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Case Report

Homozygous SCN1B c.265C>T (p.Arg89Cys) Variant Presenting with Early-Onset Developmental and Epileptic Encephalopathy: The Fourth Reported Case Worldwide

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Abstract

SCN1B variants are increasingly recognized causes of developmental and epileptic encephalopathies (DEE), while homozygous variants remain exceptionally rare and are often associated with severe early-onset epilepsy. We report a 9-month-old male infant presenting with focal impaired awareness seizures progressing to frequent daily episodes and drop attacks. EEG demonstrated focal epileptiform discharges and brain MRI was normal. Genetic testing identified a homozygous likely pathogenic SCN1B variant, c.265C>T (p.Arg89Cys). Family history was notable for a sibling with severe refractory epilepsy and significant neurodevelopmental impairment, suggesting a severe familial phenotype. Oxcarbazepine was ineffective, while valproic acid resulted in partial seizure control. This case highlights the phenotypic spectrum and intrafamilial variability of SCN1B-related epilepsy and emphasizes the importance of early genetic diagnosis and individualized management. To our knowledge, this represents the fourth genetically confirmed case reported worldwide with homozygous SCN1B c.265C>T (p.Arg89Cys).

Introduction

The SCN1B gene encodes the β1 subunit of voltage-gated sodium channels, which plays a critical role in neuronal excitability and modulation of channel kinetics [3]. Pathogenic variants in SCN1B are associated with a spectrum of epileptic disorders ranging from generalized epilepsy with febrile seizures plus (GEFS+) to severe developmental and epileptic encephalopathies (DEE).

Homozygous or compound heterozygous variants in SCN1B are linked to DEE type 52 (DEE52), characterized by early-onset seizures, pharmacoresistance, and neurodevelopmental delay. Clinical overlap with Dravet syndrome and other sodium channelopathies has been reported, complicating diagnosis and management [4].

Here, we present a genetically confirmed homozygous SCN1B c.265C>T (p.Arg89Cys) case who appears to represent the fourth reported genetically confirmed patient worldwide. The family history of a similarly affected sibling, who was not genetically tested, suggests a second affected familial case and highlights the severe intrafamilial phenotype associated with this rare variant.

Case Presentation

We report a 9-month-old male infant born at term via normal vaginal delivery following an uncomplicated pregnancy, with no perinatal complications and appropriate early developmental milestones. The parents are consanguineous. Family history was significant for a 13-year-old sister with severe refractory epilepsy, initially triggered by febrile seizures and later progressing to afebrile seizures. She failed multiple anti-seizure medications and currently has severe global developmental delay with persistent daily seizures. During early infancy, the patient remained clinically stable, with two febrile illnesses not associated with seizures, and a screening EEG at 6 months was normal. At 9 months of age, he developed focal impaired awareness seizures characterized by sudden staring episodes with brief gaze deviation lasting a few seconds. Seizures initially occurred once weekly but rapidly increased over two weeks to 2–3 episodes daily, with subsequent evolution to atonic seizures (drop attacks). EEG demonstrated focal epileptiform discharges, while brain MRI was normal. The differential diagnosis included Dravet syndrome, other sodium channelopathies, genetic developmental epileptic encephalopathies, and less likely structural or metabolic epilepsy. Genetic testing identified a homozygous likely pathogenic variant in SCN1B: c.265C>T (p.Arg89Cys). Initial treatment was delayed because of parental concerns regarding anti-seizure medications. Oxcarbazepine was started prior to the genetic diagnosis but was ineffective, after which valproic acid was introduced with partial seizure reduction. The patient remains on valproic acid monotherapy with persistent but reduced seizure frequency and ongoing developmental monitoring; long-term neurodevelopmental outcome remains uncertain.

Discussion

This case illustrates several key aspects of SCN1B-related epilepsy:

Genotype–Phenotype Correlation

Homozygous SCN1B variants are rare but consistently associated with severe epileptic phenotypes and developmental impairment [2,3]. The identified p.Arg89Cys variant affects a conserved region of the β1 subunit, likely disrupting sodium channel modulation and neuronal excitability.

Clinical Spectrum

The patient's presentation is consistent with previously described cases of DEE52, including early-onset seizures, multiple seizure types, and initially normal development followed by potential deterioration. However, the presence of significant intrafamilial variability is notable, as the affected sibling exhibits a more severe phenotype with refractory epilepsy and marked developmental delay.

Treatment Considerations

Response to anti-seizure medications in SCN1B-related epilepsy is variable. Sodium channel blockers such as oxcarbazepine may exacerbate seizures in some sodium channelopathies, whereas valproic acid is often more beneficial [5].

Challenges:

A unique challenge in this case was parental reluctance to initiate therapy due to prior experience with an affected sibling. This underscores the importance of:

- Genetic counseling
- Clear communication regarding disease pathophysiology
- Addressing misconceptions about treatment-related harm

Literature Review

Pathogenic variants in SCN1B, the gene encoding voltage-gated sodium channel b1/b1B subunits are associated with a spectrum of epileptic disorders [2]. SCN1B mutations were first associated with epilepsy in GEFS+ families but later linked to severe DEE phenotypes [1,2]. The β1 subunit modulates sodium channel gating and neuronal excitability, and its dysfunction leads to hyperexcitability. Several pathogenic SCN1B genetic variants have been reported in individuals with DEEs including Dravet-like syndrome, genetic epilepsy with febrile seizures plus (GEFS+), and focal epilepsy [7]

Several studies have described homozygous SCN1B variants presenting with:

- Early-onset seizures (often <1 year)
- Multiple seizure types
- Developmental delay
- High mortality in severe cases

Compared to reported cases:

- The onset at 9 months is consistent
- Seizure evolution aligns with DEE patterns
- The relatively preserved early development may suggest a milder initial trajectory

However, the strong familial phenotype suggests a severe underlying genetic predisposition.

The SCN1B c.265C>T (p.Arg89Cys) variant remains extremely rare. To our knowledge, three genetically confirmed human patients with homozygous/biallelic SCN1B c.265C>T (p.Arg89Cys) have been reported previously: two siblings reported by Darras et al [10]. and one unrelated patient briefly described by Chen et al [11]. Therefore, the present genetically confirmed patient appears to represent the fourth reported patient worldwide with this specific homozygous SCN1B p.Arg89Cys variant. In addition, the patient's sibling had a severe, clinically similar epileptic encephalopathy but did not undergo genetic testing. This sibling should therefore be considered a clinically suspected, but genetically unconfirmed, additional familial case, if confirmed, this would represent the fifth affected patient worldwide.

Therapeutic Evidence

Because SCN1B-related developmental and epileptic encephalopathy may clinically overlap with Dravet-like sodium channelopathies, treatment should be individualized. In Dravet syndrome, expert consensus supports valproic acid as a first-line maintenance therapy and recommends avoidance of maintenance sodium-channel blockers such as carbamazepine, oxcarbazepine, lamotrigine, and phenytoin because they may worsen seizures [9]. Precision medicine approaches based on genetic findings are still evolving

Conclusion

This case expands the clinical spectrum of SCN1B-related DEE and highlights significant intrafamilial variability [2,3]. Early genetic diagnosis is crucial for guiding management and counseling. Addressing parental concerns is essential to ensure timely initiation of therapy and optimize outcomes.

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