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Case Report

Expanding the Phenotypic Spectrum of *KCNT2*-Related Encephalopathy: A Novel *De Novo* Stop-Gain Variant with Coffin–Siris–Like Features

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Abstract

Pathogenic variants in *KCNT2* have recently been recognized as a rare cause of Developmental and Epileptic Encephalopathy (DEE-57), characterized by early-onset refractory seizures and severe neurodevelopmental impairment, with only a limited number of cases reported worldwide. We describe a 7-month-old female infant, born to non-consanguineous parents, who presented with recurrent afebrile seizures since the neonatal period, global developmental delay, failure to thrive, and microcephaly. Seizures began on day 6 of life and evolved into drug-resistant epilepsy with multifocal onset. On examination, the child exhibited dysmorphic features including cleft palate, hirsutism, thick eyebrows, long eyelashes, broad nasal tip, smooth philtrum, and spatulate fingers. Electroencephalography revealed multifocal epileptiform discharges with migrating seizure activity, while neuroimaging showed only minor birth-related hemorrhages. Whole exome sequencing identified a novel heterozygous nonsense variant in *KCNT2* (c.2836A>T; p.Lys946Ter), consistent with developmental and epileptic encephalopathy-57. In addition, a variant of uncertain significance in *ARID1A* was detected, raising the possibility of phenotypic overlap with Coffin–Siris–like features. The child required multiple anti-seizure medications with only partial seizure control and persistent developmental delay. This case expands the genotypic and phenotypic spectrum of *KCNT2*-related encephalopathy and highlights a potential syndromic overlap, emphasizing the importance of comprehensive genetic evaluation in infants with early-onset refractory epilepsy.

Introduction

Developmental and Epileptic Encephalopathies (DEEs) comprise a group of severe neurodevelopmental disorders characterized by early-onset, treatment-resistant seizures and progressive impairment of cognitive and motor functions. Recent advances in next-generation sequencing have identified several genetic etiologies underlying these disorders, particularly involving ion channel–related genes. Among these, *KCNT2*, which encodes a sodium-activated potassium channel subunit ($K_{Na}1.2$), has emerged as a rare but important contributor to early infantile epileptic syndromes. Pathogenic variants in *KCNT2* have been associated with a spectrum of clinical presentations, including epilepsy of infancy with migrating focal seizures and infantile spasms, often accompanied by global developmental delay. However, the number of reported cases remains limited, and the phenotypic spectrum is still evolving. Emerging evidence suggests significant heterogeneity, with variable neurological and extra-neurological manifestations, indicating that the full clinical profile of *KCNT2*-related disorders is yet to be clearly delineated. In this context, we report an infant with early-onset refractory seizures, developmental delay, and dysmorphic features, contributing to the expanding clinical spectrum of *KCNT2*-associated encephalopathy and highlighting the role of comprehensive genetic evaluation in such complex presentations.

Case Presentation

A 7-month-old female infant, born to non-consanguineous parents, presented with recurrent afebrile seizures. The current episode consisted of three generalized tonic seizures lasting 30 to 45 seconds, associated with postictal drowsiness. There was no history of fever, trauma, or preceding illness. The child had a significant neonatal history of seizures beginning on day 6 of life, requiring admission to the neonatal intensive care unit. At that time, hypoglycemia was documented and corrected; however, given the persistence of seizures beyond metabolic correction and abnormal electroencephalographic findings, she was initiated on phenobarbitone and continued on therapy until 2

months of age. Neonatal EEG reportedly showed a discontinuous background with multifocal epileptiform discharges, suggestive of an underlying epileptic encephalopathy rather than purely metabolic seizures.

Following a transient seizure-free period, the child developed recurrent seizures from early infancy, with increasing frequency and poor response to monotherapy, raising concerns for drug-resistant epilepsy. Differential diagnoses considered at this stage included early infantile epileptic encephalopathy (including epilepsy of infancy with migrating focal seizures), structural brain injury, inborn errors of metabolism, and genetic epileptic syndromes. She was born at term by forceps-assisted vaginal delivery, with a birth weight of 2.5 kg, and an uneventful antenatal history. There was no history of maternal infections, teratogenic exposures, or family history of seizures or neurodevelopmental disorders. Developmentally, the child had global delay. At 7 months of age, she had not achieved head control. She was able to fix and follow visually and had attained a social smile, but had significant delay in gross motor and language domains. There was associated failure to thrive.

On examination, the child was hemodynamically stable. Anthropometry revealed microcephaly (head circumference ≤ 3 SD) and undernutrition. Dysmorphic features included cleft palate, hirsute extremities, thick eyebrows, long eyelashes, broad nasal tip, smooth philtrum, and spatulate fingers with deep-set nails. Musculoskeletal examination revealed a positive Galeazzi sign suggestive of developmental dysplasia of the hip. The abdomen was distended, and a gastrostomy tube was present. Neurologically, the child was irritable with preserved tone and no focal deficits. Laboratory evaluation including complete blood count, serum electrolytes, calcium, magnesium, renal and liver function tests, and metabolic screening was within normal limits. Electroencephalography at the time of current admission demonstrated a diffusely slowed background with multifocal epileptiform discharges and independent seizure activity arising from different cortical regions, with migration across hemispheres, consistent with a severe epileptic encephalopathy phenotype. Magnetic resonance imaging of the brain revealed thin extra-axial hemorrhages along the posterior fossa and parieto-occipital regions, likely related to birth trauma, without major structural abnormalities. Echocardiography showed a small ventricular septal defect and patent foramen ovale. Ultrasound of the hips confirmed developmental dysplasia. Karyotyping was normal. The laboratory and diagnostic investigations are summarized in Table 1 (Figure 1).

During hospitalization, the child continued to have breakthrough seizures despite escalation of anti-seizure medications, including levetiracetam and phenobarbitone, consistent with drug-resistant epilepsy. Given the normal metabolic and structural workup, a genetic etiology was strongly suspected.

Whole Exome Sequencing (WES) was performed using next-generation sequencing on an Illumina platform with a mean sequencing depth of >100×. Genomic DNA extracted from peripheral blood underwent targeted capture of coding regions, followed by sequencing and bioinformatic analysis. Sequence reads were aligned to the human reference genome (GRCh38) using the Burrows–Wheeler Aligner (BWA), and variant calling was performed using the GATK/Sentieon pipeline. Variant annotation was carried out using the Variant Effect Predictor (VEP) against Ensembl gene models. Clinically relevant variants were filtered based on allele frequency in population databases including gnomAD, 1000 Genomes, TOPMed, and internal population datasets, and correlated with phenotype using ClinVar, OMIM, HGMD, and DECIPHER databases [1].

Table 1: Summary of laboratory and diagnostic investigations highlighting normal metabolic and structural evaluation, with electroencephalographic and genetic findings supporting a diagnosis of developmental and epileptic encephalopathy.

Laboratory parameter	Value	Normal range
Hemoglobin (g/dL)	Within normal limits	10.5-13.5
Total leukocyte count (cells/cumm)	14,800	5,000-15,000
Differential count (N/L)	Neutrophil predominant	-
Platelets (lakhs/cumm)	Normal	1.5-4.5
C-reactive protein (mg/L)	16.2 (elevated)	<5
Blood glucose (mg/dL)	128	70-140
Serum sodium (mEq/L)	Normal	135-145
Serum potassium (mEq/L)	Normal	3.5-5.5
Calcium (mg/dL)	Normal	8.5-10.5
Magnesium (mg/dL)	Normal	1.5-2.5
Phosphorus (mg/dL)	Normal	4-7
Renal function tests	Normal	-
Liver function tests	Normal	-
Sepsis screen	Negative	-
Tandem mass spectrometry	Normal	-
Electroencephalogram (EEG)	Generalized spike–wave discharges with chaotic background activity	-
MRI brain	Mild extra-axial hemorrhages; no structural abnormality	-
Echocardiography	Small VSD (2 mm - 3 mm), PFO	-
Ultrasound hip	Developmental dysplasia of hip	-
Karyotype	Normal female karyotype	-
Whole exome sequencing	*KCNT2* pathogenic variant; *ARID1A* VUS	-

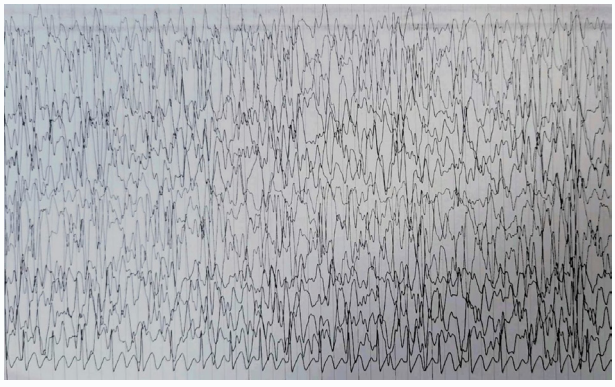

Figure 1: Electroencephalogram showing generalized epileptiform spike–wave discharges with markedly disorganized, high-amplitude background activity, indicative of a severe developmental and epileptic encephalopathy.

The identified variant in the *KCNT2* gene (ENST00000294725.14) was a heterozygous nonsense variant located in exon 25 [c.2836A>T; p.Lys946Ter; chr1:g.196280934T>A; read depth: 42×], predicted to introduce a premature stop codon leading to truncation of the protein. This variant was absent in population databases including gnomAD and 1000 Genomes. In silico prediction tools, including MutationTaster2, suggested a damaging effect, and the affected residue was evolutionarily conserved. The variant was classified as likely pathogenic according to the American College of Medical Genetics and Genomics (ACMG) criteria, fulfilling PVS1 (null variant in a gene where loss-of-function is a known disease mechanism) and PM2 (absent in population databases).

Additionally, a heterozygous missense variant in the *ARID1A* gene (ENST00000324856.13) [c.5570C>T; p.Thr1857Ile] was identified. This variant was absent in major population databases and predicted to be deleterious by multiple in silico tools including SIFT, PolyPhen-2, and LRT. However, due to insufficient clinical and functional evidence, it was classified as a Variant of Uncertain Significance (VUS) based on ACMG criteria (PM2, PP3) [2].

At first follow-up (1-month post-discharge), the child continued to have intermittent breakthrough seizures, though reduced in frequency. Weight gain remained suboptimal, and developmental progress was minimal. At second follow-up (3 months), seizures persisted with clustering episodes, and an additional anti-seizure medication was planned. Brainstem Evoked Response Audiometry (BERA) was planned to assess hearing, and ophthalmological evaluation was advised to rule out visual impairment, given the risk of sensory deficits in epileptic encephalopathies. Orthopedic follow-up was continued for developmental dysplasia of the hip. The child was planned for optimization of anti-seizure therapy, consideration of ketogenic diet, and enrollment in early intervention programs including physiotherapy and developmental therapy. Genetic counseling was provided to the family regarding prognosis, recurrence risk, and the need for parental testing.

Discussion

With the advent of next-generation sequencing, several genetic causes of DEE have been identified, particularly involving ion channel dysfunction, leading to the concept of epileptic channelopathies [3].

Among these, *KCNT2* has emerged as a rare but distinct genetic cause of early infantile epileptic encephalopathy [3]. The *KCNT2* gene encodes the sodium-activated potassium channel subunit $K_{Na}1.2$, which plays an important role in regulating neuronal excitability by contributing to membrane repolarization during periods of increased neuronal firing [4]. Activation of these channels by intracellular sodium provides a negative feedback mechanism to limit excessive neuronal discharge. Pathogenic variants in *KCNT2* disrupt this regulatory mechanism, resulting in abnormal neuronal firing patterns and epileptogenesis [5]. Unlike classical potassium channel disorders, *KCNT2*-related disease demonstrates functional heterogeneity, with both gain-of-function and loss-of-function variants reported in the literature [6]. This variability in channel behavior is thought to contribute to the wide clinical spectrum observed in affected individuals.

Clinically, *KCNT2*-related encephalopathy is characterized by early-onset seizures, often presenting in the neonatal period or early infancy, and typically evolving into drug-resistant epilepsy [3]. Electroencephalographic findings described in previous reports include multifocal epileptiform discharges and patterns consistent with Epilepsy of Infancy with Migrating Focal Seizures (EIMFS), reflecting a diffuse epileptic network [7]. The evolution of electroencephalographic abnormalities over time, from early background discontinuity to later multifocal and migrating epileptiform activity, suggests a dynamic and progressive disturbance of cortical networks. A major clinical challenge is the early attribution of seizures to metabolic or perinatal causes. Transient metabolic abnormalities, such as hypoglycemia, may coexist and lead to initial diagnostic anchoring. However, persistence of seizures beyond correction and the presence of abnormal background activity should prompt early evaluation for an underlying genetic etiology [8]. This distinction is critical, as delayed diagnosis may impact counseling and long-term management planning.

Comparison with *KCNT1*-related epilepsies provides further insight into disease mechanisms. Both *KCNT1* and *KCNT2* encode sodium-activated potassium channels and are associated with similar electroclinical phenotypes, particularly EIMFS. However, *KCNT1* mutations are more consistently associated with gain-of-function effects, whereas *KCNT2* mutations demonstrate broader functional diversity, suggesting distinct but converging mechanisms of neuronal hyperexcitability [9]. From a therapeutic perspective, seizures associated with *KCNT2* mutations are frequently refractory to conventional anti-seizure medications. While quinidine has been explored as a targeted therapy in *KCNT1* gain-of-function mutations due to its potassium channel blocking properties, its efficacy in *KCNT2*-related disorders remains uncertain and likely depends on the specific functional impact of the variant [9]. Extra-neurological features in *KCNT2*-related disorders have been inconsistently reported, and their significance remains unclear. The presence of dysmorphic features in this case raises the possibility of phenotypic expansion. The identification of an additional variant in *ARID1A*, a gene associated with Coffin–Siris syndrome, suggests a potential role for genetic modifiers. Although currently classified as a variant of uncertain significance, such co-existing variants may influence phenotypic expression and contribute to blended or overlapping syndromes [10].

The coexistence of a variant in the *ARID1A* gene introduces the possibility of a blended or modified phenotype. *ARID1A* encodes a key component of the SWI/SNF chromatin-remodeling complex and is implicated in Coffin–Siris syndrome, characterized by developmental delay, coarse facial features, feeding difficulties, and digital anomalies. The presence of overlapping dysmorphic features in our patient raises the possibility that the *ARID1A* variant may contribute to phenotypic modulation rather than representing an incidental finding. However, given its current classification as a variant of uncertain significance and the absence of segregation analysis, a definitive causal role cannot be established. Increasing recognition of dual molecular diagnoses in neurodevelopmental disorders suggests that such variants may act additively or modify the primary phenotype, highlighting the importance of comprehensive genomic interpretation [11].

Among reported cases of *KCNT2*-related encephalopathy (Table 2) [6,10,12-14], the phenotypic spectrum has ranged from Epilepsy of Infancy with Migrating Focal Seizures (EIMFS) and West syndrome to Lennox-Gastaut syndrome, with most patients demonstrating early-onset drug-resistant epilepsy and severe global developmental delay. Both gain-of-function and loss-of-function variants have been implicated, highlighting the functional heterogeneity of *KCNT2*-related disease. Extra-neurological features such as dysmorphism and hirsutism have been reported in a subset of cases, particularly those with gain-of-function variants at the p.Arg190 residue. However, truncating variants with associated Coffin–Siris–like dysmorphic features, as observed in our patient, have not been previously described, representing a potential expansion of the phenotypic spectrum. Furthermore, the co-occurrence of a second variant in a syndromic gene (*ARID1A*) has not been reported in prior *KCNT2* cases, underscoring the importance of comprehensive genomic interpretation in patients with complex or atypical presentations.

At present, management remains largely supportive, focusing on seizure control, nutritional support, and early developmental interventions. This case contributes to the limited literature on *KCNT2*-related encephalopathy and highlights several important aspects, including the evolving electroclinical phenotype, the potential for diagnostic delay due to coexisting metabolic factors, and the possibility of genetic interaction influencing phenotypic expression. Further accumulation of cases and functional studies will be essential to refine genotype–phenotype correlations and to explore targeted therapeutic strategies [15]. Compared to previously reported cases (Table 2) [6,10,12-14], our patient uniquely demonstrates a truncating variant with associated dysmorphic features, suggesting a possible expansion of the phenotypic spectrum [16].

Conclusion

This case emphasizes that persistent or evolving seizures in early infancy, even when initially associated with correctable metabolic disturbances, should prompt early consideration of an underlying genetic epileptic encephalopathy. *KCNT2*-related disorders represent a rare but severe channelopathy with dynamic electroclinical evolution and high risk of pharmacoresistance. The coexistence of dysmorphic features and an additional genetic variant in this patient suggests a broader and potentially modified phenotypic spectrum, highlighting the complexity of genotype–phenotype interactions. Early use of genomic testing in such presentations is critical not only for diagnosis but also for avoiding diagnostic delay and guiding long-term management and counseling. Accumulation of similar cases will be essential to better define disease mechanisms and explore future targeted therapies.

Learning Points

Persistence of seizures beyond correction of hypoglycemia should immediately raise suspicion for an underlying genetic epileptic encephalopathy.

Abnormal neonatal EEG background is a critical early clue distinguishing primary epileptic encephalopathy from acute symptomatic seizures.

KCNT2-related epilepsy shows evolving electroclinical patterns, often progressing to multifocal and migrating seizure activity.

Drug resistance early in the disease course is a hallmark of *KCNT2*-associated encephalopathy.

Dysmorphism in an infant with epilepsy should trigger evaluation for blended or syndromic genetic disorders.

Co-existing variants (e.g., *ARID1A*) may modify phenotype and explain atypical or expanded clinical features.

Early exome sequencing is not optional in refractory infantile epilepsy-it is diagnostically decisive.

Multisystem evaluation (neurological, developmental, auditory, visual) is essential for comprehensive care and prognostication.

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Table 2: Comparative analysis of previously reported cases of *KCNT2*-related developmental and epileptic encephalopathy and the present case, emphasizing clinical, electroencephalographic, and genetic features.

S. No	Case report	Year	Age/Gender	Clinical features	EEG findings	Mutation (Protein change)	Functional effect	Outcome
1	Ambrosino P et al.	2018	Infant/F	Early-onset seizures, developmental delay	Multifocal discharges, EIMFS pattern	Missense variant	Gain-of-function	Drug-resistant epilepsy
2	Mao X et al.	2020	Infant/M	Migrating focal seizures, hypotonia	Migrating epileptiform activity	*KCNT2* variant	Loss-of-function	Severe developmental delay
3	Alagoz M et al.	2020	Infant/F	Refractory seizures, developmental delay	Multifocal spikes	Variant reported	Not specified	Poor seizure control
4	Kessi M et al.	2020	Infant/M	Epileptic encephalopathy, regression	Diffuse epileptiform activity	Variant reported	Mixed/uncertain	Persistent seizures
5	Gong P et al.	2021	Infant/F	Early infantile seizures, developmental delay	Multifocal epileptiform discharges	Variant reported	Not specified	Developmental impairment
6	Present case	2026	7 months/F	Neonatal onset seizures, dysmorphism, global delay	Generalized spike–wave discharges with chaotic background	c.2836A>T (p.Lys946Ter)	Likely loss-of-function	Drug-resistant epilepsy with syndromic features

Consent Confirmation

Written informed consent was obtained from the legal guardian of the patient for the publication of this case report, including all clinical details and images. A copy of the signed consent form is available for editorial review upon request.

Author Contributions

Dr. Hari Prasath C contributed to patient management, data collection, literature review, and drafting of the manuscript. Dr. P Anil Kumar contributed to conceptualization, supervision, critical revision of the manuscript, and final approval. All authors read and approved the final manuscript.

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