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Research article

Genetic epilepsy and role of mutation variants in 27 epileptic children: results from a "single tertiary centre" and literature review

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Abstract: Aim and scope: The wide use of next-generation sequencing has allowed professionals to reach relevant progress in the medical field including diagnoses, prognoses, and genetic counselling and to help in recognizing the pathogenic mechanisms which underlie several epileptic disorders. Genetic epilepsy refers to a disorder in which genetic mutations are recognized as the primary cause of epileptic seizures in the patients. Various types of epilepsy have been highlighted alongside a clear etiologic relationship with genetic mutations; however, for a select number of patients, some doubts remain on the role played by the variant mutations, as well as the adverse pathologic events which may interfere with the clinical manifestations. In this study, twenty-seven children affected by epileptic seizures are reported, with the aim to describe the clinical and neurological involvement presented by the children according to the genes and variant mutations, and to compare the neurological signs observed in these children with those reported in children with similar genetic mutations. Additionally, the roles played by single or associated variants on the clinical expression of the affected children are discussed. **Material and methods:** A retrospective observational study was conducted on the gene mutations observed in 27 children affected by a clinical history and diagnosis of epilepsy, alongside an electroencephalographic analysis performed with the Pediatric Department of the University-Hospital S. Marco during the years ranging from January 2020 to January 2022. A genetic analysis was performed using an array comparative genomic hybridization (array CGH), a gene panel for epilepsy, Whole Exome Sequencing (WES), and a single nucleotide polymorphism (SNP) array.

Results: Nineteen children showed a single nucleotide variant, eight children carried two or more gene mutations in different genes, and one child was not reported. In this study, we identified a total of thirty-six gene mutations, where seventeen were de novo mutations, and twenty-two had either a maternal or paternal inheritance. The genes in which one or more allelic variants were found included *GRIN2A*, *GABRA1*, *SCN2A1, KCNT1*, *PCDH19*, *SCN8A*, *KCNK4*, *SLC2A1*, *DNM1*, *ARID1B*, *WWOX*, *GABRG2,* and others. **Conclusions:** Genetic analyses are recognized to have a central role in the diagnostic process of children with epileptic seizures, alongside their family history, and clinical, neuroradiologic, and neurophysiologic examinations. The gene mutation anomalies reported in this study may be useful to be included in the wide field of factors related to epileptic seizures in children. The roles played by single or associated variant mutations in the clinical expression of the affected epileptic children remain difficult to be defined. Moreover, other factors such as pre-, peri-, and post-natal adverse events may negatively interfere with the severity of the clinical manifestations.

Keywords: epilepsy; genetic; mutation variants; children; NGS

1. Introduction

In the past decade, next-generation sequencing (NGS) has brought significant advancements to the field of epileptic genetics. It has become a powerful diagnostic tool, thereby providing the foundation for optimal diagnostic and genetic. NGS is widely available in many countries as part of routine work, resulting in an improved diagnostic yield and greater insights into the underlying pathological mechanisms. Several NGS technologies are currently available: single-gene sequencing, targeted gene panels, whole exome sequencing (WES), and single nucleotide polymorphisms arrays (SNP-Array), which is a technology which utilize chips containing probes specific for various single nucleotide polymorphisms (SNPs) uniformly distributed across the entire genome. While epilepsy can arise from several factors, a significant number of individuals with epilepsy are believed to have an underlying genetic factor [1].

In epilepsy with a genetic etiology, the seizures represent the primary symptom of the disorder, which directly children with severe developmental and epileptic encephalopathies [2].

Understanding the phenotypic spectrum associated with mutations in a specific gene is crucial, as the identification of a mutation alone in a specific gene does not predict the clinical features nor the outcome. In epileptic genetics, the interpretation of the mutation's significance must be considered in the context of the clinical and electroclinical presentations of the affected children. Currently, most genes exhibit a heterogeneous phenotypic expression, and most syndromes are underpinned by a genetic heterogeneity. An increasing number of de novo mutations are frequently identified in both severe and mild types of epilepsies [3,4].

Genetic etiology refers to a pathogenic variant (mutation) that significantly influences epilepsy causation, though, in some cases, it does not exclude the role of environment contributions. Epilepsy is a prevalent neurological disorder which affects over 50 million individuals worldwide, is characterized by recurrent epileptic seizures with possibly related cognitive, psychological, and social consequences, and has a higher incidence in children compared to adults. The disease's prevalence is estimated to be approximately 1%, with a lifetime incidence of 3% [1,2]. Epilepsy is a polygenic and multifactorial disorder. The clinician's ultimate goal is to determine the etiology to enhance the clinical

and therapeutic approaches, to provide an accurate prognosis, and to offer appropriate genetic counselling. The new classification incorporates etiology at every level, thus emphasizing the need to consider etiology at each diagnostic step, as it often holds significant implications for treatments. Epilepsy etiology is subdivided into six subgroups—structural, genetic, infectious, metabolic, autoimmune, and unknown—thus acknowledging that a single type of epilepsy may have multiple etiologies and may be classified under more than one etiological category.

This study, which was conducted at a "single tertiary hospital" re-discussed.

2. Materials and methods

Observational study was conducted on gene mutations found in children affected by epilepsy within the Pediatric Department of the University-Hospital San Marco-G.Rodolico, Catania, Italy, between January 2020 and January 2022. At the onset of their epilepsy, all the children were aged under 11 years old, and most of them nder the age of 2 years. The diagnosis of epilepsy was performed by their clinical history and confirmed by an electroencephalographic examination, which was performed both when the child was awake and while they were asleep. All children underwent genetic investigations using an array comparative genomic hybridization (array CGH) gene panels for epilepsy, Whole Exome Sequencing (WES), and an SNP-Array. In general, the affected children underwent a comparative genomic hybridization microarray the primary genetic investigation if they had a family history of epilepsy/neurological pathology, dysmorphic signs, and a first episode of a seizure. For those with a positive family history of epilepsy (first-degree relatives), a gene panel for epilepsy was performed if the clinical phenotype was characterized by more than one seizure, a psychomotor delay, neuropsychiatric disorders. Five patients (18.6%) underwent a comparative genomic hybridizationmicroarray (CGH-Array), nineteen (70.3%) underwent sequencing of specific genes associated with pediatric epileptic seizures, two were screened using an SNP-Array at another facility, and one (3.7%) underwent ES due to the absence of mutations identified through the CGH-Array and the sequencing of epilepsy genes in a single panel. None the children underwent single-gene sequencing due to the absence of distinct clinical signs for a probable monogenic disorder. Patients with a definitive genetic diagnosis (e.g., Rett Syndrome, Sturge-Weber Syndrome, metachromatic leukodystrophy, and mitochondrial disorders) were excluded from the study.

The transcript used for variant nomenclature was procured from the Human Genetic Mutation Database (HGMD) and the International Human Genome Sequencing Consortium, University of California (UCSC), USA. The variants were reported according to the guidelines of the American College of Medical Genetics (ACMG) Laboratory Practice Committee Working Group and were interpreted based on the patient's phenotype.ents. The interpretation remained challenging, especially in cases where the nucleotide variants were not present in the existing databases, where their pathogenicity remained unknown (VOUS-variant of uncertain significance), or in cases where potentially pathogenic mutated variants were inherited from apparently healthy parents.

3. Results (see Table 1)

Nineteen children showed a single nucleotide variant, eight children carried two or more gene mutations in different genes. In this study group, we identified a total of thirty gene mutations, where seventeen had either a maternal or paternal inheritance.

The identified nucleotide variants were classified into the following:

1. Pathogenic (9 variants out of 38): this includes abnormalities associated with well-known syndromes, those inherited from a parent with a similar phenotype, or those as de novo variants;

2. Likely pathogenic (7 variants out of 38): abnormalities that affect genes or genomic regions whose association with clinical phenotypes has not yet been clearly defined but can be inferred from databases; and,

3. Variants of uncertain significance (VOUS) (22 variants out of 38): this includes alterations not described or those with conflicting definitions in various databases. In the group of 27 epileptic children reported in this study, we found a wide number of genes in which one or more allelic variants were identified including the genes *GRIN2A*, *GABRA1*, *SCN2A*, *KCNT1, PCDH19*, *SCN8A* and *KCNK4*, *SLC2A1-DNM1-ARID1B-WWOX-GABRG2,* among others.

From the analyzed clinical data, the male to female ratio was determined as M11/F 16. The types of seizures were mainly focal or focal to generalized, and two children presented with infantile epileptic spasms syndrome (IESS). Nineteen out of the twenty-seven children (70.4%) had a positive family history of epilepsy or neurological disorders. Notably, two patients had epileptic mothers, five had epileptic fathers, and two had epileptic siblings. Epilepsy was observed in the uncles of four patients (paternal uncles in three patients and a maternal uncle in one patient). Two patients had epileptic maternal grandparents, and four patients had first-degree maternal cousins with epilepsy. Additionally, two patients had a family history of an intellectual disability, one of Down Syndrome, one of Attention-deficit/hyperactivity disorder (ADHD), two of spinal muscular atrophy (SMA), one of Huntington's chorea, and one of schizophrenia. The pregnancy histories revealed anomalies in seventeen cases: in particular, two children were conceived through assisted reproductive techniques, two were born from twin pregnancies, and one was born prematurely (33 weeks of gestation). Twelve children complained of positive perinatal histories, including jaundice that required phototherapy (four children), hypotonia, dysmorphic signs, hypoglycemia (two children), autoimmune hemolytic anaemia due to ABO incompatibility, delayed meconium expulsion, respiratory distress, and neonatal asphyxia in a single child.

Dysmorphic signs were noted in six children (22.2%), five children had cutaneous manifestations (18.5%), seven children had ocular anomalies (25.9%), and fifteen children had skeletal abnormalities (55.5%).

Table 1. Familial, pre-perinatal factors, age, gender, and genetic data of the 27 epileptic children.

ID	FH	PRH	PH	Age	Gender	Genetic analysis	Mutations	H	Gen Class.
MBE	+	+	+	8 m	Female	CGH-array	Dupl. 14q32.2q32.33 Del. 21q22.2q22.3	/ /	Lp Lp
DL	+	−	−	8 m	Female	Epilepsy panel	Dupl. 15q11.2-q12	/	Lp
SC	+	−	−	1 y	Male	Epilepsy panel	GRIN2A c.2797G>A KCNT1 c.104_107delinsT POLG c.2195A>G	M / /	PAT VOUS VOUS
TE	+	+	+	7 d	Female	Epilepsy panel	KCNT1 c.2623A>T	M	VOUS
ZNA	+	+	−	8 m	Female	Epilepsy panel	GABRA1 c.640C>T	/	PAT
SM	−	−	+	8 y	Male	CGH-array	Del. 14q31.1-q32.1	/	Lp
ZA	+	+	+	2 y	Male	SNP-array	Microdel. 16p11.2	M	PAT
SN	−	+	−	2 y	Female	Epilepsy panel	PCDH19 c.707C>T	/	PAT
BG	−	−	−	1 y	Female	Epilepsy panel	SLC6A1 c.719T>C	/	VOUS
CA	+	+	−	1 y	Male	Epilepsy panel	ATP1A2 c.2023C>T SCN2A c.104A>G	M F	VOUS VOUS
AG	−	+	−	8 m	Male	Epilepsy panel	GRIN2A c.2434C>A	/	PAT
JM	−	−	−	6 m	Female	Epilepsy panel	SCN8A c.5630A>G KCNK4 c.328G>A	/ M	PAT VOUS
CL	+	+	+	11m	Male	Exome NGS	UZAF2 c.445C>T	/	VOUS
LS	+	+	−	1 y	Female	CGH-array	Dupl. 19q13.12	/	VOUS
RM	+	+	−	4 y	Male	Epilepsy panel	GABRA1 c.871C>T	/	PAT
BA	+	+	−	2 y	Female	Epilepsy panel	SLC2A1 c.152G>A DNM1 c.1349C>T ARID1B c.6040_6042del WWOX c.790C>T	F M F F	VOUS VOUS VOUS VOUS
NG	−	+	−	7 m	Male	CGH array	Dupl 9q21.12	M	VOUS
DAE	+	+	+	10 m	Female	CGH array	Microdupl. 22q11.21	M	Lp
MIL	+	+	+	6 m	Female	Epilepsy panel	GABRG2 c.904A>C	/	VOUS
MCP	+	−	+	4 m	Female	Epilepsy panel	PRRT2c.649dupC.	M	Lp
AE	+	−	−	6 y	Male	Epilepsy panel	DEPDC5	F	PAT
LA	+	+	−	6 y	Female	Epilepsy panel	KCNT1c.3496G>A	M	VOUS
VD	+	−	+	4 m	Female	Epilepsy panel	CHD2c.4033C>T SCN2Ac.373A>G	M VOUS	VOUS VOUS
SS	−	−	−	11 m	Female	Epilepsy panel	KCNT1c.2582G>C MBD5 c.1499C>G	F VOUS	VOUS VOUS
DSN	−	−	+	4 m	Male	SNP array	Microdel. 15q13.2q13.3	F M	PAT
SF	+	+	+	11 y	Male	Epilepsy panel	PIGV c.1312C>T TBC1D24 c.169C>T	/ /	VOUS VOUS
TA	+	+	+	4 y	Female	Epilepsy panel	SPTAN1c.5968del	F	Lp

Note: ID: Identification; FH: Family history; PRH: Pregnancy history; PH: Perinatal history; Gen Class: Genetic variant classifications; H: Hereditariety; F: Father; M: Mother; /: de novo; Lp: Likely pathogenetic; PAT: Pathogenetic; VOUS: Variant of uncertain significance.

4. Discussion

Development in genetics has widely contributed to define the etiological events of patients with epilepsy, to increase the number of genes associated with epilepsy, to enhance clinical and therapeutic approaches, to provide an accurate prognosis, and to offer appropriate genetic counselling [2,5–12].

Epilepsy is a polygenic and multifactorial disorder with many etiological factors. In addition, a single type of epilepsy may recognize multiple events, and thus be classified under more than one etiological category. Epilepsy in children may differ from epilepsy in adulthood, namely the types of clinical manifestations, electroencephalographic patterns, etiological factors, and the responses to anticonvulsant treatments [13,14]. In the group of 27 children that presented with epilepsy, various genes mutations and variants have been reported that are singularly discussed here. The role of a VOUS as either direct or indirect causal factors in various genetic disorders including epilepsy remains to be clarified. The recognition of the possible noxious effect of the a VOUS in causing clinical manifestations is made difficult by various factors, including the following: similar a VOUS may be found in many different disorders that affect various body organs; the poor results of the functional evidence in the obtained results; the different evaluations of the results by the clinicians on one side and from the researches on the other; and the previous and recent enormous number of variants observed in the course of the clinical investigation.

4.1. GRIN2A

Mutations in the *GRIN2A* gene are associated with a broad phenotypic spectrum, ranging from a mild intellectual disability to epileptic encephalopathies [15,16]. Although mutations in *GRIN2A* associated with a normal phenotype are described in the literature, they are among the minority. In most cases, as reported in the literature, the mutated *GRIN2A* phenotype includes various types of epilepsy, various degrees of intellectual disabilities, and language delay (i.e., dysarthria, dyspraxia, dysphasia, aphasia) [15,16]. The most frequently associated epilepsy disorders with *GRIN2A* mutations are Landau-Kleffner syndrome (LKS), epileptic encephalopathy with continuous spikes and waves during sleep (ECSWS), and autosomal dominant Rolandic epilepsy. *GRIN2A* mutations exhibit incomplete penetrance, as they can be inherited from either an unaffected carrier parent or a parent with a mild phenotype, and shows intrafamilial variability [15,16].

GRIN2A (ID-SC). This case presents a twelve-month-old male with an inherited variant from his mother. Two additional genetic variants related to the *KCNT1* and *POLG* genes were classified as a VOUS. At the six-month follow up, the child was partially responsive to the levetiracetam treatment and showed a mild developmental delay. In line with the literature, we assume that this child has a less severe phenotype solely characterized by seizures, which is currently well controlled by an antiepileptic therapy. It is hypothesized that the child may carry only one or two pathogenetic variants, specifically *GRIN2A* c.2797 G>A and *KCNT1* c.104-107 delins T, excluding *POLG* c.2195>G. On the other hand, we can not exclude that nucleotide variants in *GRIN2A*, *KCNT1*, and *POLG*, which are classified as a VOUS, may have ameliorating effects on the patient's phenotype. Nonetheless, it is crucial to monitor the clinical course of *GRIN2A* as the gene mapped to the short arm of chromosome 16 (locus 16p13.2), which encodes the GluN2A subunit of the N-methyl-D-aspartate receptor (NMDAR), and whose expression significantly increases shortly after birth. It plays a crucial role in

mediating excitatory neurotransmission, neuronal development, and synaptic plasticity, and is essential for learning, memory, and high cognitive functions [15].

GRIN2A (ID-AG). This case presents an eight-month-old male with a displayed de novo mutation. The child was born from a pregnancy complicated by gestosis from the fifth month of gestation and gestational diabetes. At six months of age, he started to experience epileptic spasms and was diagnosed with IESS. Neuroimaging revealed faint areas of altered signals, a hyperintense FLAIR (Fluid Attenuated Inversion Recovery) in the bilateral posterior periventricular and parieto-occipital subcortical areas, which was associated with a mild thinning of the corpus callosum and dilation of the subarachnoid spaces of the base, and cerebral convexity, which was more evident in the anterior portion of the interhemispheric fissure. The child is currently undergoing adrenocorticotropic hormone (ACTH) therapy. Developmental delay is marked.

4.2. GABRA1

Gamma-Aminobutyric Acid (GABA) is the main inhibitory neurotransmitter in the mammalian brain, where it acts on GABA-A receptors, which are ligand-gated chloride channels.

The *GABRA1* gene, which is located on the long arm of chromosome 5 (locus 5q34), encodes the α1 subunit of the gamma-aminobutyric acid type A (GABA-A) receptor. Mutations in the *GABRA1* gene have been associated with a broad phenotypic range of severe early-onset epileptic encephalopathies, including Ohtahara syndrome, IESS, myoclonic atonic epilepsy (Doose syndrome), and Dravet syndrome [17,18]. These conditions are often associated with severe intellectual disabilities and, more generally, neurodevelopmental disorders.

GABRA1 (ID-ZNA). This case presents an eight-month-old female with a de novo variant classified as pathogenic.

The girl has a family history of epilepsy and neurological disorders. She was born through in vitro fertilization and was born from a pregnancy complicated by placenta previa and a threatened abortion. Since an early age, she experienced a developmental delay and, at eight months of age, developed frequent episodes of afebrile seizures that were resistant to treatment. Neuroimaging revealed faint hyperintensity signals in long TR sequences of the posterior periventricular white matter, which is suggestive of areas of terminal myelination. She was initially given a treatment of valproic acid; later, levetiracetam was added due to suboptimal seizure control. At a subsequent follow up, the child still experienced a developmental delay, and at seven years of age, her scholastic performance was slightly insufficient.

The girl's presented phenotype seemed to be less severe compared to the phenotypic spectrum described in the literature for *GABRA1* mutations [17,18].

GABRA1 (ID-RM). This case presents a four-year-old boy with a *de novo* variant and a family history of epilepsy. Since the first few months of his life, the child showed a developmental delay. At four years of age, he experienced serial episodes of epileptic seizures that were resistant to treatments. Neuroimaging identified a slight asymmetry in the cortex of the hippocampal heads, with a thinning of the left cortex compared to the contralateral side. Despite treatment with levetiracetam, the persistence of seizures and a predominantly focal electroencephalographic pattern led to the introduction of carbamazepine, with a subsequent addition of valproic acid and a decrease in the dosage of levetiracetam. The carbamazepine treatment was discontinued due to persistent epileptic episodes,

and topiramate was introduced. The patient currently exhibits notable intellectual disability, language, and behavioral disorders.

The boy presents a phenotype that was previously described in the literature for *GABRA1* mutations; however, contrary to what is stated in the literature [18], we note a later onset of epilepsy compared to the early-onset types described in association with *GABRA1* mutations.

4.3. SCN2A

The *SCN2A* gene, which is located on the long arm of chromosome 2 (locus 2q24.3), encodes the voltage-dependent sodium channel Na(v)1.2, which plays a crucial role in the generation and propagation of action potentials. Mutations in *SCN2A* have long been considered as a cause of epilepsy. Epilepsy linked to *SCN2A* variants typically begins in early childhood and has a broad phenotypic spectrum, ranging from self-limiting epilepsy with a favorable outcome to epileptic encephalopathies [19–21]. Additionally, it has been reported that the majority of de novo variants are associated with moderate to severe intellectual disabilities [22].

SCN2A (ID-CA). This case presents a twelve-month-old male with a variant inherited by his father and was classified as a VOUS. In addition to the nucleotide variant in *SCN2A*, the infant carries another nucleotide variant in *ATP1A2*, which was inherited from the mother and was also classified as a VOUS. The infant has a family history of epilepsy, which is also present in his sibling. He was born through a difficult delivery due to an oblique presentation. He had a developmental delay, and at the present age of two years, he started to manifest focal seizures that were resistant to treatments with levetiracetam. Neuroimaging revealed a bilateral and symmetric dilation of the perivascular spaces of Virchow-Robin with gliotic cuffing in the peritrigonal white matter. Treatment with levetiracetam resulted in a partial seizure control. A developmental delay remains present.

We noted nucleotide variants in genes associated with epilepsy that are currently classified as a VOUS and were inherited from both parents who are healthy. Conditions such as epileptic encephalopathy seen in *ATP1A2* and *SCN2A* may co-occur. The variant *ATP1A2* c..2023C>T is categorized as a VOUS: when the phenotype does not align with the expected manifestations, it is advisable to consider ruling out locus variations. In the present child, the factors that have caused the pathological phenotype remain to be understood.

SCN2A (ID-VD). This case presents a four-month-old girl who carries a nucleotide variant in *SCN2A* classified as a VOUS, alongside a second nucleotide variant in *CHD2,* which is also classified as a VOUS. Both genetic variants were inherited from the mother, who had epilepsy during her childhood. The child's psychomotor development was delayed, and at four months of age, she experienced her first episodes of infantile seizures; at six months of age, she was diagnosed as IESS. Neuroimaging showed a faint hyperintense signal alteration in the long TR sequences in the peri/supraventricular posterior white matter of an unspecific significance. Due to the IESS diagnosis, treatment with ATCH was started, followed by treatment with valproate.

Similar to the previous case, in this case we highlight how two nucleotide variants in two genes associated with epilepsy, which are currently classified as a VOUS, may contribute to the development of the maternal phenotype and the proband.

4.4. KCNT1

KCNT1, which is mapped to the long arm of chromosome 9 (locus 9q34.3), encodes for a sodium-activated potassium channel that is widely expressed in the nervous system. Epilepsy associated with *KCNT1* is often linked to two phenotypes: Epilepsy of Infancy with Migrating Focal Seizures (EIMFS) and Autosomal Dominant Nocturnal Frontal Lobe Epilepsy (ADNFLE) [23]. EIMFS is characterized by epileptic seizures, which are typically focal and asynchronous and start within the first six months of life with associated autonomic manifestations and a regression of the psychomotor development. The seizures are generally intractable, and become frequent by the age of six to nine months. ADNFLE is characterized by nocturnal motor seizures ranging from simple awakenings to hyperkinetic events with either tonic or dystonic features. Individuals with *KCNT1*-related ADNFL*E* are more likely to develop seizures at a young age, may present with brain malformations, and are often carriers of intellectual disabilities, psychiatric, and behavioral disorders [24,25]. For mutations in the *KCNT1* gene associated with EIMFS, complete penetrance is reported, while for those associated with ADNFLE and brain malformations, incomplete penetrance has been found.

KCNT1 nucleotide variants were reported in each of the four different children of this series, all classified as a VOUS.

KCNTI (ID-TE). This case presents a seven-day-old female newborn with a variant inherited from her mother. The infant has a family history of epilepsy. She was born from a twin pregnancy with an intrauterine death of the co-twin. The first seizures happened at six months of age. The personal history revealed a patent foramen oval with a left-to-right shunt, which led to the massive passage of microbubbles into the middle and posterior cerebral arteries on transcranial color-coded doppler ultrasonography. The neuroimaging results were negative. At 8 months of age, the developmental delay was reported as mild. An antiplatelet therapy with aspirin was started, and additional treatments with valproate and levetiracetam resulted in a relatively good seizure control.

In this infant, we note that nucleotide variants in *KCNT1*, which were inherited from the healthy mother, may be associated with seizures and a mild developmental delay.

KCNT1 (ID-LA). This case presents a six-year-old girl with a variant inherited from her mother. The child has a family history of epilepsy and was born from a twin pregnancy resulting from in vitro fertilization and an embryo transfer. She was born preterm at 33 weeks of gestation. At birth, cardio-pulmonary resuscitation was required due to a cardio-circulatory arrest. Since the first days of life, the patient presented with seizures that were treated with phenobarbital. The patient developed spastic diplegia, which was associated with a psychomotor delay and a severe intellectual disability. Additionally, the girl presented with bilateral flat feet, a valgus deformity of the knees, a lower limb asymmetry, in which the right limb was greater than the left, a divergent strabismus of the right eye, a bilateral horizontal nystagmus, a left unilateral gynecomastia, and a functional impairment of the optic pathways (OD > OS). Neuroimaging reveals lesions attributable to a perinatal hypoxic-ischemic insult, with a reduced volume of periventricular white matter and a thin and hypoplastic corpus callosum. Phenobarbital was progressively replaced with valproic acid; subsequently, topiramate was added due to a poor seizure control. In this case, the hypoxic-ischemic insult related to prematurity may be considered as not the sole cause of the epileptic disorders, especially on the basis of the presence of a nucleotide variant in *KCNT1*, even if it has been currently classified as a VOUS.

In this case, we are unable to affirm how the presence of the genetic variant in *KCNT1* may have influenced the patient's phenotype.

KCNTI (ID-SS). This case presents an eleven-month-old female with a variant that was inherited from her father. Alongside the nucleotide variant in *KCNT1*, the girl presented with another nucleotide variant in *MBD5*, which was also inherited from the father, and was classified as a VOUS. Epilepsy and/or other neurological disorders are absent from her family history. At five months of age, a development delay was noted. At eleven months of age, the girl presented with her first episode of a seizure. Associated signs and/or symptoms included the presence of a café-au-lait spot approximately one centimeter in diameter on the right side, a small hypochromic spot on her face, and an overlapping region between the second and third toes of the left foot. Neuroimaging highlighted the presence of a millimetric ectasia of the subdural space with cerebrospinal fluid content bilaterally in the frontal region, along with associated microcysts of the choroid plexuses. Treatment with valproic acid resulted in a good seizure control. At eighteen months of age, the patient currently presents with a severe developmental delay and a marked generalized hypotonia. Moreover, in this case, we emphasize the association of two nucleotide variants in *KCNT1* and *MBD5* inherited from a healthy father and classified as a VOUS, which may play a crucial role in the onset of the patient's phenotype.

KCNTI (ID-SC). This case presents a variant that was inherited from the mother. Two additional nucleotide variants in *POLG* and *GRIN2A*, classified as a VOUS, were identified. For the patient's details, a reference is made to the second case discussed in the *GRIN2A* section.

4.5. PCDH19

PCDH19, which is mapped to the long arm of the X chromosome (locus Xq22.1), encodes for protocadherin-19, which is particularly expressed in the central nervous system, specifically in the hippocampus and cortex, thus suggesting a crucial role in cognitive function [26]. On the 38 individuals reported by Smith et al. [27] with *PCDH19*, all suffered with various types of epilepsies, though they were mainly characterized by clustering of seizures and an association with fever. Intellectual disabilities with a wide range of severities, such as autism spectrum disorder, behavioral anomalies, and sleep disturbances, were also reported [26,27]. Previous studies have highlighted the high onset frequencies for convulsive and non-convulsive status epilepticus [28]. These disorders primarily manifest in heterozygous females due to X-chromosome inactivation, which leads to somatic mosaicism. Rare cases have been reported in male children that carried postzygotic pathogenic somatic variants with somatic mosaicism, thus exhibiting clinical features similar to females. Conversely, asymptomatic males with germline-inherited nucleotide variants in *PCDH19* can transmit the pathogenic variant [29].

In our case series, we identified a nucleotide variant in *PCDH19* reported in HGMD, GnomAD, and DGV. The variant was absent in the parents, thus indicating a *de novo* occurrence, and was classified as pathogenic.

(ID-SN). This case presents a girl without a family history of epilepsy or neurological disorders. Her neonatal and infant periods were normal, as well her psychomotor development milestones. At 24 months of age, she experienced a febrile seizure followed by afebrile episodes. Laboratory investigations revealed a high-titer IgM positivity for Herpes Simplex Virus (HSV) types 1 and 2. Consequently, she underwent an exploratory lumbar puncture, which led to a positive polymerase chain reaction (PCR) for HSV-1 in the cerebrospinal fluid. The electroencephalogram (EEG) recording indicated diffuse cortical anomalies that were more pronounced in the right hemisphere, and neuroimaging revealed a faint hyperintensity signal in the posterior periventricular white matter on the

long TR sequences. However, the child continued to experience seizures even after the acute event related to the HSV-1 infection. She was initially treated with valproic acid and was later treated in combination with levetiracetam due to a suboptimal seizure control. Currently, the girl has a good seizure control with the combination of two anticonvulsants, and there are no ongoing neurocognitive disturbances. A follow-up is crucial to assess any potential evolution of the phenotype.

4.6. SCN8A and KCNK4

SCN8A, which is located on the long arm of chromosome 12 (locus 12q13.13), encodes Na(v)1.6, which is a voltage-dependent sodium channel widely expressed in the central nervous system. Previously, *SCN8A* variants were primarily associated with the onset of early-infantile epileptic encephalopathies; however, recent studies have demonstrated a much broader phenotypic spectrum linked to mutated *SCN8A*. Moreover, there is a genotype-phenotype correlation based on the type of mutation. Generally, gain-of-function variants in *SCN8A* are more frequently associated with phenotypes that feature early-onset focal and multifocal seizures, whereas loss-of-function variants are associated with a generalized epilepsy [30]. Beyond epilepsy, the wide phenotypic spectrum includes varying degrees of intellectual disabilities with possible cognitive and motor regressions, movement disorders that primarily affect the extrapyramidal pathways, and motor disorders such as dyskinesia, ataxia, and choreoathetosis [30–32].

KCNK4, which is mapped to the long arm of chromosome 11 (locus 11q13.1), encodes for TRAAK, which is a tandem-pore potassium channel particularly expressed in the nervous system and contributes to the resting membrane potential. Literature reports indicated that *de novo* mutations in *KCNK4* cause a syndrome known by the acronym FHEIG, characterized by facial dysmorphism, hypertrichosis, epilepsy, intellectual/ developmental delay, and gingival overgrowth [33,34].

In our case series, we identified a nucleotide variant in *SCN8A* and another in *KCNK4*, both present in female patient and reported in HGMD, GnomAD, and DGV. The *SCN8A* nucleotide variant was absent in the parents, thus indicating a *de novo* occurrence, which was classified as pathogenic. The *KCNK4* nucleotide variant was inherited from the mother and was classified as a VOUS.

(ID-JM). This case presents a six-month-old girl without a family history of epilepsy or neurological disorders. The birth was regularly conducted, and a developmental delay was noted since the first months of life. At six months of age, she presented with an onset of episodic seizures. In addition, the girl showed other various signs including ichthyosis vulgaris and biliary lithiasis. Neuroimaging revealed a slight dilatation of the liquoral spaces in the vault and base, a focal bilaterally at the temporopolar region, and a cistern of the velum interpositum. Her treatment initially involved levetiracetam; subsequently, due to a suboptimal seizure control, valproic acid was added, which resulted in satisfactory clinical results. Currently, the patient presents with a significant psychomotor delay alongside a language delay. Extrapyramidal motor disorders are absent, as are clinical signs and/or symptoms associated with FHEIG.

In this case, the pathogenic *SCN8A* nucleotide variant seems to have a more clinical significance and predominance over the VOUS variant in *KCNK4* in shaping the neurological phenotype. However, the potential interplay between these two variants remains unknown.

4.7. SLC2A1–DNM1–ARID1B–WWOX

SLC2A1, which is located on the short arm of chromosome 1 (locus 1p34.2), encodes for GLUT1, which is the most important glucose transporter expressed in the central nervous system. Mutations in *SLC2A1* are associated with early onset infantile seizures, developmental delays, microcephaly, and ataxia. Typically, a favorable response to the ketogenic diet is observed [35]. Recently, the broad phenotypic spectrum found in carriers of *SLC2A1* variants has been linked to mutations in genes other than *SLC2A1*, thus demonstrating that a phenotypic spectrum can have a polygenic origin [35,36].

DNM1, which is located on the long arm of chromosome 9 (locus 9q34.1), encodes dynamin-1, which is a GTPase that is critical for synaptic vesicle recycling in the brain, particularly during postnatal development. Mutations in *DNM1* are associated with a severe phenotypic picture characterized by intellectual disabilities ranging from moderate to severe, muscle hypotonia, and epilepsy that often begins as IESS and evolves into Lennox-Gastaut syndrome [37]. However, recent pathogenic variants in *DNM1* have led to a milder clinical presentation characterized by dysmorphic features, developmental delays, and self-limiting epilepsy [38].

ARID1B, which is located on the long arm of chromosome 6 (locus 6q25.3), encodes for the *ARID1B* subunit belonging to the SWI/SNF protein complexes, which are involved in chromatin remodelling. Mutations in *ARID1B* are often associated with a broad phenotypic spectrum that includes Coffin-Siris syndrome, which is a rare congenital malformation disorder characterized by aplasia or hypoplasia of the fingers or toes, varying degrees of developmental delays, a range of facial features, hypotonia, hypertrichosis, and sparse scalp hair. Other features that are easily identifiable in the phenotypic spectrum of the syndrome include feeding difficulties, slow growth, ophthalmological abnormalities, hearing problems, seizures, attention deficit/hyperactivity disorder (ADHD), and autism spectrum disorder (39). Seizures are more frequently described as focal seizures, which begin in early childhood and may be associated with febrile episodic seizures [39,40].

WWOX, which is located on the long arm of chromosome 16 (locus 16q23.1-q23.2), encodes for the WW domain-containing oxidoreductase transcriptional regulator. Recent evidence has associated *WWOX* with non-cancerous disorders [41]. Specifically, biallelic germline pathogenic variants in *WWOX* have been implicated in autosomal recessive spinocerebellar ataxia type 12 (SCAR12) and early infantile epileptic encephalopathy, while germline copy number variants in the gene have also been associated with autism spectrum disorder [41,42].

In our case series, we identified a nucleotide variant in *SLC2A1*, one in *DNM1*, one in *ARID1B*, and one in *WWOX*. All variants were identified in a single patient and were reported in HGMD, GnomAD, and DGV. The nucleotide variants in *SLC2A, ARID1B,* and *WWOX* were inherited from the father. The nucleotide variant in *DNM1* was inherited from the mother. All four identified variants are classified as VOUS.

(ID-BA). This case presents a girl that has a family history of epilepsy in the paternal uncle. Her birth was regular, as were her first months of life. At 24 months of age, she experienced complex febrile seizures and later developed severe episodes of afebrile seizures. Additionally, an angioma was noted on the lower lip. Neuroimaging revealed multiple microcysts containing cerebrospinal fluid, with the two most prominent located subcortically on the left paramedian vertex at 5 mm and in the periventricular white matter of the left semioval center, which are attributable to ectasias of the perivascular spaces. Treatment with levetiracetam resulted in a good seizure control. Currently, the patient shows an adequate psychomotor development and leads a life appropriate for her age.

Despite having numerous nucleotide variants in different genes related to epilepsy inherited from both healthy parents, the girl does not present catastrophic phenotypic pictures as previously described. To date, the only clinical manifestation is epilepsy, which is well-controlled by a single anticonvulsant medication. It is interesting and useful to follow up with the girl to assess the onset of new disturbances that may be linked to one or more of the aforementioned phenotypes. Presently, in the girl, it is possible to describe a compensatory genotypic picture among the various nucleotide variants.

4.8. GABRG2

GABRG2, which is mapped to the long arm of chromosome 5 (locus 5q34), encodes for the γ2 subunit o*f* the gamma-aminobutyric acid type A receptor, which is a ligand-gated chloride channel. Mutations in *GABRG2* have been associated with simple febrile seizures and generalized epilepsies, including childhood absence epilepsy, generalized epilepsy with febrile seizures plus, and Dravet syndrome [43,44]. The phenotypic heterogeneity observed in epilepsy associated with *GABRG2* mutations may be correlated with the extent of the reduction in function of the GABA-A receptor channel [43].

In our case series, we identified a nucleotide variant in *GABRG2*, which was found in a single patient and reported in HGMD, GnomAD, and DGV. The variant was absent in the parents, this indicating a *de novo* occurrence, and is classified as a VOUS.

(ID-MIL). The case presents a girl that has a family history of epilepsy and neurological disorders (paternal aunt with epilepsy, first-degree cousin on the paternal line with febrile seizures, and a maternal grandfather affected by amyotrophic lateral sclerosis). She was born from a pregnancy complicated by gestational hypertension. The neonatal screening was positive for congenital hypothyroidism, which was promptly treated with a replacement hormone therapy. At six months of age, she experienced her first critical episode of afebrile seizures. Subsequently, there was an increased frequency of such episodes, occurring 2–3 times per day. The neuroimaging was positive for a faint hyperintensity on the long TR sequences in the posterior periventricular white matter, with a punctate hyperintensity containing cerebrospinal fluid in the posterior right region. Treatment with valproic acid was initiated; however, due to an inadequate seizure control and the occurrence of atypical absence seizures, ethosuximide was added in combination, which resulted in a satisfactory clinical response. We believe that, as reported in the literature, the variant in this patient may play a crucial role in determining the phenotype. It is of interest to follow the patient's long-term outcome and assess the evolution of the phenotype over time.

Among the present group of 27 children affected by genetic epilepsy, aside from the aforementioned genes, we found other genes involved in the diagnostic assessment (see Table 1) such as *SLC6A1* (ID-BG), *UZAF2* (ID-CL), *PRRT2* (ID-MCP), *DEPDC5* (ID-AE), *PIGV* in association to *TBC1D24* (ID-SF), and *SPTAN1* (ID-TA). In addition, chromosome deletions and/or duplications (ID-MBE, ID-DL, ID-SM, ID-ZA, ID-LS, ID-NG, ID-DAE, ID-DSN) were found.

As previously reported, this study shows that in the majority of the cohort, where one or more nucleotide variants were identified, the onset of epileptic symptoms occurred within the first two years of life. Only in six patients out of twenty-seven did the onset of seizures manifest after two years of age, which suggests that the earlier the onset of the epileptic phenotype, the more likely it acts as a causative role for genetics.

However, uncertainty remains about the exclusive role of genetics in the onset of the phenotype, with other factors such as environmental adverse influences potentially playing a role in seizure occurrences.

Furthermore, most nucleotide variants identified in genes associated with epilepsy are reported as VOUS. In this case series, more than half of the identified nucleotide variants (22 out of 38) were VOUS, despite being associated, in the majority of cases as described above, with a pathological phenotype. Currently, this prevents the generation of a definitive genotype-phenotype correlation. In the future, with larger datasets, variants currently classified as a VOUS might be reclassified as truly pathogenetic or not, in relation to the presented clinical picture.

The interpretation of the data becomes even more challenging when multiple nucleotide variants are identified in genes related to epilepsy. Little is known about the beneficial or detrimental effects that different genetic variants may have on each other and in causing the epileptic phenotype. Our data show that six patients out of twenty-seven have two or more nucleotide variants in genes related to epilepsy. Currently, we do not know the causative impact that these different variants have had on the phenotypes of the children within this cohort. We can only speculate, as in the cases of variants identified in *SCN2A1* associated with variants in either *ATP1A2* or *CHD2*, that these variants may have a worsening effect, thus leading to a severe phenotype, even if they are currently considered as a VOUS. In other cases, such as the four nucleotide variants in *SLC2A1*, *DNM1*, *ARID1B*, and *WWOX* identified in a single patient who presented with a less significant symptomatology than expected, where the only clinical manifestation was well-controlled epilepsy with a single drug, it could be suggested that the genotypic pattern is a direct consequence of compensation between different nucleotide variants as an improving effect.

5. Conclusions

With the introduction of the molecular genetic investigations, such as a CGH-Array, NGS, and others, the possibility of identifying a genetic cause associated with the epileptic phenotype has been widely increased. Therefore, these investigations have become an indispensable diagnostic pathway in pediatric disorders. Genetic analyses, combined with a thorough clinical, electroencephalographic, and laboratory evaluation and frequent follow-ups, can be extremely useful in better defining the genotype-phenotype relationship, prognosis, and response to pharmacological treatments in children with several neurological disorders including epilepsy.

This study offers a further confirmation of the relevance of genetic investigations in children affected by epilepsy; the results obtained together with other similar studies may be useful to better clarify the direct association between the genotype and the phenotype of children with these disorders. The results obtained in epileptic children that manifest with a VOUS may be provided for a proper placement for such cases in various international databases (i.e., International Human Genome Project consortium, Human Genome Project, and Human Gene Mutation Database). In this regard, the clinic plays a central role in the diagnostic and therapeutic process, as well as genetic investigations in the presence of subjects with a family history of neurological pathologies, seizures, dysmorphic and skeletal alterations, and language and behavior disorders. We hope that genetic investigations can be performed as early as possible, especially in subjects with a family history of neurological pathologies and are clinically suggestive of paroxysmal episodes. In children, the genetic cause and pre-peri-

postnatal adverse events are often recognized events of epilepsy; however, the role, boundary, and clinical expressivity of each of these factors, either singularly or in addition, remain to be established.

6. Limitations

The results obtained by this study presents some limitations, including the following: the small number of affected children involved in the study; the absence of modelling algorithms such as Poly-Phen2 or SIFT; the lack of CNV to detect new CNV variants; and the heterogeneity of nucleotide variants identified in the cohort, making it impractical to perform meaningful statistical analyses.

In addition, the study involved children with epileptic seizures, but without a defined type of epilepsy; however, this was not the primary objective. The present study underscores the limited information available in literature and current databases regarding detectable mutations in genes associated with epilepsy, and the various data made it difficult to assemble a database for a more precise definition of the correlation between mutated genes and phenotype.

Author contributions

Piero Pavone, Ottavia Avola, and Raffaele Falsaperla: diagnosed and followed the children; Raffaele Falsaperla, Piero Pavone, Chiara Nannola, Agata Polizzi, Tiziana Timpanaro, Ottavia Avola, Claudia Oliva, and Alessandra Di Nora: reviewed the literature, critically discussed various aspects of epilepsy and read the manuscript; Piero Pavone, Filippo Greco, Agata Polizzi, Chiara Nannola, Raffaele Falsaperla, Claudia Oliva, Filippo Greco, Alessandra Di Nora, and Tiziana Timpanaro: wrote the manuscript and prepared the tables.

Use of AI tools declaration

The authors declare they have not used Artificial Intelligence (AI) tools in the creation of this article.

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Ethics approval of research and informed consent

Ethics approval of research was obtained (number of protocol P-V-S 12456/2020) and we confirm that we have obtained the patients' informed consent and Ethical approval prior to study.

Conflict of interest

The authors declare no conflict of interest.

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