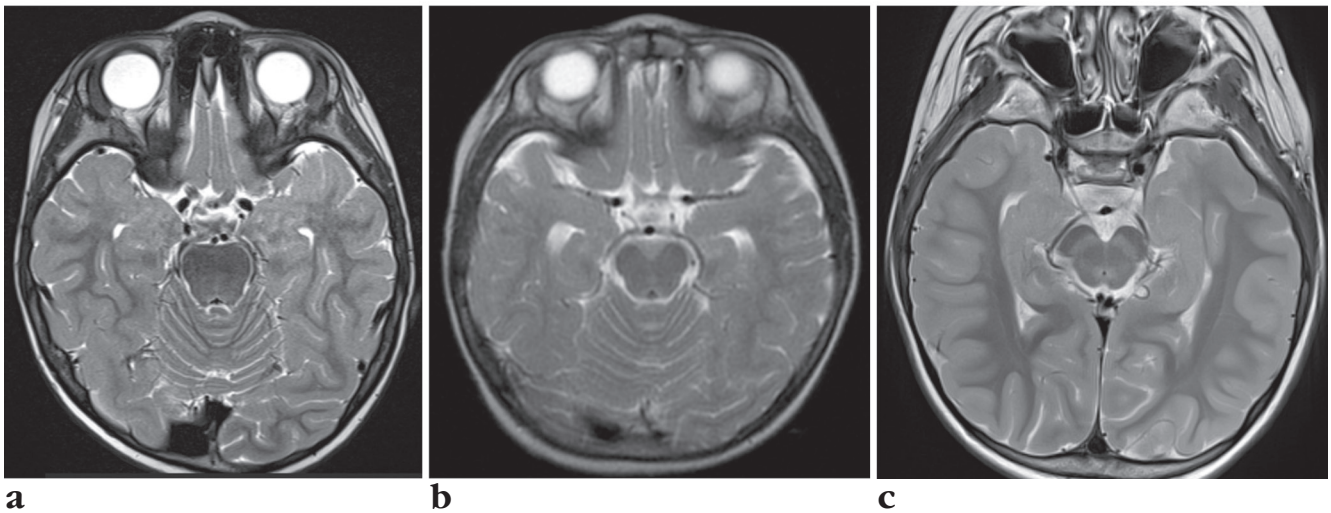
DISCUSSION / ОБСУЖДЕНИЕ

A pathogenic variant of the *PCDH19* gene was first described in 2009 in a male with somatic mosaicism. This discovery inspired to propose a theory for the disease pathogenesis: *PCDH19* clustering epilepsy occurs when two distinct cell populations coexist within the same host (cells expressing normal and aberrant PCDH19 protein counterparts) that putatively disrupts intercellular communication (**Fig. 4**). It may account for why heterozygous carriers (females) are susceptible to the disease onset, whereas homozygotes (men) become ill only in the case of somatic mosaicism [3].

PCDH19 promotes cell adhesion specificity in a combinatorial manner so that mosaic *PCDH19* expression in heterozygous female mice results in targeted sorting between wild-type *PCDH19*-positive and -negative cells in developing cortex that correlates with altered neural activity. Complete deletion of the *PCDH19* gene in heterozygous mice removes abnormal cell sorting and restores normal network activity [8].

Randomly inactivated X chromosome in females results in emergence of somatic mosaicism due to a mixture of both normal and abnormal protocadherin expressing-cell types. Such somatic mosaicism elicits alterations in interplay between both cell types followed by dysfunctional cell sorting and synaptogenesis. In contrast, males with hemizygous mutations generate only one cell type bearing certain protocadherin deficient subclass, but remain asymptomatic due to the lack of cellular intervention. However, for males with somatic mosaicism of the *PCDH19* gene, a phenotype resembling that of heterozygous females is typical that results from altered cellular crosstalk between both distinct cell types [7, 9–14].

Both girls and boys display similar clinical picture of epilepsy associated with the *PCDH19* gene mutation (girls clustering epilepsy *PCDH19*-GCE) that includes early onset of the disease (at the age of 6–36 months, on average at the age of 4–18 months); generalized tonic-clonic or/and focal epileptic seizures, often provoked by fever; short seizures with a cluster course; and pharmacoresistance [1, 2, 15, 16]. The disease is featured with a progressive course along with rising seizure rate and seizure number per a cluster, gradually developing mental retardation of varying severity [17–19]. Three clinical stages of *PCDH19*-GCE have been identified: clusters of seizures without fever within the first 2 years of life, clusters of seizures during fever between age of 2 and 10 years old, and rare epileptic seizures and



a b c

Figure 3. Magnetic resonance imaging results:
a – Patient T. (myelination disorder in the basal regions and poles of both temporal lobes); b – Patient S. (norm); c – Patient K. (slight expansion of the external liquor spaces in the anterior parts and signs of delayed myelination of cerebral hemispheres white matter)

Рисунок 3. Результаты магнитно-резонансной томографии:
a – пациент Т. (нарушение миелинизации в базальных отделах и полюсах обеих височных долей); b – пациент С. (норма); c – пациент К. (незначительное расширение наружных ликворных пространств в передних отделах и признаки замедленной миелинизации белого вещества полушарий головного мозга)

Table 1 (beginning). Detailed clinical information

Таблица 1 (начало). Подробные клинические характеристики пациентов

Clinical picture / Клиническая картина	**Patient T. (Krasnoyarsk) / Пациент Т. (Красноярск)**	**Patient S. (Novosibirsk) / Пациент С. (Новосибирск)**	**Patient K. (Moscow) / Пациент К. (Москва)**
Gender / Пол	Male / Мужской	Male / Мужской	Male / Мужской
Perinatal period / Перинатальный период	Antepartum rupture of amniotic fluid with an anhydrous interval of 14 hours, discoordination of labor / Дородовое излитие околоплодных вод с безводным интервалом 14 ч, дискоординация родов	Discoordination of labor, emergency caesarean section, mild asphyxia / Дискоординация родов, экстренное кесарево сечение, легкая асфиксия	Antepartum rupture of amniotic fluid / Дородовое излитие околоплодных вод
Apgar score at birth / Оценка по шкале Апгар при рождении	8/9 points // 8/9 баллов	7/8 points // 7/8 баллов	7/8 points // 7/8 баллов
Development before the onset / Развитие до начала заболевания	Norm / Нормальное	Norm / Нормальное	With tempo-motor and psycho-speech delay / С темпомоторной и психоречевой задержкой
Age of onset / Возраст дебюта	8 months / 8 мес	7 months / 7 мес	5 months / 5 мес
Previously described variant of *PCDH19* gene (NM_001184880.1) / Ранее описанный вариант гена *PCDH19* (NM_001184880.1)	chrx:99663134G>C (p.Tyr154Ter) [PMID: 28669061]	chrx:99661914G>C (p.Pro561Arg) [PMID: 32425876]	chrx:99663003C>G (p.Arg198Pro) [PMID: 23712037, PMID: 26765483, PMID: 19214208]
Percentage of mosaic pathogenic variant / Процент мозаичного патогенного варианта	50%	50%	40%
Inheritability of the pathogenic variant / Наследование патогенного варианта	No. *De novo* mutation / Нет. Мутация *de novo*	No. *De novo* mutation / Нет. Мутация *de novo*	No. *De novo* mutation / Нет. Мутация *de novo*
Type of onset seizure / Тип дебюта приступа	Focal seizure with impaired consciousness / Фокальный приступ с нарушением сознания	Focal, motor seizure(s) with impaired consciousness / Фокальный(е) моторный(е) приступ(ы) с нарушением сознания	Focal seizure with impaired consciousness, with a transition to bilateral tonic seizure on the background of pneumonia (low-grade fever) / Фокальный приступ с нарушением сознания и переходом в двусторонний тонический приступ на фоне пневмонии (субфебрильная лихорадка)
Type of further seizures / Тип дальнейших приступов	Focal non-motor behavioral seizures with impaired consciousness, myoclonic, cluster course, bilateral tonic-clonic seizures / Фокальные немоторные поведенческие приступы с нарушением сознания, миоклонические, кластерное течение, двусторонние тонико-клонические приступы	Focal motor seizures, infantile spasms / Фокальные моторные приступы, инфантильные спазмы	Focal seizures with impaired awareness (tonic (right hand placement) and hypermotor), bilateral tonic, myoclonic seizures / Фокальные приступы с нарушением сознания (тонические (положение правой руки) и гипермоторные), двусторонние тонические, миоклонические приступы
Febrile seizures / Фебрильные судороги	+	+	+
Cluster course / Течение кластерных припадков	+	+	+
Epileptic status / Эпилептический статус	–	+	–
Mental retardation / Умственная отсталость	Moderate / Умеренная	Moderate / Умеренная	Moderate / Умеренная
Development regression / Регресс развития	–	+	–

Table 1 (continuation). Detailed clinical information

Таблица 1 (продолжение). Подробные клинические характеристики пациентов

Clinical picture / Клиническая картина	Patient T. (Krasnoyarsk) / Пациент Т. (Красноярск)	Patient S. (Novosibirsk) / Пациент С. (Новосибирск)	Patient K. (Moscow) / Пациент К. (Москва)
Speech development / Развитие речи	Motor alalia, limited understanding of speech / Моторная алалия, ограниченное понимание речи	Motor alalia, limited understanding of speech / Моторная алалия, ограниченное понимание речи	Motor alalia (only 2 short words), understands 30–40% of speech / Моторная алалия (только 2 коротких слова), понимание 30–40% речи
Neurological abnormalities / Неврологические нарушения	Late onset of pelvic control. Diffuse increase in muscletone. The stereotypes are predominantly in the hands. Self-care disorder / Позднее начало тазового контроля движений. Диффузное повышение мышечного тонуса. Стереотипные движения преимущественно в руках. Нарушение самообслуживания	Ataxia, stereotypes / Атаксия, стереотипные движения	Walks since 1 year 2 months. By the age of 2.5 did not speak. Late onset of pelvic control (6 years). Atactic gait. Mongoloid eye shape, upturned tip of the tongue, long filter, downward angles of the mouth, cone-shaped fingertips, chubby cheeks / Ходит с возраста 1 год 2 мес. К 2,5 годам не говорил. Позднее начало тазового контроля (6 лет). Атактическая походка. Монголоидный разрез глаз, поднятый кончик языка, длинный фильтр, опущенные углы рта, конусовидные кончики пальцев, пухлые щеки
Psychiatric/behavioral disorders // Психиатрические/поведенческие расстройства	Autism spectrum disorder / Расстройства аутистического спектра	Autism spectrum disorder, aggressiveness, hyperexcitability / Расстройства аутистического спектра, агрессивность, гипервозбудимость	Autism spectrum disorder / Расстройства аутистического спектра
Antiepileptic drugs and therapeutic effect / Противоэпилептические препараты и терапевтический эффект	LEV: +/– (AR); ZNS: – (AR); CLN: ++/–; RUF: ++/–; OXC, LTG, VPA, LAC, TPM, CBZ: +/– // LEV: +/– (HP); ZNS: – (HP); CLN: ++/–; RUF: ++/–; OXC, LTG, VPA, LAC, TPM, CBZ: +/–	VPA: –; VPA + CBZ: +/–; LEV: +/–; hormones: ++/–; LEV: +; CBZ: +/–; VPA + LEV: ++/–; VPA + LEV + LAC: +/– // VPA: –; VPA + CBZ: +/–; LEV: +/–; гормоны: ++/–; LEV: +; CBZ: +/–; VPA + LEV: ++/–; VPA + LEV + LAC: +/–	PHB: +/–; PHB + VPA: – (AR); PHB + VPA + CLN: +/– (AR); LTG: (AR); CBZ: – (AR); VPA + TPM + CLN: +/–; VPA + TPM + LEV (4 months): ++/–; potassium bromide: +/–; PHT: ++/– // PHB: +/–; PHB + VPA: – (HP); PHB + VPA + CLN: +/– (HP); LTG: – (HP); CBZ: – (HP); VPA + TPM + CLN: +/–; VPA + TPM + LEV (4 мес): ++/–; бромид калия: +/–; PHT: ++/–
Current therapy / Текущая терапия	VPA + OXC, VNS: 1.75 mA, 500 W, 30 Hz, On 30 sec., Off 5 min; Mag 2.0 mA, On 60 sec., 500 W // VPA + OXC, VNS: 1,75 мА, 500 Вт, 30 Гц, вкл. 30 с, выкл. 5 мин; усиление до 2,0 мА, вкл. 60 с, 500 Вт	VPA + LEV + nitrazepam / VPA + LEV + нитразепам	LEV + VPA + TPM + PHT
Current age and seizure frequency / Текущие возраст пациента и частота приступов	12 years old, clusters once in 10–12 days with 15–17 attacks in a cluster (1–2 days) / 12 лет, кластеры происходят каждые 10–12 сут, с 15–17 атаками в кластере (1–2 сут)	11 years old, no seizures for 3 years / 11 лет, отсутствие приступов в течение 3 лет	7 years old, remission since March 2020 / 7 лет, ремиссия с марта 2020 г.

Table 1 (continuation). Detailed clinical information

Таблица 1 (продолжение). Подробные клинические характеристики пациентов

Clinical picture / Клиническая картина	Patient T. (Krasnoyarsk) / Пациент Т. (Красноярск)	Patient S. (Novosibirsk) / Пациент С. (Новосибирск)	Patient K. (Moscow) / Пациент К. (Москва)
EEG after the onset / ЭЭГ после дебюта	Main background activity 2–4 Hz, interictal epileptiform activity in the temporal lobe of brain right hemisphere / Основная фоновая активность 2–4 Гц, интериктальная эпилептиформная активность в височной доле правого полушария мозга	Main background activity 2–4 Hz, regional slowing down in the frontal-central-temporal regions, ictal regional deceleration in the right temporal leads with the appearance of diffuse peak-wave activity / Основная фоновая активность 2–4 Гц, региональное замедление в лобно-центрально-височных областях, иктальное региональное замедление в правых височных отведениях с появлением разлитой пик-волновой активности	Diffuse slowing down of the background rhythm with a predominance of theta activity, with smooth zonal differences. Atypical vertices in the initial dream. No epileptiform activity registered / Диффузное замедление фонового ритма с преобладанием тета-активности, с плавными зональными различиями. Атипичные вертекс-потенциалы в начальной фазе сна. Эпилептиформной активности не зарегистрировано
Intermediate EEG / Промежуточная ЭЭГ	Diffuse rhythmic theta slowdown of the background rhythm. The main rhythm is not clearly differentiated. Multiregional interictal epileptiform activity was registered in the state of wakefulness and superficial stages of sleep: in the left frontotemporal regions, the right frontotemporal region, bifrontal-central, bifrontal-central-temporal, diffuse flashes with a pronounced amplitude accent in the frontal regions. A focal seizure with hypermotor manifestations was registered, with a transition to an asymmetric tonic seizure and bilateral tonic-clonic seizures (ictal pattern from the left frontotemporal regions) / Диффузное ритмическое тета-замедление фонового ритма. Основной ритм четко не дифференцируется. В состоянии бодрствования и поверхностных стадиях сна регистрировалась мультирегиональная интериктальная эпилептиформная активность: в левой лобно-височной области, правой лобно-височной области бифронтально-центральные, бифронтально-центрально-височные, диффузные вспышки с выраженным амплитудным акцентом в лобных областях. Зарегистрирован очаговый приступ с гипермоторными проявлениями с переходом в асимметричный тонический приступ и двусторонние тонико-клонические приступы (иктальный паттерн в левых лобно-височных областях)	Hypsarrhythmia / Гипсаритмия	Diffuse rhythmic theta slowdown of the background rhythm. The basic rhythm is not clearly differentiated. Sleep is structured in stages, physiological sleep patterns are presented satisfactorily. During sleep, bifrontal adhesions (involving the anterior vertex regions) were quite often recorded, the morphology of which, in most cases, satisfies the EEG pattern of “atypical vertex waves”. However, in some cases, graphoelements of the “peak-slow wave” type were recorded, which is indicative of epileptiform activity / Диффузное ритмическое тета-замедление фонового ритма. Основной ритм четко не дифференцирован. Сон структурирован по стадиям, физиологические паттерны сна представлены удовлетворительно. Во время сна часто регистрировались бифронтальные спайки (с вовлечением передних вертексных отделов), морфология которых в большинстве случаев удовлетворяет ЭЭГ-паттерну «атипичных вертексных волн». Однако в ряде случаев регистрировались графоэлементы типа «пик – медленная волна», что свидетельствует об эпилептиформной активности

Table 1 (end). Detailed clinical information

Таблица 1 (окончание). Подробные клинические характеристики пациентов

Clinical picture / Клиническая картина	Patient T. (Krasnoyarsk) / Пациент Т. (Красноярск)	Patient S. (Novosibirsk) / Пациент С. (Новосибирск)	Patient K. (Moscow) / Пациент К. (Москва)
Last EEG / Последняя ЭЭГ	Diffuse delta-range flashes, generalized discharges of grouped peak-slow wave complexes with bifrontal dominance / Диффузные вспышки дельта-диапазона, генерализованные разряды сгруппированных комплексов «пик – медленная волна» с бифронтальным доминированием	No epiactivity / Нет эпиактивности	Transient regional slowdown in left hemisphere temporal lobe. Ictal pattern – regional slowing F3–C3–T3 (focal seizure with hypermotor manifestations, dystonia in the right hand, impaired consciousness) / Транзиторное региональное замедление в височной доле левого полушария. Иктальный паттерн – региональное замедление F3–C3–T3 (очаговый приступ с гипермоторными проявлениями, дистония в правой руке, нарушение сознания)
MRI result and age / Данные МРТ и возраст пациента	3 years, myelination disorder in the basal regions and poles of both temporal lobes / 3 года, нарушение миелинизации в базальных отделах и полюсах обеих височных долей	5 years, 3 T, variant of the norm / 5 лет, 3 Тл, вариант нормы	3 years, slight expansion of the external liquor spaces in the anterior parts and signs of delayed myelination of cerebral hemispheres white matter / 3 года, незначительное расширение наружных ликворных пространств в передних отделах и признаки замедленной миелинизации белого вещества полушарий головного мозга
Additionally / Дополнительно	Thin layer chromatography of blood acids is normal; phenylalanine is normal; tandem mass spectrometry mass spectrometry – hereditary aciduria and mitochondrial diseases were not identified; aCGH – no pathogenic microstructural rearrangements were identified [1] / Тонкослойная хроматография уровня кислот крови в норме, фенилаланин в норме, тандемная масс-спектрометрия – наследственной ацидурии и митохондриальных заболеваний не выявлено; aCGH – патогенных микроструктурных перестроек не выявлено [1]	–	Chromosomal microarray analysis extended – no pathology. *SCN1A* targeted sequencing – no significant variants / Расширенный хромосомный микроматричный анализ – патологии нет. Целевое секвенирование *SCN1A* – значимых вариантов нет

Note. *EEG – electroencephalography; MRI – magnetic resonance imaging; LEV – levetiracetam; ZNS – zonisamide; CLN – clonazepam; RUF – rufinamide; OXC – oxcarbazepine; LTG – lamotrigine; VPA – valproic acid; TPM – topiramate; CBZ – carbamazepine; PHT – phenytoin; PHB – phenobarbital; LAC – lacosamide; AR – adverse reactions; VNS – vagus nerve stimulation; "–" – no effect; "+/–" – weak effect; "++/–" – medium effect; aCGH – array comparative genomic hybridization.*

Примечание. *ЭЭГ – электроэнцефалография; МРТ – магнитно-резонансная томография; LEV (англ. levetiracetam) – леветирацетам; ZNS (англ. zonisamide) – зонисамид; CLN (англ. clonazepam) – клоназепам; RUF (англ. rufinamide) – руфинамид; OXC (англ. oxcarbazepine) – окскарбазепин; LTG (англ. lamotrigine) – ламотриджин; VPA (англ. valproic acid) – вальпроевая кислота; TPM (англ. topiramate) – топирамат; CBZ (англ. carbamazepine) – карбамазепин; PHT (англ. phenytoin) – фенитоин; PHB (англ. phenobarbital) – фенобарбитал; LCM (англ. lacosamide) – лакосамид; НР – неблагоприятная реакция; VNS (англ. vagus nerve stimulation) – стимуляция блуждающего нерва; «–» – без эффекта; «+/–» – слабый эффект; «++/–» – средний эффект; aCGH (англ. array comparative genomic hybridization) – массив сравнительной геномной гибридизации.*

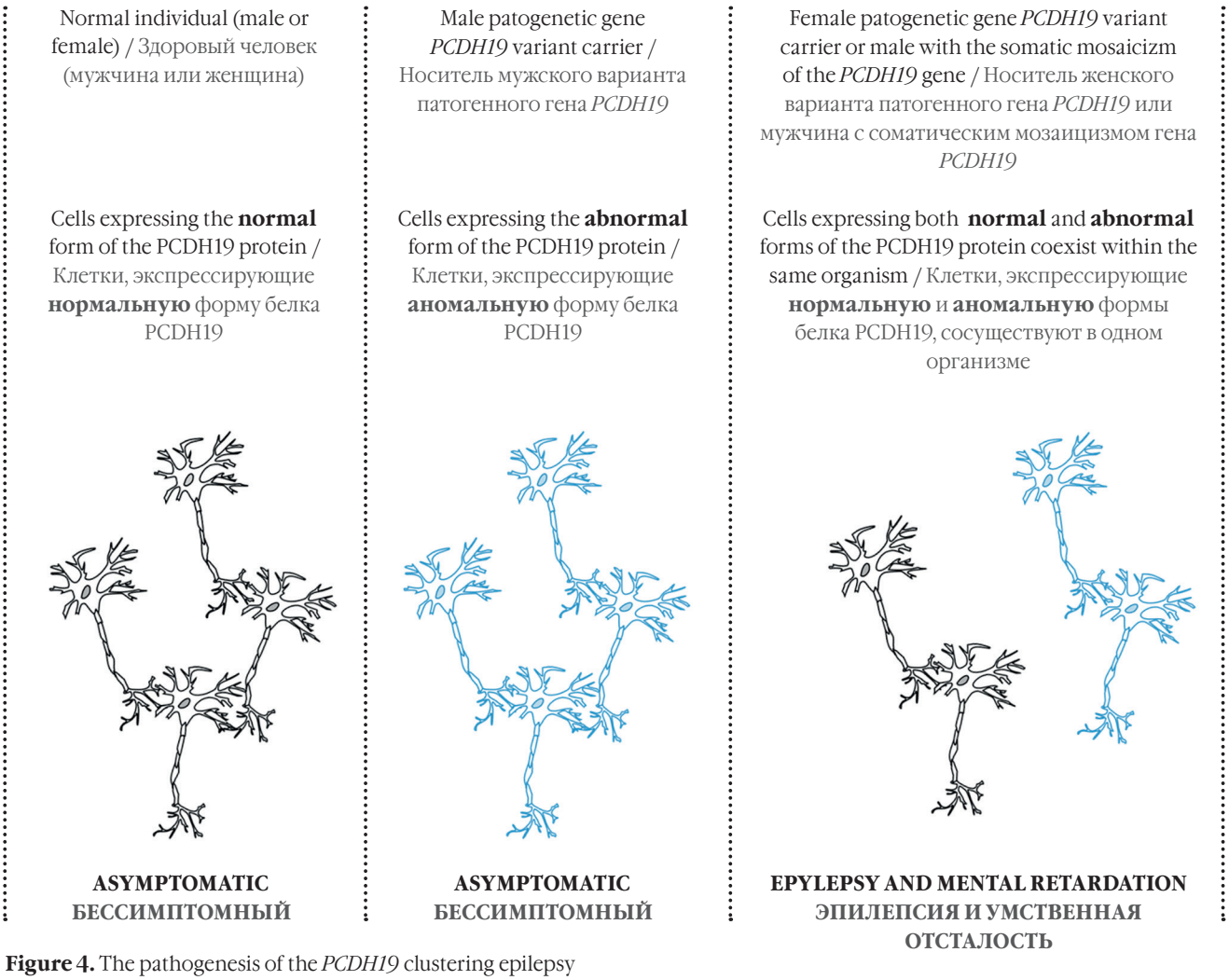


Figure 4. The pathogenesis of the *PCDH19* clustering epilepsy

Рисунок 4. Патогенез кластерной эпилепсии, связанной с мутацией в гене *PCDH19*

behavioral disturbances observed at age over 10 years old. We registered and described clusters of epileptic seizures in patients under the age of 2 years old [20].

Patients with *PCDH19*-GCE may be also observed to show stereotypical movements, hyperreflexia, autism spectrum disorders, and other neuropsychiatric disorders with aggression, obsessive disorders, schizophrenia, hysteria, depression, a tendency to self-harm as well as attention deficit in case of hyperactivity disorder [14, 18, 21].

The rate of seizures in *PCDH19*-GCE girls often declines during puberty potentially due to hormonal changes [17, 20, 22–24]. However, an age-related decrease in seizure rate was reported in the patients examined as well as some other identified male patients. Therefore, this tendency seems unlikely to occur solely in females being associated with female hormones [6]. N. Higurashi et al. (2015) suggest that remission of seizures in adolescence occurs due to maturation of the blood-brain barrier [25].

The *PCDH19* protein is expressed stronger in endothelial cells in the central nervous system than in other organs. N. Higurashi et al. (2015) consider that seizures, resulting from *PCDH19* gene mutation usually occur in the limbic region located closer to the periventricular regions [25].

EEG often shows focal or multifocal epileptiform changes and background slowdown [26]. Registration of focal and multifocal activity based on EEG data alerts researchers to the presence of structural changes in patient brain. Four out of five girls with focal cortical dysplasia (FCD) were recorded to have multifocal changes, and one girl – diffuse changes without focal activity [27].

MRI data often reveal a variant of the normal pattern. In addition, various cortical malformations have been identified in patients with epilepsy associated with *PCDH19*-GCE [8]. Study by N. Trivisano et al. (2018) detected FCD in 4% patients, with 10% of them suspected to have same diagnosis [22].

Similar data were observed in a series of studies: in 3 patients reported by Y. Tan et al. (2018) [8]; in 2 patients – by A. Liu et al. (2019) [15]; and in 6 to 9 patients – by I.M. de Lange et al. (2017) [3]. A dilated perivascular and subarachnoid spaces were found in 2 out of 9 observed patients reported in the study by I.M. Lange et al. (2017) [3] similar to MRI changes in found by us in Patient K.

Analysis of MRI images reveals cortical sulcus abnormalities in 4 girls with *PCDH19*-GCE [23]. The patients had various cerebral cortex abnormalities, including dysplasia of the

bottom of the sulcus, abnormal cortex fold, thickened cortex as well as blurred transition between gray and white matter [8, 23]. M. Kurian et al. (2018) described an improved seizure control in 2 patients after FCD resection [27].

The coincidence between pathogenic *PCDH19* variants and cortical malformations including FCD remains controversial. FCD may not occur accidentally and could be accounted for by a putative role that *PCDH19* might play in neuronal migration demonstrated in some animals or *in vitro* in human pluripotent stem cell-derived neurons [5, 11, 27, 28].

However, the process of abnormal cell sorting and its potential to cause the above alterations have not yet been well understood. The variability of the abnormalities is consistent with the random X-chromosome inactivation as well as the phenotypes observed in patients with *PCDH19*-GCE [8, 29, 30].

It is likely that males with about 50% brain mosaicism intrinsically bearing high level of cellular interference may display a more severe clinical picture than males with a lower or higher percentage of mosaicism [3]. The high or low percentage of mosaicism resembles that of skewed X-inactivation in female patients, which has also been thought to result in a milder phenotype [26, 30], which, however, revealed no clear correlation [7, 21, 25, 31].

The generation of differential adhesion affinity in neuronal progenitor cells induced by mosaic *PCDH19* expression appears underlie the essential cellular mechanism responsible for the unique X-linked inheritance for *PCDH19*-GCE. Even the lack of *PCDH19* observed in hemizygous males results in no emergence of incompatible adhesion specificity that allows for normal position of neuronal progenitor cells and neural activity. An abnormal rearrangement of neuronal progenitor cells in the nascent cortex of the heterozygous brain points that at least some of their neuronal descendants may be located aberrantly, regardless of whether they support postpartum *PCDH19* expression. Such reorganization may disrupt functional boundaries of the cortex and affect links between cortical and subcortical regions [8].

If the entire cerebral cortex were to undergo segregation, it might likely lead to aberrant organization of the functional cortical columns. In case an abnormal cell sorting occurs throughout the cortex, a difference in neuronal architecture between humans and mice could contribute to a more severe phenotype observed in *PCDH19*-GCE patients [8].

In addition, the identification of altered cortical sulcus suggests that aberrant cell sorting may cause diverse morphological phenotypes in the gyrencephalic vs. lissencephalic brain. The cortical fold of the human brain largely results from varying proliferation of the basal radial glia cells comprising a small proportion of progenitor cells in the lissencephalic vs. gyrencephalic brain [8, 29, 32]. The overgrowth of the basal radial glia cells triggers formation of “wedges” emerging from cell dense areas that ultimately accounts for brain fold. Segregation within basal radial glial cells in developing human brain may result in abnormal development due to improper “wedge” formation [8].

On the other hand, neurodevelopmental disorders associated with mutations in other non-clustered members belonging to the protocadherin family (NC PCDH) may be caused by impaired cell adhesion affinity [8, 33, 34]. It is likely that mosaic disruption of adhesion specificity occurs via a process other than X-inactivation primarily due to random monoallelic NC PCDH expression [35]. Individuals with a heterozygous germline mutation in certain autosomal NC PCDHs may bear some cells expressing either a functional or a non-functional allele resulting in impaired adhesion specificity. The proportion of cells affected by random monoallelic NC PCDH expression is likely to affect the penetrance or expressivity of any resulting phenotype [8].

The *in vivo* interaction of the relevant adhesion affinities for each of such closely related families of NC PCDH proteins can lead to diverse outcomes. The coordinated expression of grouped protocadherins is believed to result in repulsion involved in neuron self-recognition [8, 36, 37]. On the other hand, it has been shown that NC PCDH-expressing cells are able to selectively interact *in vivo*. Given the multi-layered and overlapping pattern of NC PCDH expression throughout development, it seems likely that this property might regulate spatial arrangement of neuronal cell progenitors to be potentially exploited during the morphogenesis of other organs [8, 38].

Thus, the loss of *PCDH19* is associated, e.g., with altered columnar organization and elevated cell proliferation in the optical membrane [24, 27] additionally triggering brain hyperexcitability in zebrafish models [39]. Although no major morphological defects were observed in the mutant brain, the loss of mouse *PCDH19* similarly enhances neuronal cell migration [27, 28].

Cerebral cortical malformations comprise an important cause of developmental abnormalities and *PCDH19*-GCE, so that some of them are related to defects in specific genes [22, 40]. When FCD emerges, the co-occurrence of pathogenic variants of *SCN1A* is not considered to account for the overall clinical picture, but the loss or dysfunction of the relevant protein, action of susceptibility factors and genetic modifiers of phenotypic expression may collectively play a certain role [41]. In addition, MRI signs related to FCD were detected in patients with other monogenic forms of epileptic encephalopathies [42]. Such associations discussed here by us highlight a need for further study to provide deeper insights into underlying mechanisms and, consequently, examination and clinical management of such patients [43–45].

CONCLUSION / ЗАКЛЮЧЕНИЕ

Early recognition of the above features should improve early diagnostics and long-term management of patients with epilepsy coupled to *PCDH19* mutations. In this context, MRI plays a unique role in establishing the phenotypic signature of such associations *in vivo*. It is important to note that a specialized assessment is required prior to drawing a conclusion that no structural changes in the brain take place. Stereotypical focal epileptic seizures observed in such patient cohort require exclusion of structural changes in the brain as well as performing pre-surgical examination.

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