

# Novel *SCN1A* and *GABRA1* Gene Mutations With Diverse Phenotypic Features and the Question on the Existence of a Broader Spectrum of Dravet Syndrome

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## Abstract

In the light of modern molecular technologies, the understanding of the complexity of the numerous genotype–phenotype correlations regarding Dravet syndrome is mandatory. Motivated by 2 patients, whose whole-exome sequencing revealed novel mutations that exemplify the phenotypic and genetic heterogeneities associated with typical and atypical Dravet syndrome presentations, the authors discuss the existence of a broader spectrum of Dravet syndrome. The first patient is a 4-year-old boy with fairly typical Dravet syndrome and a novel *sodium channel  $\alpha 1$  subunit* gene mutation of high-predicted combined pathogenicity likelihood. The second patient is a 15-year-old boy with some atypical features of Dravet syndrome, harboring a novel mutation of the  *$\gamma$ -aminobutyric acid receptor  $\alpha 1$  subunit* gene, whose role in this syndrome pathogenesis has recently been highlighted. A brief review of the literature reveals that none of the current diagnostic criteria is thoroughly predictive of the disease, and phenotypic discrepancies are common among patients carrying atypical Dravet syndrome mutations. The authors conclude that the discussion of a Dravet syndrome spectrum is relevant.

## Keywords

epileptic encephalopathy, infant, genetics, mutation, next generation sequencing

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Genetic testing in complex clinical presentations that include pharmaco-resistant epilepsy is nowadays part of a rational diagnostic strategy. For the clinician, a genetic diagnosis that fits a specific clinical phenotype confirms the diagnosis, predicts outcome, and usually has therapeutic implications. In contrast, novel mutations in uncommon genetic loci create uncertainty and raise questions about the existence of phenotypic spectrums, rendering positive genotype–phenotype associations difficult.

Dravet syndrome, also known as “severe myoclonic epilepsy of infancy”, is a rare form of genetic, epileptic encephalopathy, characterized by a variety of both febrile and afebrile treatment-resistant seizures, followed by cognitive decline and neurological signs.<sup>1</sup> In 75% of cases, it is attributed to disease-causing, dominant, and mainly *de novo* mutations in the sodium channel  $\alpha 1$  subunit gene.<sup>2</sup> Other genes have been sporadically implicated in the pathogenesis of Dravet syndrome,

specifically *PCDH19*,<sup>3,4</sup>  *$\gamma$ -aminobutyric acid receptor  $\gamma$ -2 precursor*,<sup>5,6</sup> *sodium channel beta-1 subunit*,<sup>7,8</sup> *CHD2*,<sup>9</sup> and *syntaxin binding protein 1*.<sup>10</sup>

*$\gamma$ -Aminobutyric acid receptor  $\alpha 1$  subunit* mutations have been mostly related to mild forms of generalized epilepsy,<sup>11</sup> and only recently, they have been connected to severe forms of epileptic encephalopathy, in specific, Dravet,<sup>10</sup> Ohtahara, and West syndromes.<sup>12</sup>

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In this report, the authors present the clinical and genetic findings on 3 patients: first, a 4-year-old boy with typical Dravet syndrome, in whom whole-exome sequencing revealed a novel *de novo* sodium channel  $\alpha 1$  subunit gene mutation, and second, a 15-year-old boy with an atypical Dravet syndrome phenotype, harboring a novel *de novo*  $\gamma$ -aminobutyric acid receptor  $\alpha 1$  subunit gene mutation. The authors move forward to a brief review of the current literature regarding possible phenotypic discrepancies among patients with Dravet syndrome with atypical gene mutations. Our goal is to expand our understanding of Dravet syndrome and highlight the phenotypic and genetic heterogeneities associated with the disease.

## Methods

### Patient Evaluation—Clinical Methods

Patients were evaluated in the Department of Neurology of Pendeli Children's Hospital, Athens, Greece. A detailed clinical history was obtained, followed by thorough clinical examination. Electroencephalogram (EEG), brain magnetic resonance imaging (MRI), and metabolic and routine genetic tests were carried out, according to the existing protocols for children with early-onset seizures and developmental delay.

### Whole-Exome Libraries

Pretest genetic counseling of the families was performed, and informed consent was obtained in accordance with approved internal institutional guidelines and the American College of Medical Genetics recommendations.<sup>13</sup>

Genomic DNA was isolated using the QIAamp DNA Blood Mini Kit (Qiagen, Valencia, CA, USA), assessed on the Agilent TapeStation 2200 (Genomic DNA ScreenTape kit, Agilent Technologies, Santa Clara, CA, USA) and  $\sim 120$  ng was subjected to whole-exome DNA library construction using the Ion AmpliSeq Whole Exome RDY (Life Technologies, Thermo Fisher Scientific, Waltham, MA USA) essentially as described in the manufacturer's protocol, with barcode incorporation. AmpliSeq HiQ libraries for sequencing were prepared on the Ion OneTouch 2 system, quantified using the Qubit 2.0 fluorometer (Life Technologies, Thermo Fisher Scientific) and massive parallel sequencing was subsequently performed on the Ion Proton System on a PI chip (Life Technologies, Thermo Fisher Scientific).

### Data Analysis and Interpretation

Primary sequence data analysis was performed using Torrent Suite (4.2.0) with default parameters, and variant calling was performed using the Ion Torrent Variant Caller plug-in (version 4.2-8-r87740) using default settings and relative to NCBI37/hg19 reference assembly. The resulting variants (vcf file) were annotated through the Ion Reporter 4.4 or 5.0 variant annotation analysis function, and the annotated variants were subsequently imported for filtering, prioritization, and evaluation into an in-house management application custom bioinformatics pipeline, which includes a family trio-analysis function. In parallel, the 3 whole-exome BAM files were also uploaded to Ion Reporter Cloud and analyzed through the Ion Reporter AmpliSeq exome trio (version 4.6) workflow. Selected clinically significant variants were confirmed by standard DNA Sanger sequencing.

## Results

### Case 1

This boy was evaluated at 4 years and 6 months of age. He had an unremarkable prenatal and perinatal history. At the age of 9½ months, he experienced his first episode of febrile seizures following vaccination. This was a generalized tonic seizure with eye deviation and cyanosis, lasting around 5 minutes. He remained seizure-free, and his psychomotor development was marginally normal. At the age of 2 years and 3 months, he had a new episode, this time an afebrile, focal tonic seizure. Following this, he experienced a series of epileptic events, both febrile and afebrile and of multiple types, especially generalized tonic-clonic, focal tonic, or hemiclonic seizures. Cognitive and motor development started regressing and the seizures deteriorated under treatment with carbamazepine and later, levetiracetam. Valproic acid was added with poor response and later topiramate, leading to some improvement. Neurologic examination revealed ataxia, global developmental delay, and autistic characteristics. Wakefulness and sleep EEG was moderately organized, with no epileptogenic activity and 3 Tesla brain MRI was normal.

Genetic testing through whole-exome sequencing was requested and performed for the proband only, which revealed the heterozygous presence of a novel c.4244T>A (p.Leu1415-His) missense variant/mutation in exon 21 of the sodium channel  $\alpha 1$  subunit gene. This mutation has not been previously reported in the literature in patients; it is neither present in international databases (NHLBI Exome Variant Server, ExAC consortium) nor in our in-house database (100 Greek exomes), thus representing a new sodium channel  $\alpha 1$  subunit gene mutation. The mutation was not present in either parent (*de novo* mutation), while its pathogenicity was being assessed *in silico* through the built-in function of the evaluation into an in-house management application variant prioritization algorithm, leading to a predicted combined pathogenicity likelihood score of 92%—likely pathogenic. Furthermore, a known pathogenic mutation c.4244T>G (p.Leu1415Arg) in the same highly conserved amino acid position has been previously reported.<sup>14</sup>

### Case 2

This boy has been followed since infancy for developmental delay, epilepsy, increased muscle tone of the lower limbs, ataxia, and behavioral problems with autistic characteristics. There were no prenatal or neonatal concerns, and he achieved appropriate early developmental milestones. At 13 months old, he had a series of brief but frequent generalized tonic seizures, within a 24-hour period, followed by pyrexia. Brain MRI showed a grade of immaturity of the white matter around the occipital horns and the sleep EEG was of moderate organization, with no epileptic activity. At about 15 months, he had further, afebrile, epileptic events, around 1 per week, of focal onset, with impaired awareness and automatisms. A further

**Table 1.** Patients' Clinical and EEG Characteristics That Meet Dravet Syndrome Diagnostic Criteria as Per Guerrini and Oguni.<sup>15</sup>

Clinical and EEG Criteria of Dravet Syndrome (Guerrini and Oguni <sup>15</sup> )	Patient 1	Patient 2
Family history of epilepsy or febrile seizures	No	No
Development before onset, normal	Yes in general, borderline motor delay	Yes in general, borderline motor delay
Seizures: first year of life: generalized, unilateral, or alternating unilateral febrile and afebrile clonic seizures, subsequently myoclonic seizures, and sometimes, partial seizures	<ul style="list-style-type: none"> <li>• 9.5 months, generalized tonic febrile seizure. 2 years, afebrile focal seizure.</li> <li>• Febrile and afebrile, GTCS, focal or hemiclonic seizures.</li> </ul>	<ul style="list-style-type: none"> <li>• 13 months: cluster of febrile, generalized clonic seizures</li> <li>• Focal afebrile seizures</li> <li>• Myoclonic seizures</li> </ul>
EEG:	Yes	Yes
<ul style="list-style-type: none"> <li>• Absence of epileptiform discharges in initial EEGs studies,</li> <li>• Later generalized spike-wave and polyspike-wave discharges, focal abnormalities,</li> <li>• Early photosensitivity</li> </ul>	-	15 years old: focal epileptiform discharges
Delayed development from the second year of life onward.	Yes	Yes
Ataxic gait	-	Yes
Pyramidal signs (sometimes)	-	Yes
Interictal myoclonus	-	-
Refractoriness of all seizure types to all forms of treatment	Yes	Myoclonic seizures (infrequent for 10 years)

Abbreviations: EEG, electroencephalogram; GTCS, tonicoclonic seizure.

EEG was performed with no abnormalities, and he was started on carbamazepine, resulting in clinical deterioration, so medication was switched to sodium valproate. Over the following 2 years, he developed other seizure types, infrequently while febrile, but mostly in the absence of fever, including generalized myoclonic seizures, focal onset seizures with impaired awareness, drop attacks, tonic-clonic seizures, and generalized tonic episodes. Repeated or slightly prolonged seizures were vigorously treated with diazepam rectal. He remained well controlled on valproate, topiramate, and clobazam for 10 years, except for occasional myoclonic jerks. Through this decade, all EEGs demonstrated slow background rhythms, without epileptiform activity, while brain imaging, chromosomal analysis, and detailed neurometabolic testing were normal, as was the genetic testing through array comparative genomic hybridization and also for Angelman and Prader-Willi syndrome.

At 15 years of age, he had a new focal tonic seizure, and the EEG showed epileptiform activity at C4, P4, T4, and T6 electrodes. At that time, the patient underwent together with the parents whole-exome sequencing testing (trio-whole-exome sequencing), which revealed the heterozygous presence of a novel c.226A>C (p.Ser76Arg) missense variant/mutation of the  $\gamma$ -aminobutyric acid receptor  $\alpha 1$  subunit gene in the affected child. As with case 1, the mutation was not present in either parent (*de novo* mutation), has not been previously reported in the literature, is not present in international or our local databases, and is predicted as likely pathogenic. Mutations of the  $\gamma$ -aminobutyric acid receptor

$\alpha 1$  subunit gene are known to be associated with Dravet syndrome<sup>10</sup> and with early infantile epileptic encephalopathy,<sup>12</sup> both expressed and inherited as autosomal dominant genetic disorders.

## Discussion

The authors report 2 cases within the Dravet syndrome phenotype, as defined by Guerrini and Oguni,<sup>15</sup> on the basis of their unique genetic background (Table 1). Whole-exome sequencing revealed on the one hand, a new sodium channel  $\alpha 1$  subunit mutation of high-predicted combined pathogenicity likelihood and on the other hand, a novel mutation of  $\gamma$ -aminobutyric acid receptor  $\alpha 1$  subunit, whose role in Dravet syndrome pathogenesis has recently been highlighted.<sup>10</sup>

The first patient had a rather typical Dravet syndrome presentation (Table 1) and a new, *de novo*, sodium channel  $\alpha 1$  subunit gene mutation. Mutations of sodium channel  $\alpha 1$  subunit gene are known to be associated with the expression of clinical phenotypic characteristics of Dravet syndrome and of generalized epilepsy with febrile seizures, both inherited in an autosomal dominant manner.

Although the first patient manifested a quite typical Dravet phenotype, our second patient has proven to be a diagnostic challenge, making a positive genotype-phenotype correlation difficult. He carries a novel, *de novo* mutation of the  $\gamma$ -aminobutyric acid receptor  $\alpha 1$  subunit gene. Mutations of this gene are known to be associated with Dravet syndrome<sup>10</sup> and with early infantile epileptic encephalopathy.<sup>12</sup> However, while his

**Table 2.** Phenotypic Discrepancies Among Dravet Syndrome–Related Genes.<sup>2-10</sup>

	Sodium Channel $\alpha 1$ Subunit		PCDH19	GABRG2(1)	GABRG2(2)	SCN1B(1)	SCN1B(2)	CHD2	STXBPI	$\gamma$ -Aminobutyric Acid Receptor $\alpha 1$ Subunit	Patient
Age at onset	First year, mostly 5 to 8 months of age	First year, later onset around 9.5 months of age	First year, 3 months of age	Dizygotic twins, 2 months of age	First year, 3 months of age	First year, 6 months of age	Second to fourth year of life	First year	First year	13 months of age	
Seizure type at onset	Mostly complex febrile	Febrile-GTCS, febrile-unilateral, FS	Febrile clonic FS	No data	GTCS after vaccination	Afebrile, H& Myo	Febrile seizures	Mostly febrile	Mostly febrile	Febrile generalized tonic (°4, 42° C)	
Febrile seizures	Yes	Yes (>50%)	Yes, often	No data	Yes, often	Yes	Yes	Yes	Yes	Yes	
Seizure types	Febrile, Ab, Myo, FS, H, GTCS	Febrile, GTCS, FS, H, clusters	Febrile, FS, GTCS, Ab, Myo, atonic	No data	Myo, febrile Myo	Febrile Myo, Myo, Myo-atonic, GTCS, Ab, FS (dyscognitive), clusters	Febrile, Myo, Ab, GTCS, H, FS (dyscognitive), atonic head-drops	Myo, Ab, GTCS, H, FS (dyscognitive), atonic, tonic attacks	Myo, Ab, GTCS, H, FS (dyscognitive), atonic drop attacks	FS, GTCS, Myo, Ab, tonic, drop attacks, one episode with prolonged right-sided weakness	
Seizure types missing	—	Myo, Ab (rare)	—	No data	Ab, FS	—	FS	—	—	—	
Status epilepticus	Yes; common	Rare (<50%)	Not reported	No data	Not reported	Yes, often	Yes	Yes (rare)	Yes	—	
Precipitants	Febrile illness, raised body temperature, warm environment, photic and pattern stimulation	No photic stimulation	Yes, photic stimulation	No data	No data	Yes, raised body temperature	Yes, febrile illness	Yes, febrile illness	Yes, photic stimulation, febrile illness	Yes, febrile illness	
Developmental regression	Yes, mostly after seizures onset	Yes	Yes, moderate	No data	Yes	Yes	Yes, even prior to seizures onset	Yes	Yes	Developmental plateau prior, regression after seizures onset	
Cognitive deficit	Mainly severe	Mild to moderate	Speech delay	No data	Severe	Severe	Mild	Mostly severe	Mild to moderate	Significant global developmental delay	
Motor deficit	Ataxia, pyramidal symptoms, hypotonia	Ataxia, pyramidal symptoms, hypotonia	Normal early developmental milestones achieved	No data	Yes, pronounced global hypotonia	Ataxia mostly	Normal to mild ataxia, dysarthria	Ataxia, pyramidal symptoms	Ataxia, pyramidal symptoms	Ataxia, pyramidal symptoms	

(continued)

**Table 2.** (continued)

Sodium Channel $\alpha$ I Subunit		PCDH19		GABRG2(1)		GABRG2(2)		SCNIB(1)		SCNIB(2)		CHD2		STXBPI		$\gamma$ -Aminobutyric Acid Receptor $\alpha$ I Subunit		Patient		
Autistic behavior	Yes	Rare	No	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	Yes		
Treatment	Polypharmacy, resistance	Polypharmacy, seizure remission	Polypharmacy, resistance/myoclonic exacerbation with lamotrigine	Polypharmacy, resistance	No data	Polypharmacy, resistance	No data	Polypharmacy, resistance	No data	Polypharmacy, resistance	Polypharmacy, seizure remission, exacerbation with carbamazepine	Polypharmacy, seizure remission, exacerbation with carbamazepine	Polypharmacy, seizure remission, exacerbation with carbamazepine							
EEG	Normal background, progressive deterioration/no discharges, generalized PS-SW, 2 Hz S-W predominant on one side	No data	More active overtime, irregular PS-W complexes	1st EEG with Rolandic discharges	No data	No discharges, then generalized or multifocal S-W complexes, predominantly of frontal origin	No data	Generalized SW, PS	Normal, multifocal discharges	Normal, multifocal discharges	Delta activity at onset, moderate organization with no discharges, focal discharges	Delta activity at onset, moderate organization with no discharges, focal discharges	Delta activity at onset, moderate organization with no discharges, focal discharges							
MRI	Usually normal	No data	Normal	Normal	No data	Nonspecific atrophy	No data	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal
Outcome	Psychomotor retardation, progressive neurologic signs, high mortality	Favorable	Aggressive, persisting GTCS and Ab after 17 years of age	Death at 5 months of age	One died at 3 years and 5 months of age	Psychomotor retardation, persisting GTCS	No data	Mild to moderate psychomotor retardation, some persisting GTCS	Normal, nonspecific atrophy	Mild to moderate psychomotor retardation, progressive neurologic signs	Mild to moderate psychomotor retardation, progressive neurologic signs	Mild to moderate psychomotor retardation, progressive neurologic signs	Mild to moderate psychomotor retardation, progressive neurologic signs							

Abbreviations: Ab, absence; ADHD, attention deficit hyperactivity disorder; EEG, electroencephalogram; FS, focal seizure; GTCS, tonicoclonic seizure; H, hemiclonic; Myo, myoclonic; PS, polyspike; S, spike; SE, status epilepticus; W, wave.

phenotype combines some of the key features of the syndrome, there are important aberrations, regarding the age at onset, type of seizures, EEG findings, and response to therapy. Therefore, he can be considered as an atypical Dravet syndrome phenotype.

By reviewing the available literature, the authors concluded that phenotypic discrepancies are usual among patients with Dravet syndrome carrying atypical, non-sodium channel  $\alpha 1$  subunit mutations, as presented in Table 2. The age at onset ranges from the first to fourth year of life; mandatory types of seizures, such as myoclonic and focal seizures or status epilepticus can be absent or rare; and exceptional types such as atonic seizures and drop attacks can be manifested. Polypharmacy resistance is usually present, but it can be followed by subsequent seizure remissions in some patients, whereas the clinical outcome can either be favorable with mild cognitive and motor deficits or devastating leading to syndrome-related death.

The authors came to wonder whether in the light of modern molecular technologies and the subsequent understanding of the complexity of the numerous genotype–phenotype correlations, the authors should more suitably refer to Dravet syndrome as a “spectrum.” This term combines all the typical and atypical clinical cases and their variable genetic background, coiled around a key core. This core remains to be clarified. Toward this direction, in 2011, Fountain-Capal et al<sup>16</sup> claimed that no individual criterion of the International League Against Epilepsy can be 100% accurate in predicting mutations in the sodium channel  $\alpha 1$  subunit gene. According to them, the 3 criteria that best distinguish mutation-positive from mutation-negative children comprise exacerbation with hyperthermia, normal development before the onset of seizures, and the appearance of ataxia, pyramidal signs, or interictal myoclonus.<sup>16</sup> All 3 criteria are met by our own patient.

The idea of a spectrum is not novel. In 2011, Guerrini and Oguni<sup>15</sup> objected to the use of the common term “borderline Dravet syndrome” to describe nonmyoclonic or mild Dravet syndrome cases, considering these cases as phenotypes at the margins of a spectrum, whose criteria of semiology and severity should and need to be defined. Even though our second patient is not a mild form of Dravet syndrome based on his overall severe clinical presentation, the few atypical features that he has for Dravet syndrome cannot in our opinion rule out this diagnosis that covers most aspects of his severe and debilitating illness.

## Conclusion

The authors conclude that modern molecular technologies hold place in patients with severe, undiagnosed neurologic conditions, regarding early diagnosis, prognosis, genetic counselling, and targeted therapeutic decisions. Both our case reports trigger the discussion around a broader spectrum of Dravet syndrome, making its diagnosis a challenge and highlighting the importance of clinical vigilance of pediatric neurologists worldwide.

## Authors' Note

The authors confirm that they have read the *Journal's* position on issues involved in ethical publication and affirm that this report is consistent with these guidelines.

## Author Contributions

MPG contributed to design, acquisition, analysis, and interpretation; drafted the manuscript; gave final approval; and agreed to be accountable for all aspects of work ensuring integrity and accuracy. CK contributed to design, acquisition, analysis, and interpretation; drafted the manuscript; gave final approval; and agreed to be accountable for all aspects of work ensuring integrity and accuracy. CP contributed to conception and design, acquisition, analysis, and interpretation; critically revised the manuscript; gave final approval; and agreed to be accountable for all aspects of work ensuring integrity and accuracy. AP contributed to conception and design, acquisition, analysis, and interpretation; drafted and critically revised the manuscript; gave final approval; and agreed to be accountable for all aspects of work ensuring integrity and accuracy.

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## Ethical Approval

This study was part of a clinical diagnostic work-up. The families (cases 1 & 2) were seen at the authors' clinic. They received all relevant information regarding genetic testing and provided informed consent.

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