Advances in Medicine and Engineering Interdisciplinary Research, 2025, Volume 3, Issue 1
DOI: 10.32629/ameir.v3i1.3702
ISSN Online: 2972-3825
ISSN Print: 2972-3833

Advances and Perspectives in Epilepsies of Genetic Origin: A Case Report

Cindy Leonela Delgado Salcedo[1,2], Lina Johanna Moreno Giraldo[3]

1. Pediatrics Resident, Universidad Libre, Cali Branch, Cali, Colombia.
2. Pediatric Research Group (GRINPED), Cali, Colombia.
3. Medical Genetics, Postgraduate in Clinical Bioinformatics and Genomics, Postgraduate Professor in the Research Line of Neurogenetic and Metabolic Disorders, Cali, Colombia.

Abstract: Progress in genomics has allowed the identification of multiple genetic variants involved in epilepsies, which facilitates early diagnosis and the development of personalized therapies. This case describes a 15-year-old male patient with a clinical picture since the age of 10 months consisting of generalized tonic-clonic seizures, accompanied by moderate intellectual disability with compromised behavioral and adaptive skills, the product of non-consanguineous parents, with no history related to the patient's clinical presentation. Given the age of presentation, characteristics, progression and the need for multiple anticonvulsants, de novo epilepsy of genetic origin was suspected, so whole exome sequencing and copy number variant (CNV) analysis of 110 genes associated with refractory epilepsy were performed, and the results showed a pathogenic hemizygous variant in the PCDH19 gene. Variants of this gene (PCDH19) are associated in databases such as ClinVar with sporadic infantile epileptic encephalopathy, female-limited epilepsy (EFMR or PCDH19RE), and Dravet syndrome. The PCDH19 gene was initially identified in 2008 as responsible for epilepsy and mental retardation limited to females. In 2009, the first mosaic deletion of the gene was described in a male patient, revealing a unique X-linked inheritance pattern. Both heterozygous females and males with mosaicism are affected. Dravet syndrome is a rare and severe childhood epilepsy; some variants of the PCDH19 gene, encoding protocadherin 19, are associated with a Dravet syndrome-like phenotype, known as DS-like. Genetic factors are the major contributors to the cause of epilepsy in up to 80% of epileptics. Research to elucidate the genetic landscape of epileptic and developmental encephalopathies contributes to the elucidation of molecular pathogenesis and the development of personalized targeted therapies in these disorders. Since epilepsy and cognitive disorders have advanced in the knowledge of their genetic cause, it is important to have a specific diagnosis, in order to establish targeted and personalized treatments (pharmacogenomics), follow-up, prognosis, genetic counseling and thus get closer and closer to the 7P medicine (Preventive, Proactive, Participatory, Predictive, Personalized, Pleasant).

Key words: epilepsy; whole-exome sequencing; de novo variant; PCDH19 gene; developmental epileptic encephalopathy 9; Dravet syndrome; precision medicine

1. Introduction

The International League Against Epilepsy defines epilepsy as a brain disorder characterized by an enduring predisposition to epileptic seizures and by the neurobiological, cognitive, psychological and social consequences of this

condition [1]. The incidence of epilepsy is highest during the first years of life [1]. There is evidence that epileptic activity has the potential to progressively impair the function of established brain circuits. In addition, young children have networks that are still being established and disruption may cause their development, which depends on functional activity patterns, to slow, stall or regress [1].

Genetic factors are believed to be the major contributors to the cause of epilepsy in up to 80% of people with epilepsy [2]. The term "epileptic encephalopathy" refers to the concept that such abnormal activity may contribute to cognitive and behavioral impairments beyond that expected from the underlying cause of the epileptic activity [1]. Epileptic and developmental encephalopathies comprise a group of rare neurodevelopmental disorders characterized by frequent, early-onset, refractory seizures associated with significant developmental delay [3]. Up to date, variants have been reported in hundreds of different genes coding, not only for ion channels and proteins that regulate synaptic transmission but also in genes coding for DNA repair, chromatin remodeling, transcriptional regulation, axon myelination, metabolite transport, and peroxisomal function [3]. Investigations to enlighten the genetic landscape of the developmental and epileptic encephalopathies contribute to the elucidation of molecular pathogenesis and the development of personalized targeted therapies in these devastating disorders [3].

The genetic heterogeneity of epileptic disorders is extensive, with a high number of underlying pathogenic variants in many different genes, including PCDH19 [4]. The PCDH19 gene is located in the Xq22.1 gene and consists of six exons encoding a transmembrane protein of 1,148 amino acids; the protein encoded by this gene is a member of the delta-2 protocadherin subclass of the cadherin superfamily. The encoded protein is thought to be a calcium-dependent cell-adhesion protein that is primarily expressed in the brain. Mutations in this gene on human chromosome X are associated with epilepsy limited to females (EFMR; also known as PCDH19RE) or Early Infantile Epileptic Encephalopathy, 9, in addition to Dravet syndrome. Multiple transcript variants encoding different isoforms have been found for this gene [5].

Currently, variants in the PCDH19 gene associated with pathologies have been documented in gene ontology platforms such as The Human Phenotype Ontology (HPO): Dravet syndrome (ORFA:33069) and early infantile epileptic encephalopathy, 9 (OMIM:300088) [5].

Dravet syndrome (DS) is a rare and severe epileptic syndrome of childhood. Approximately 80% of patients with this syndrome present SCN1A pathogenic variants, which encodes an alpha subunit of a neural voltage-dependent sodium channel. There is a correlation between PCDH19 pathogenic variants, which encodes the protocadherin 19, and a similar disease to DS known as DS-like phenotype [6]. The DS-like phenotype of Dravet syndrome is due to the presence of other genes involved in encephalopathy, such as the PCDH19 gene, responsible for encoding delta 2, a non-clustered protocadherin of calcium-dependent cadherins. This encoded protein, protocadherin-19, seems to play a role in the development of neuronal circuits. This gene is located on the X chromosome; therefore, the development of the disease is uncommon in males and is associated with seizures from infancy, mild to moderate cognitive impairment, as well as behavioral cognitive alterations such as autism. Relatedly, the c.1091dupC variant of the PCDH19 gene is frequently associated with a severe phenotype of encephalopathy related to profound cognitive deficit [6].

Developmental and epileptic encephalopathy-9 (DEE9) is an X-linked disorder characterized by childhood onset of seizures and mild to severe intellectual impairment. Psychiatric and autistic features have been described in some individuals [7]. The hallmark clinical features of PCDH19-associated epilepsy are seizures that tend to be tonic-clonic, atonic, myoclonic, absent. These are brief, often clustering for hours or days before stopping, and are often refractory to treatment.[8]. Seizures begin at age 6 to 36 months and subside during adolescence, but neuropsychiatric dysfunction and behavioral disorders such as attention deficit hyperactivity disorder (ADHD), autism spectrum disorders (ASD), obsessive-

compulsive disorder (OCD), and executive dysfunction persist [9]. Seizures become less severe with adolescence, whereas cognitive delay and behavioral disorder represent the main disabilities of adult patients with PCDH19 genomic variants. Brain MRI is usually normal, and there are not electroencephalographic features peculiar to the PCDH19 variant [10].

Advances in genomic technologies have led to whole-genome sequencing and microarray-based genotyping of millions of human genomes; also, potential benefits of genomic research, such as improved understanding of disease etiology, early detection and diagnosis, rational drug design, and improved clinical care [11]. The concept of genomics has become increasingly prevalent in neurological clinics. In the field of epilepsy, technological advances, detailed analysis and interdisciplinary cooperation have driven significant gene identification in this area, revealing a wide variety of genetic mechanisms and neurobiological pathways involved in these disorders. This new genomic era poses a strong challenge for clinicians, who must face the challenge of interpreting and applying genetic information in the day-to-day management of patients with epilepsy [12].

2. Method

The case describes a 15-year-old male patient with a pathological history of generalized tonic-clonic seizures since 10 months of age. The patient exhibits moderate intellectual disability with behavioral and adaptive skills compromised, who on two occasions presented status epilepticus requiring intensive care unit management. The patient without syndromic phenotype with a perinatal history of asphyxia, reported by the mother, required stimulation at the time of birth, and no orotracheal intubation; the parents are non-consanguineous and are asymptomatic. The patient has two healthy sisters and denies a family history of epilepsy or neurodegenerative syndromes.

The patient underwent metabolic paraclinical tests to rule out hereditary metabolic disorders, with results normal ranges (lactic acid: 17.39 mg/dL, venous gases: pH: 7.36, pO_2: 16.3 mmhg, pCO_2: 45 mmHg, HCO_3: 25.5 mEq/L, BE: 0 mEq/L, ammonium: 23 µ/dL, uric acid: 7.8 mg/dL, basal glycemia: 91.2 mg/dL). In addition, normal electroencephalogram and neuroimaging studies (brain MRI and brain CT reported as normal) were obtained. The patient was managed by neurology with valproic acid and levetiracetam, followed by occupational and speech therapy.

Considering the clinical diagnosis of difficult-to-manage epilepsy associated with intellectual disability and the high suspicion of epilepsy of genetic origin, it was requested a molecular panel study of genes associated with refractory epilepsy: sequencing of the complete exome (the entire coding region of the genome) in a DNB-SEQ400 last generation massive sequencer + analysis of CNV (copy number variants) by NGS in genes related to refractory epilepsy (110 genes).

3. Results

Gene	Variant	Variant type	Allelic radius (VAF)	Cigosis	Clinical significance	Reference
PCDH19 (NM-001184880.2)	c.1091dup p.(Tyr366LeufsTer10)	Frameshift	0.3	Hemizygosity	Pathogenic	rs758946412

Given the high suspicion of epilepsy of genetic origin, a molecular panel study of genes associated with refractory epilepsy was requested: sequencing of the complete exome + analysis of CNV (copy number variants) by NGS in genes related to refractory epilepsy (110 genes).

With this diagnostic method, whole exome sequencing (the entire coding region of the genome) was performed on a DNB-SEQ400 next-generation mass sequencer. 110 genes related to the patient's clinical picture were analyzed from this data. The genes evaluated were analyzed with an average coverage of over 98% and a minimum depth of 20x. The sequencing results were analyzed bioinformatically, the analysis was directed to the identification of variants included in exonic regions or splicing regions (at least 20 bp), insertions and small deletions. This analysis allowed the identification of

exonic deletions and duplications (also known as Copy Number Variants, CNV) and variants involving large regions of the gene, which were reported.

Genetic result: positive, in which a hemizygous pathogenic variant was identified in the PCDH19 gene (NM_001184880.2) variant c.1091dup; p.Tyr366LeufsTer10.

The pathogenic hemizygous variant in the PCDH19 gene generated by a duplication of a guanine at position 1091 of the cDNA, in exon 1 of the gene (c.1091dup) and that at the protein level produces the frameshift change of a tyrosine to leucine at amino acid 366 that produces a premature stop 10 amino acids later (p.Tyr366LeufsTer10), an evolutionarily conserved amino acid. This variant is reported in the databases ClinVar (ID: 206353), The Human Gene Mutation Database (HGMD) and Leiden Open Variation Database (LOVD); nor in the scientific literature consulted. Its allelic frequency is 0.00001074 in the general population (gnomAD).

The deleterious variants in the PCDH19 gene are associated with epileptic and developmental encephalopathy 9 of X-linked inheritance and Dravet syndrome. This PCDH19 gene is located in the Xq22.1 gene, which consists of six exons encoding a transmembrane protein of the delta-2 protocadherin subclass of the cadherin superfamily [5].

The gene and its variant are currently found in ClinVar and Franklin by Genoox with pathogenic clinical significance, in ClinGen CA200395: they report Haploinsufficiency Sufficient Evidence and triplosensitivity no Evidence, DECIPHER HI score 6.65, Curated DBs: Pathogenic LOF variants 276, Missense Benign Variants: 32 and Missense Pathogenic Variants 137.

Vriant: NM_001184880.2, Variation ID: 206353, Accession: VCV000206353.44

Type and length: duplication, 1 bp; Cytogenetic location: Xq22.1; Genomic coordinates: GRCh37: X: 100407506-100407507, GRCh38: X: 99662504-99662505; Molecular consequence: frameshift varint (germline), dbSNP: rs758946412.

With level of evidence given by query in population databases: PM2: Extremely low frequency in population databases of gnomAD v4.1, Exomes: $f = 0.0000118$ (coverage: 39.8×); Genomes: not found (coverage: 24.9×).

Conservation scores: phyloP100: 9.917, Gene context: PCDH19 (NCBIGene:57526) according to Human Phenotype Ontology (HPO).

Synonyms: DEE9, EFMR, EIEE9; Definition: The protein encoded by this gene is a member of the delta-2 protocadherin subclass of the cadherin superfamily. The encoded protein is thought to be a calcium-dependent cell-adhesion protein that is primarily expressed in the brain. Mutations in this gene on human chromosome X are associated with sporadic infantile epileptic encephalopathy and to an epilepsy limited to females. (EFMR; also known as PCDH19RE). Multiple transcript variants encoding different isoforms have been found for this gene. It has 73 term associations and 2 disease associations:

- ORPHA:101039 - MONDO:0010246

Disease name: Epilepsy limited to females with intellectual disability. Definication: A rare X-linked epilepsy syndrome characterized by febrile or afebrile seizures (mainly tonic-clonic, but also absence, myoclonic, and atonic) starting in the first years of life and, in most cases, developmental delay and intellectual disability of variable severity. Behavioral disturbances (e.g. autistic features, hyperactivity, and aggressiveness) are also frequently associated. Inheritance amd affected population: This disease affects exclusively females, with male carriers being unaffected, despite an X-linked inheritance. Inheritance pattern: Unknown. Synonym(s): EFMR, Juberg-Hellman syndrome, Early Infantile Epileptic Encephalopathy 9 (EIEE9). Epidemiology: Epilepsy limited to females with Mental Retardation. Prevalence: < 1/1000000, OMIM: 300088. Age of onset: antenatal, infancy, neonatal. Clinical synopsis: In male carriers,it shows rigid personality, obsessive features, controlling and inflexible traits.

- ORPHA:33069 - Dravet Syndrome

Definition: A rare, genetic, developmental and epileptic encephalopathy characterized by infantile onset of intractable seizures that are often febrile and associated with cognitive and motor impairment. Synonym(s): SMEI (Severe Myoclonic Epilepsy of Infancy), Severe myoclonus epilepsy of infancy. Prevalence: Unknown. Inheritance pattern: Autosomal dominant. Age of onset: infancy, neonatal. Classification: ICD-10: G40.4, ICD-11: 8A61.11, OMIM: 607208, 612164, 615744.

According to Richards et al. (2015) Standards and Guidelines for the Interpretation of Sequence Variants (ACMG/AMP/ClinGen), this variant is classified as pathogenic with the following supporting evidence criteria: PM2 (absent or extremely low frequency in gnomAD and population databases), PS4 (strong statistical evidence from case-control studies), PVS1 (null variant in a gene where loss-of-function is a known disease mechanism), and PP5 (supportive computational prediction data from validated algorithms).

The use of artificial intelligence tools, such as GenAI, VarChat, Alphafold, Mastermind, Alliance of Genome Resources Version: 7.1.0, refers that the patient's genomic variant has gene product functions that are typically elucidated through various experimental approaches including, among others, biochemical assays, cellular localization studies, and phenotypic characterization of model organisms with variants in the gene of interest. In view of the above, genotype-endotype-phenotype correlation (reverse phenotyping) was established, with multimodal tools, in the interest of personalized and precision medicine.

4. Discussion

We propose to evaluate copy number variants (CNVs), including deletions (losses) and duplications or triplications (gains), as a first-line strategy for postnatal screening of individuals with intellectual disability, developmental delay and/or autism spectrumdisorders [13].

For over a decade, CNV analysis using chromosomal microarrays (CMA) has been broadly implemented in the clinical setting for detection of genomic imbalances with considerably higher resolution than traditional cytogenetic methods such as G-banding karyotyping. On specific occasions, exon-focused array designs have also been used to detect CNVs affecting individual genes related to monogenic disorders. Recently, next-generation sequencing (NGS)-based CNV analysis has gained prominence in clinical testing, being employed in genome, exome, or gene panel sequencing [13].

According to the OMIM database, 1506 genes were identified to be associated with epilepsy and were classified into three categories based on their potential association with epilepsy or other abnormal phenotypes, including 168 epilepsy genes that were associated with epilepsies as pure or core symptoms, 364 genes that were associated with neurodevelopmental disorders as the main symptom and epilepsy, and 974 epilepsy-related genes that were associated with severe physical/systemic abnormalities accompanied by epilepsy/seizures [2].

These 168 epilepsy genes that were associated with epilepsies as pure or central symptoms were listed according to the clinical features of epileptic phenotypes. Most of the epilepsy genes, 90 were of autosomal dominant inheritance; 62 genes were of autosomal recessive inheritance; 4 genes were of autosomal dominant and recessive inheritance; 9 genes were of X-linked inheritance; and 3 genes had an undefined inheritance pattern. Among these genes, 68.5% (115/168) were epileptic encephalopathy-causing genes. [2].

A single altered gene (PCHD19) can be associated with different pathologies (Early Childhood Epileptic Encephalopathy type 9, also known as limited to women with intellectual disability and Dravet syndrome), and these can have different affectations. For this reason, it is necessary to correlate genotype-endotype-phenotype (reverse phenotyping) in order to clarify genetic and phenotypic relationships in patients.

Although early infantile epileptic encephalopathy type 9 mainly affects females, male carriers with clinical features with a predominant cognitive-behavioral alteration may be affected. Therefore, it is not disregarded that in the clinical case described, the patient presents Dravet syndrome as a cause of his epilepsy and behavioral disorder.

In 2008, Dibben et al. initially identified the PCDH19 gene as a causative gene of epilepsy and mental retardation limited to females (EFMR). In 2009, Depienne et al. discovered the first mosaic deletion of the PCDH19 gene in a male epileptic patient [8]. According to their findings, PCDH19-related epilepsy (PCDH19-RE) has a unique X-linked inheritance pattern. Both female heterozygotes and male mosaicism were affected, but male hemizygotes were asymptomatic carriers. The cell-cell interference hypothesis, which refers to the coexistence of mutant and wild-type cell populations that interfere with normal cell-cell communication, was postulated as a crucial pathogenic mechanism in PCDH19-RE. This theory of PCDH19-RE pathogenesis also includes reduced GABA A receptor function, allopregnanolone deficiency, and blood-brain barrier dysfunction [14].

PCDH19-related epilepsies are among the eight most common single-gene epilepsies, with an incidence of 1 per 20,600 live-born females, and a prevalence of 4.85/100,000 (95% CI 1.97–9.15) [4].

Kolc and colleagues reviewed 271 PCDH19-variant individuals and found hyperactive, autistic and obsessive-compulsive features to be the most frequently observed neuropsychiatric manifestations, while no genotype-phenotype associations emerged in individuals with recurrent variants, or in the group overall. An earlier seizure onset was significantly associated with more severe intellectual disability, but no correlations were observed between the type or location of PCDH19 mutation, neuropsychiatric profile, and age at seizure onset [4].

Gene expression of the PCHD19 gene was reviewed and found to be associated with alterations in multiple systems, as can be seen in Figure 1 [15] and as can be seen in Figure 2, its bulk tissue gene expression for PCDH19 [16].

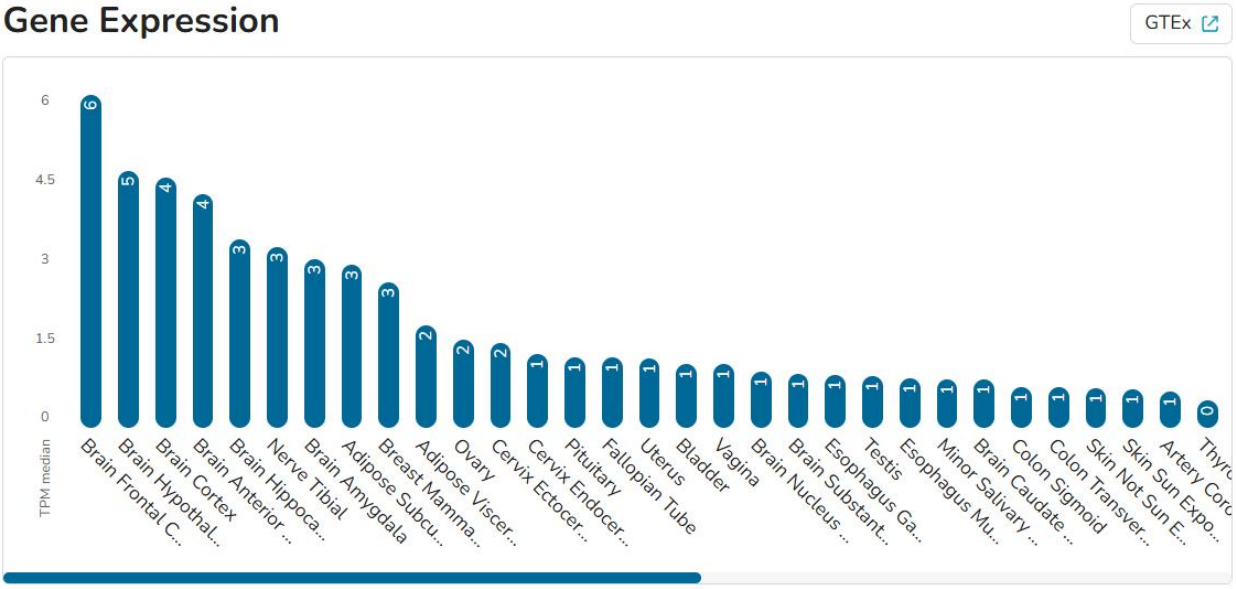

Figure 1. From Database franklin genoox.

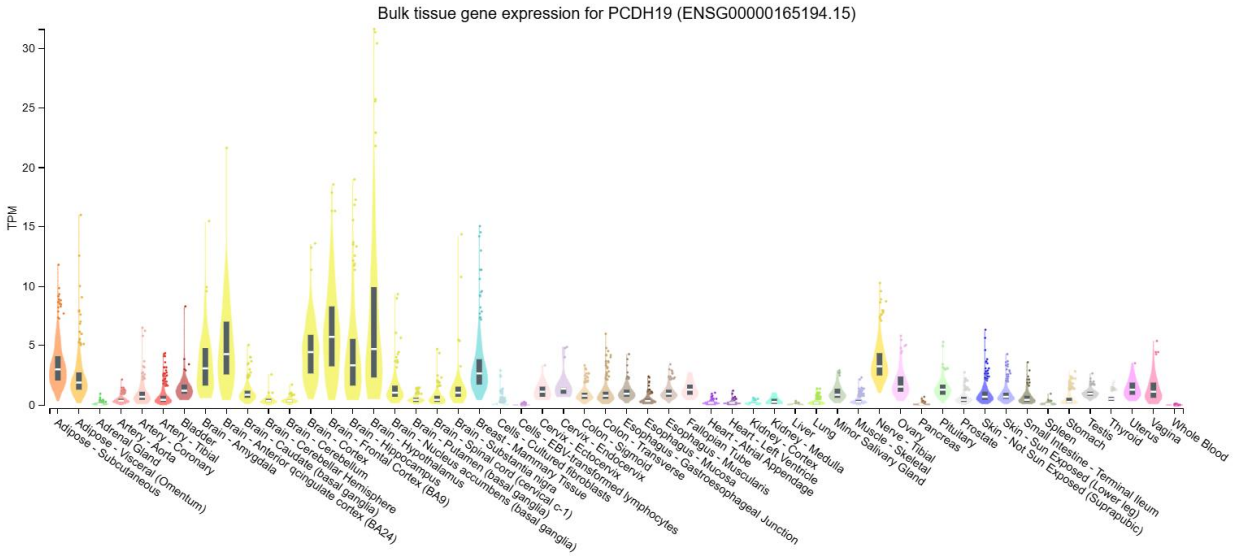

Figure 2. From Database GTEX Portal.

The PCDH19 protein is composed of six extracellular cadherin repeats (EC1-6) with conserved calcium-binding sequences (homologous to those of classical cadherins), a transmembrane region, and a conserved cytoplasmic domain (cytoplasmic motif CM 1 and CM2). The PCDH19 gene is located at Xq22.1 and consists of six exon coding sequences. Exon 1 encodes the entire extracellular and transmembrane region, as well as a small part of the cytoplasmic domain. The remainder of the cytoplasmic domain is encoded by exons 2 to 6, with exons 5 and 6 encoding CM1 and CM2, respectively [14].

PCDH19 is a calcium-dependent cell adhesion molecule involved in neuronal circuit formation. In individuals with variants in the PCDH19 gene, the macroscopic morphology of the human brain usually appears normal on MRI, and mild, ill-defined malformations of the cortical mantle have been described in isolated patients [4] . PCDH19 expression starts during embryonic development and persists in adulthood, with a peak in the first postnatal period, when intense remodeling of neuronal wiring and circuit assembly occurs. The adhesive properties and synaptic expression of PCDH19 make this protein well equipped for neuronal circuit organization, as suggested by its involvement in neuronal migration, sorting and clustering [17]. PCDH19 is highly expressed in the central nervous system, especially in the limbic system and cortex. It acts in the regulation of several functions: neurulation, proliferation, homotypic cell adhesion, neurite self-avoidance, axon guidance and synaptogenesis [9].

Developmental abnormalities affecting limbic structures, particularly the parahippocampal and entorhinal gyri, are likely to be a measurable anatomical consequence of altered PCDH19 protein expression in cortical folding and white matter organization in these anatomical areas. These alterations are functionally manifested in the characteristic phenotype involving neuropsychiatric symptoms, cognitive and communicative abilities, as well as in local epileptogenesis [4].

To date, approximately 150 variants in PCDH19 have been discovered, which contained non-sense, missense, and frameshift variants. Among these variants, missense variants were mostly reported, of which c.1019A > G (p.Asn340Ser) heterozygous variant was one of the common types. Besides, while a high variant frequency was found in the extracellular domain (EC) of PCDH19, the variant in the intracellular domain impacting signal transduction was also reported. In addition to the genetic variant diversity, the phenotypic spectrum of the disease varied widely including mild epilepsy to epileptic encephalopathy [18].

The main result obtained in the study analysis of patients who underwent whole exome sequencing between 2017 and 2023 was the detection rate of variants in genes associated with developmental and epileptic encephalopathy (21.7%; 71/331). Of these, 35/71 (49.3%) had pathogenic and probably pathogenic variants of the nucleotide sequence. Based on the results of whole exome sequencing, patients were selected for the most effective targeted antiepileptic drugs [19].

The treatment of PCDH19-related epilepsy is limited by drug resistance and lack of specific treatment indications. These patients often require polytherapy frequently, with little efficacy due to the natural fluctuating seizure tendency and various cluster triggers. Treatment of drug-refractory patients represents a high challenge for clinicians, especially for syndromes with heterogeneous seizure semiology and evolution. Currently, different drug associations have been tested, and none has proven to be definitively superior [20].

5. Conclusion

Epileptic and developmental encephalopathies comprise a group of rare neurodevelopmental disorders; to date, variants in hundreds of genes that can generate such pathology have been reported, as in the case of the previously presented male patient who had a history of generalized tonic-clonic seizures and moderate intellectual disability, to whom it was decided to apply molecular panel study of genes associated with refractory epilepsy: whole exome sequencing + CNV analysis where a pathogenic hemizygous variant in the PCHD19 gene was identified.

This PCHD19 gene, located in the Xq22.1 gene, consists of six exons encoding a transmembrane protein of the delta-2 protocadherin subclass of the cadherin superfamily. PCDH19-related epilepsy (PCDH19-RE) has a single X-linked inheritance pattern. Both heterozygous females and male mosaicism were affected, but hemizygous males were asymptomatic carriers. The cell-cell interference hypothesis refers to the coexistence of mutant and wild-type cell populations that interfere with usual cell-cell communication. This gene is largely expressed in the central nervous system, especially in the limbic system and cortex. Mutations in this gene generate alterations in cortical folding and white matter organization and are functionally reflected in the phenotype: features involving neuropsychiatric symptoms, cognitive and communicative abilities, and local epileptogenesis.

Genomics is transforming neurological clinics, especially in epilepsies, thanks to technological advances, analysis, and collaboration, which have made it possible to identify genes and genetic mechanisms involved. However, this new genomic era may present a challenge for clinicians, who are now compelled to interpret and apply genetic data to their daily management of patients with epilepsy.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

References

[1] Sands T, Gelinas J. Epilepsy and encephalopathy. Neurological Pediatrics, 2024; 150, 24-31. https://doi.org/10.1016/j.pediatrneurol.2023.09.019

[2] Zhang M, Liang X, Wang J, Gao L, Liao H, He Y, et al. China epilepsy gene 1.0 project. Epilepsy-associated genes. European Journal of Epilepsy, 2024; 116, 4-13.

[3] Yalçın Ç, Yapıcı Z, Özbil M, Çağlayan H, Exome data from patients with epileptic and developmental encephalopathy reveal de novo and heritable pathological variants in epilepsy-associated genes. European Journal of Epilepsy. 2024; 116, 51-64.

[4] Lenge M, Balestrini S, Napolitano A, Mei D, Conti V, Baldassarri G, et al. Morphometric network-based abnormalities correlate with psychiatric comorbidities and gene expression in PCDH19 related epileptic and developmental encephalopathy. Psychiatry transl, 2024; 14(1), 35.

[5] HPO. PCDH19 NCBI gene. 2024. [cited 2024 Oct 12]. Available from: https://hpo.jax.org/browse/gene/NCBIGene:57526

[6] Rampazzo A, Santos R, Maluf F, Simm R, Marson F, Ortega M, et al. Dravet syndrome and Dravet syndrome-like phenotype: a systematic review of the SCN1A and PCDH19 variants. Neurogenetics, 2021; 22:105-15.

[7] Online Mendelian Inheritance in Man (OMIM). Epileptic and developmental encephalopathy 9; DEE9. 2024. [cited 2024 Oct 12]. Available from: https://www.omim.org/entry/300088?search=PCDH19&highlight=pcdh19

[8] Moncayo J, Ayala I, Argudo J, Aguirre A, Parwani J, Pachano A, et al. Understanding the protocadherin protein-driven protein-19 (PCDH19) syndrome: a review of the literature on pathophysiology. Cureus, 2022; 14(6).

[9] Kowkabi S, Yavarian M, Kaboodkhani R, Mohammadi M, Shervin R. PCDH19-clustering epilepsy, pathophysiology and clinical significance. Epilepsy & Behavior, 2024; 154.

[10] Dell'Isola G, Mencaroni E, Fattorusso A, Tascini G, Prontera P, Imperatore V, et al. Expanding the genetic and clinical features of Protocadherin 19 gene mutations. BMC Med Genomics, 2022;15(1):181.

[11] Fatumo S, Chikowore T, Choudhury A, Ayub M, Martin A, Kuchenbaecker K. A road map to increase diversity in genomic studies. Nat Med, 2022; 28:243-50.

[12] Ellis C, Petrovski S, Berkovic S. Epilepsy genetics: clinical impacts and biological insights. Lancet Neurol, 2020; 19(1):93-100.

[13] Riggs E, Andersen E, Cherry A, Kantarci S, Kearney H, Patel A, et al. Technical standards for the interpretation and reporting of constitutional copy number variants: a joint consensus recommendation from the American College of Medical Genetics and Genomics (ACMG) and the Clinical Genome Resource (ClinGen). Genet Med, 2020; 22(2):245-57.

[14] Chen Y, Yang X, Chen J, Yang X, Yang Y, Liu A, et al. PCDH19-related epilepsy in mosaic males: the phenotypic implication of genotype and variant allele frequency, Front Neurol. 2022;13.

[15] Online Database franklin genoox, PCDH19 protocadherina 19. Xq22.1, 2024 [cited 2024 Nov 30] Retrieved from https://franklin.genoox.com/clinical-db/gene/hg19/PCDH19.

[16] Online Database GTEX Portal. PCDH19, 2024 [cited 2024 Nov 30] Retrieved from https://gtexportal.org/home/gene/PCDH19

[17] Giansante G, Mazzoleni S, Zippo A, Ponzoni L, Ghilardi A, Maiellano G, et al. Neural network activity and connectivity are altered in a conditional knockout mouse model with mosaic expression of PCDH19. IRIS Institutional Research Information System - AIR Institutional Research Archive. 2023.

[18] Online Mendelian Inheritance in Man (OMIM). (n.d.). PROTACADHERIN 19; PCDH19. 2024 [cited 2024 Oct 20] Retrieved from https://www.omim.org/entry/300460?search=PCDH19&highlight=pcdh19#contributors.

[19] Kozhanova T, Zhilina S, Meshcheryakova T, Abramov A, Ayvasyan S, Zavadenko N, Whole-exome sequencing is the molecular-genetic test of the first-line in developmental and epileptic encephalopathies. Badalyan Neurological Journal, 2024; 5(2):90-98. (In Russ) https://doi.org/10.46563/2686-8997-2024-5-2-90-98.

[20] Dell'Isola G, Vinti V, Fattorusso A, Tascini G, Mencaroni E, Di Cara G, et al. The broad clinical spectrum of epilepsies associated with the protocadherin 19 gene mutation. Front Neurol, 2022; 12.