


FULL-LENGTH ORIGINAL RESEARCH

Influence of contraindicated medication use on cognitive outcome in Dravet syndrome and age at first afebrile seizure as a clinical predictor in *SCN1A*-related seizure phenotypes

Iris M. de Lange¹  | Boudewijn Gunning² | Anja C. M. Sonsma¹ | Lisette van Gemert³ | Marjan van Kempen¹ | Nienke E. Verbeek¹ | Joost Nicolai³ | Nine V. A. M. Knoers¹ | Bobby P. C. Koeleman¹ | Eva H. Brilstra¹

¹Department of Medical Genetics, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands

²The Epilepsy Institutes of The Netherlands Foundation (SEIN), Zwolle, The Netherlands

³Academical Center of Epileptology, Maastricht and Heeze, The Netherlands

Correspondence

Iris M. de Lange, Department of Medical Genetics, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands.

Email: i.m.delange-2@umcutrecht.nl

Funding information

Dutch Epilepsy Foundation, Grant/Award Number: 2017-01; Stichting Vrienden WKZ on behalf of Stichting Panta Rhei, Grant/Award Number: 1614054

Summary

Objective: Pathogenic variants in *SCN1A* can give rise to extremely variable disease severities that may be indistinguishable at their first presentation. We aim to find clinical features that can help predict the evolution of seizures into Dravet syndrome and clinical features that predict cognitive outcome in Dravet syndrome. We specifically investigate the role of contraindicated medication (CIM) as a possible modifier of cognitive decline.

Methods: A cohort of 164 Dutch participants with *SCN1A*-related seizures was evaluated. Clinical data were collected from medical records and semistructured telephone interviews. Cognitive function was classified by a child neurologist, neuropsychologist, and clinical geneticist. Several clinical variables, including duration of CIM use in the first 5 years of disease, were evaluated in univariate and multivariate analyses.

Results: A longer duration of CIM use in the first 5 years after seizure onset was significantly associated with a worse cognitive outcome at time of inclusion, and with lower interpolated intelligence quotient/developmental quotient scores after the first 5 years of disease in Dravet syndrome patients. CIM use remained a significant predictor for cognitive outcome in a multivariate regression model, as did age at the first observation of developmental delay and age at first afebrile seizure. Age at first afebrile seizure was the most accurate predictor for evolution of seizures into Dravet syndrome for the complete cohort.

Significance: Our data suggest that a longer CIM use in the first 5 years of disease can have negative effects on cognitive outcome in Dravet syndrome. An early diagnosis is essential to avoid these drugs. Furthermore, we identified age at first afebrile seizure as an important predictor for evolution of seizures into Dravet syndrome and for the severity of Dravet syndrome, which can be used to counsel parents of young patients with *SCN1A*-related seizures.

KEYWORDS

cognition, Dravet syndrome, GEFS+, *SCN1A*, sodium-channel blockers

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

© 2018 The Authors. *Epilepsia* published by Wiley Periodicals, Inc. on behalf of International League Against Epilepsy

1 | INTRODUCTION

Pathogenic variants in *SCN1A* can give rise to extremely variable disease severities.^{1–4} On the severe end of the spectrum is Dravet syndrome, characterized by intractable epileptic seizures, diminishing psychomotor development that results in mild to severe intellectual disability, and often walking difficulties and behavioral problems.^{5–8} Recently, an *SCN1A* epileptic encephalopathy that is even more severe than Dravet syndrome has been described in 9 patients.⁴ Milder phenotypes include genetic epilepsy with febrile seizures plus (GEFS+) syndrome and febrile seizures, in which intellectual disability is usually absent.^{3,9} Furthermore, there is a large phenotypic variability between Dravet syndrome patients; whereas some are severely disabled and suffer from ongoing seizures, others live much more independent lives.^{10–12} An accurate prediction of the prognosis in affected children is understandably very important to parents.

SCN1A encodes for the α -subunit of a neuronal sodium channel, Nav1.1. Pathogenic variants that lead to a complete loss of function of the channel are nearly always associated with severe phenotypes.¹³ Such variants include genomic rearrangements, splice-site, nonsense, and frameshift variants. Certain missense variants can also lead to complete loss of function when located in critical regions of the gene (eg, the pore region and voltage sensor). However, other missense variants can result in milder disturbances of channel function and thus lead to milder phenotypes, although variants causing partial loss of function or gain of function may also be associated with Dravet syndrome.^{13,14} Although missense variant location is a strong indicator for the severity of channel disruption, it still cannot fully predict the effect of the variant on channel function and phenotype.^{13,15,16} Physicochemical changes due to missense variants are similarly difficult to predict.^{15,17} Several genetic factors have already been suggested to modify the clinical outcome of *SCN1A*-related diseases, such as variants in the *SCN1A* promoter region, the 5'- and 3'-untranslated regions, and variants in other genes.^{18–20} In clinical practice, it remains difficult to predict whether a missense variant will lead to Dravet syndrome or a milder disease. A few studies have identified clinical features that can help discriminate between Dravet syndrome and milder phenotypes, such as age at seizure onset, seizure types, and number of seizures.^{16,21,22}

Studies on Dravet syndrome severity have suggested that the presence of a motor disorder, certain electroencephalographic characteristics, early myoclonia and focal seizures, more severe seizures, and an early onset of developmental delay are associated with a worse outcome.^{6,10,23–26} Perhaps even more important are studies that focus on

Key Points

- The duration of sodium channel blocker use in the first 5 years of disease may influence cognitive function in Dravet syndrome patients
- Age at first afebrile seizure is an important predictor for evolution of seizures into Dravet syndrome in *SCN1A*-positive patients
- Age at first afebrile seizure is an important predictor for Dravet syndrome severity in *SCN1A*-positive patients

factors that clinicians can influence. Although it is clear that sodium channel blockers such as lamotrigine and carbamazepine can result in more frequent or severe seizures in this patient group,^{6,27,28} and many studies have suggested a positive effect of an early diagnosis and appropriate treatment on long-term cognitive outcomes, this has not been established in large patient groups.^{10,16,29,30} Increasing knowledge about the effects of sodium channel blockers is crucial, because they are prescribed to a large proportion of patients with Dravet syndrome at some point during their disease course (21%–100%^{25,31,32}), often before a diagnosis is established.

Parents often experience great uncertainty about the prognosis of their children when a pathogenic *SCN1A* variant is found early in life, because accurate prediction of the consequences of an *SCN1A* variant is still not possible, and different *SCN1A*-related phenotypes may be indistinguishable at their first presentation. Consequently, there is still a critical necessity to identify more accurate predictors. Here, we study the effect of contraindicated medication (CIM) on cognitive function in Dravet syndrome patients (n = 104) and perform retrospective analyses of possible clinical predictors in a large cohort of Dutch patients with *SCN1A* pathogenic variants (n = 164).

2 | MATERIALS AND METHODS

2.1 | Participants

A cohort of 164 participants with *SCN1A* pathogenic variants was evaluated. A portion of this cohort (n = 124) has previously been evaluated for mosaicism.³³ We included only symptomatic participants with pathogenic variants (class V) or likely pathogenic variants (class IV) in *SCN1A*, according to the American College of Medical Genetics and Genomics criteria.³⁴ *SCN1A* variants had been detected in diagnostic laboratories (University Medical Center Utrecht, Utrecht, The Netherlands; Laboratory for

Neurogenetics, Institute Born-Bunge, University of Antwerp, Antwerp, Belgium; Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands; Duncan Guthrie Institute of Medical Genetics, Glasgow, UK) by Sanger sequencing, next generation sequencing epilepsy gene panels, whole exome sequencing, or multiplex ligation-dependent probe amplification.

All eligible individuals of at least 4 years of age known to the University Medical Center Utrecht were approached for study inclusion. We excluded patients younger than 4 years because clinical experience has shown that syndrome classification and estimation of disease severity are less reliable for younger children. Informed consent was obtained from participants or their legal caretakers, according to the Declaration of Helsinki. The study was approved by the Ethical Committee of the University Medical Center Utrecht.

2.2 | Clinical data

Detailed clinical data were collected from medical records for all participants, and from semistructured telephone interviews when possible ($n = 155$). Data on several clinical variables, depicted in Table 1, were obtained. Variables were selected based on literature and clinical experience. Afebrile seizures were defined as seizures with a body temperature $< 38^{\circ}\text{C}$, or seizures for which medical records reported “no fever” without mentioning the exact temperature. Our main outcome was cognitive function at the time of inclusion, which was classified in a consensus meeting by a child neurologist, neuropsychologist, and clinical geneticist. Cognitive function at the moment of inclusion was rated on a 5-point scale based on available data on intelligence quotient (IQ) and developmental level, adjusted for age at assessment (1 = no intellectual disability [ID]; IQ or developmental quotient [DQ] > 85 , 2 = borderline ID [IQ or DQ = 70-85], 3 = mild ID [IQ or DQ = 50-70], 4 = moderate ID [IQ or DQ = 30-50], 5 = severe or profound ID [IQ or DQ < 30]). When no (recent) IQ or DQ was available, the assessment was made based on function in school, communication, and adaptive behavior. All participants were categorized into 2 clinical subgroups: Dravet syndrome or non-Dravet syndrome. Dravet syndrome was diagnosed based on previously published criteria³⁵ and in line with recently published recommendations.³⁶ The non-Dravet group consisted of patients with either GEFS+ or febrile seizures.

2.3 | Statistical analyses

We investigated predicting factors for Dravet syndrome versus non-Dravet syndrome, and for the severity of Dravet syndrome. We specifically tested the influence of CIM

use on cognitive function. Univariate analyses were performed, and variables for which statistically significant differences between groups were observed were included in multivariate regression analyses, adjusted for age at cognitive assessment. Adjusting the models for age at cognitive assessment is necessary, because average cognition declines with older age in Dravet syndrome patients. Furthermore, sensitivity, specificity, positive and negative predictive values, and receiver operating characteristic (ROC) curves were calculated. Statistical analyses were performed using SPSS statistics software (SPSS Statistics for Windows V21; IBM, Armonk, NY, USA). All reported tests were performed 2-tailed with an alpha-level for significance of $P < .05$.

2.3.1 | Predicting factors for Dravet syndrome versus non-Dravet syndrome

Differences between the Dravet and non-Dravet groups were calculated with either Pearson chi-square test or Fisher's exact test for binary and categorical variables (type of variant, whether a patient had ever been admitted to an intensive care unit [ICU], secondary seizure types before the age of 12 months [comprising absences, myoclonias, focal seizures, and focal seizures with impaired awareness], and the presence of mosaicism for the pathogenic variant) or Mann-Whitney U test for continuous and ordinal variables (age at seizure onset and age at first afebrile seizure). A multivariate binomial logistic regression analysis was performed with statistically significant variables.

2.3.2 | Predicting and influencing factors for cognitive outcome in Dravet syndrome

Univariate binomial logistic regression analyses, adjusted for age at cognitive assessment, were performed in the subgroup of Dravet syndrome patients. Patients were divided into 2 groups: mild cognitive dysfunction (score = 1-3) and severe cognitive dysfunction (score = 4-5). The following variables were assessed: age at seizure onset, age at first afebrile seizure, age at first observation of developmental delay, variant type, whether the patient had ever been admitted to an ICU, secondary seizure types before the age of 12 months (as defined previously), the presence of mosaicism for the pathogenic *SCN1A* variant, the duration of CIM use (defined as sodium channel blockers: lamotrigine, phenytoin, carbamazepine, oxcarbazepine, vigabatrin), and age at diagnosis. The cumulative number of months CIM was used in the first 5 years after seizure onset was calculated for each patient with seizure onset at least 5 years before assessment. This time frame was chosen because cognitive decline is generally most severe in the first years following disease onset.^{6,25,26} We chose to

TABLE 1 Characteristics of the study population and univariate analyses

Variable	1a: All participants				1b: Dravet syndrome patients		
	Total	Dravet	Non-Dravet	P	Cognition score 1-3	Cognition score 4-5	P
n	164	116	48		33	83	
Age, y, median (range)	15 (4-67)	14 (4-48)	22 (4-67)		11 (4-48)	15 (4-47)	
Sex: male, n	83	65 (56%)	18 (38%)		16 (48%)	49 (59%)	
Variant type, n				<.0005			.562
Missense	87	44 (38%)	43 (90%)		14 (42%)	30 (36%)	
Pore/pore loop/voltage sensor	58	29	29		7	24	
Elsewhere	29	15	14		7	8	
Splicing	16	13 (11%)	3 (6%)		4 (12%)	9 (11%)	
Nonsense/frameshift/rearrangement	61	59 (51%)	2 (4%)		15 (45%)	44 (53%)	
Mosaicism: yes, n	9	8 (7%)	1 (2%)	.286	5 (15%)	3 (4%)	.03
Cognition score n ^a							
1	46	3 (3%)	43 (90%)		3 (9%)	0 (0%)	
2	15	10 (9%)	5 (10%)		10 (30%)	0 (0%)	
3	20	20 (17%)	0 (0%)		20 (61%)	0 (0%)	
4	31	31 (27%)	0 (0%)		0 (0%)	31 (37%)	
5	52	52 (45%)	0 (0%)		0 (0%)	52 (63%)	
Age at seizure onset, mo, median (range)	8 (1-72)	5 (1-30)	15 (4-72)	<.0005	7.6 (3-30)	5.2 (1-18)	.007
Secondary seizure types at <12 months: yes, n ^b	71	68 (59%)	3 (6%)	<.0005	13 (39%)	55 (66%)	.008
Admission to intensive care unit: yes, n	60	54 (47%)	6 (13%)	<.0005	13 (39%)	41 (49%)	.185
Age at first observation of developmental delay, n							<.0005
<12 months	15	15 (13%)	0 (0%)		1 (3%)	14 (17%)	
12-23 months	43	43 (38%)	0 (0%)		5 (16%)	38 (47%)	
24-35 months	24	23 (21%)	1 (2%)		9 (29%)	14 (17%)	
36-47 months	24	20 (18%)	4 (8%)		9 (29%)	11 (14%)	
≥48 months	15	11 (10%)	4 (8%)		7 (23%)	4 (5%)	
No delay	39	0 (0%)	39 (81%)		0 (0%)	0 (0%)	
Missing	4	4	0		2	2	
Age at first afebrile seizure, n ^c				<.0005			.001
<12 months	70	70 (65%)	0 (0%)		10 (34%)	60 (77%)	
12-23 months	31	27 (25%)	4 (9%)		15 (52%)	12 (15%)	
24-47 months	14	5 (5%)	9 (20%)		1 (3%)	4 (5%)	
≥48 months	21	5 (5%)	16 (36%)		3 (10%)	2 (3%)	
Never	16	0 (0%)	16 (36%)		0 (0%)	0 (0%)	
Missing	12	9	3		4	5	
Age at diagnosis, mo, mean		130			104	140	

(Continues)

TABLE 1 (Continued)

Variable	1a: All participants				1b: Dravet syndrome patients		
	Total	Dravet	Non-Dravet	<i>P</i>	Cognition score 1-3	Cognition score 4-5	<i>P</i>
Dravet syndrome patients with disease onset >5 years ago, n = 104					29	75	
Duration of CIM use in first 5 years of disease, mo, mean (range)		11 (0-59)			10.5 (0-56)	22 (0-59)	.015
Never used CIM, n					6 (21%)	4 (6%)	
Used CIM 1-6 months, n					9 (32%)	17 (24%)	
Used CIM 7-12 months, n					6 (21%)	10 (14%)	
Used CIM 13-24 months, n					3 (11%)	13 (18%)	
Used CIM >24 months, n					4 (14%)	27 (38%)	
Missing					1 (3%)	4 (5%)	
Interpolated IQ/DQ score after 5 years of disease, mean (range)		62 (19-100)			81 (44-100)	55 (20-96)	

Significant *P*-values are in boldface.

CIM, contraindicated medication (sodium channel blockers: lamotrigine, phenytoin, carbamazepine, oxcarbazepine, vigabatrin); DQ, developmental quotient; ID, intellectual disability; IQ, intelligence quotient.

^aBased on available data on IQ and developmental level, adjusted for age at assessment (1 = no ID [IQ or DQ > 85], 2 = borderline ID [IQ or DQ = 70-85], 3 = mild ID [IQ or DQ = 50-70], 4 = moderate ID [IQ or DQ = 30-50], 5 = severe or profound ID [IQ or DQ < 30]). When no (recent) IQ or DQ was available, the assessment was made based on function in school, communication, and adaptive behavior.

^bAbsences, myoclonias, focal seizures, and focal seizures with impaired awareness.

^cDefined as seizures with a body temperature < 38°C or seizures for which medical records reported “no fever” without mentioning the exact temperature.

analyze the duration of CIM use rather than whether CIM had ever been used, because only a small number of patients had never used CIM, thereby reducing the power of this analysis. Furthermore, we hypothesized that if CIM use is damaging, a longer use will result in more severe effects.

A multivariate binomial logistic regression analysis, adjusted for age at cognitive assessment, was performed with all statistically significant variables.

Duration of CIM use was further investigated in relation to cognitive outcome scores 1-5 (ordinal logistic regression analysis, in contrast to the previously used dichotomy 1-3 vs 4-5) and interpolated IQ/DQ scores after 5 years of disease (linear regression analysis). To obtain these approximated scores, all IQ and developmental assessment scores of each patient, conducted at different ages, were interpolated by linear regression. When the first official assessment was made >5 years after seizure onset, we used the age at which a developmental delay was first observed (by either parents or clinicians) as the first moment of decline, and IQ/DQ scores up until that age were estimated to be average (=100). The duration of CIM use may depend on disease severity. To avoid confounding, clinical variables that were shown to have significant predictive value in our main analysis were added to these last 2 regression models.

We furthermore analyzed the effects of CIM use in year 1, 2, 3, 4, and 5 after seizure onset separately in univariate

and multiple regression analyses, to investigate whether different effects are seen in different years.

3 | RESULTS

The characteristics of the study population are depicted in Table 1a, Table 1b, Table 2, and Figure 1A. The Dravet syndrome subgroup consisted of 116 patients, and the non-Dravet group of 48. The median ages of the participants were 14 and 22 years, respectively. Almost half of all Dravet syndrome patients had a cognition score of 5 (45%), whereas almost all non-Dravet patients had normal cognitive capacities (score = 1, 90%) except for 5 who had a slight delay (score = 2, 10%). In 104 Dravet syndrome patients, seizure onset was at least 5 years prior to cognitive assessment. After 5 years of disease, the average interpolated IQ/DQ score was 62 and the median duration of CIM use was 11 months. Patients older than 12 years were more likely to have used CIM for longer periods of time and to be diagnosed at a later age. It was not possible to accurately perform an ordinal logistic regression analysis with age at diagnosis as a variable and the cognitive score as outcome, as there was a very strong multicollinearity between age at diagnosis and age at cognitive assessment (variance inflating factor = 15.375; Figure S1). Due to this strong linear relation (ie, older patients had

been diagnosed at a later age), it is difficult to calculate the separate contributions of each variable to the outcome. Because a younger age at diagnosis can only positively influence outcome if clinical management is adjusted, we focused on the duration of CIM use instead.

3.1 | Predicting factors for Dravet syndrome versus non-Dravet syndrome

Five tested variables showed a significant difference between the Dravet syndrome and non-Dravet subgroups in univariate analyses (all $P < .0005$; Table 1a). Missense variants were the predominant variant type in non-Dravet patients (90%), and nonsense/frameshift/rearrangements were present in half of Dravet syndrome patients (51%). Dravet syndrome patients had a significantly earlier age of seizure onset (median 5 vs 12 months), more often had secondary seizure types before the age of 12 months (59% vs 6%), and were more likely to have been admitted to an ICU (47% vs 12%). Additionally, Dravet syndrome patients had their first afebrile seizure at an earlier age, with 65% before 12 months, whereas 36% of non-Dravet patients experienced their first afebrile seizure only after 48 months and 36% never had an afebrile seizure. Specificity, sensitivity, positive and negative predictive values, and ROC areas of all 5 significant variables are shown in Table S1a. Occurrence of a first afebrile seizure before the age of 24 months was shown to be the best predictor for Dravet syndrome, with a positive predictive value of 96% and a negative predictive value of 81%.

TABLE 2 CIM use in Dravet syndrome patients per age group

Dravet syndrome patients with disease onset >5 years ago, n = 104	5-8 years	9-12 years	13-16 years	17-20 years	21+ years
n	12	22	24	9	32
CIM use in first 5 years of disease, mo					
Mean	2.6	10.3	23.1	31.9	23.7
Median	1.5	7.5	14	40	21.5
Range	0-11	0-34	0-56	1-57	0-59
Missing	0	0	0	0	5
Age at diagnosis, mo					
Mean	26	39.6	74.8	117	239.6
Median	19.5	31.5	66	110	239
Range	12-90	10-115	39-135	83-148	110-516
Used CIM, prescribed at some point during the disease course to % of patients					
Lamotrigine	25	64	92	100	63
Phenytoin	33	36	67	56	47
Carbamazepine	33	45	71	89	88
Oxcarbazepine	0	23	29	33	22
Vigabatrin	0	9	21	44	50

CIM, contraindicated medication (sodium channel blockers).

The multivariate binomial logistic regression model, including all 5 significant variables, showed that the variables most significantly associated with Dravet syndrome were age at first afebrile seizure ($P < .0005$), a truncating or splice-site variant ($P = .006$), and admittance to an ICU ($P = .039$; Table 3a).

3.2 | Predicting and influencing factors for cognitive outcome in Dravet syndrome

Six variables analyzed in univariate binomial regression analyses differed significantly between the mild and severe groups of Dravet syndrome patients: mosaicism of the pathogenic variant ($P = .03$), age at seizure onset ($P = .007$), secondary seizure types before the age of 12 months ($P = .008$), age at first observation of developmental delay ($P < .005$), age at first afebrile seizure ($P = .001$), and the duration of CIM use in the first 5 years of disease ($P = .015$; Table 1b). Specificity, sensitivity, positive and negative predictive values, and ROC areas of all 6 significant models are shown in Table S1b. Age at first observation of delay and age at first afebrile seizure without fever were the best clinical predictors (ROC area under curve = 0.797 and 0.792, respectively).

The multivariate binomial logistic regression model, including all 6 statistically significant variables, showed that the best predictors for a worse cognitive outcome were age at first observation of developmental delay ($P = .004$), age at first afebrile seizure ($P = .019$), and duration of CIM use ($P = .022$; Table 3b).

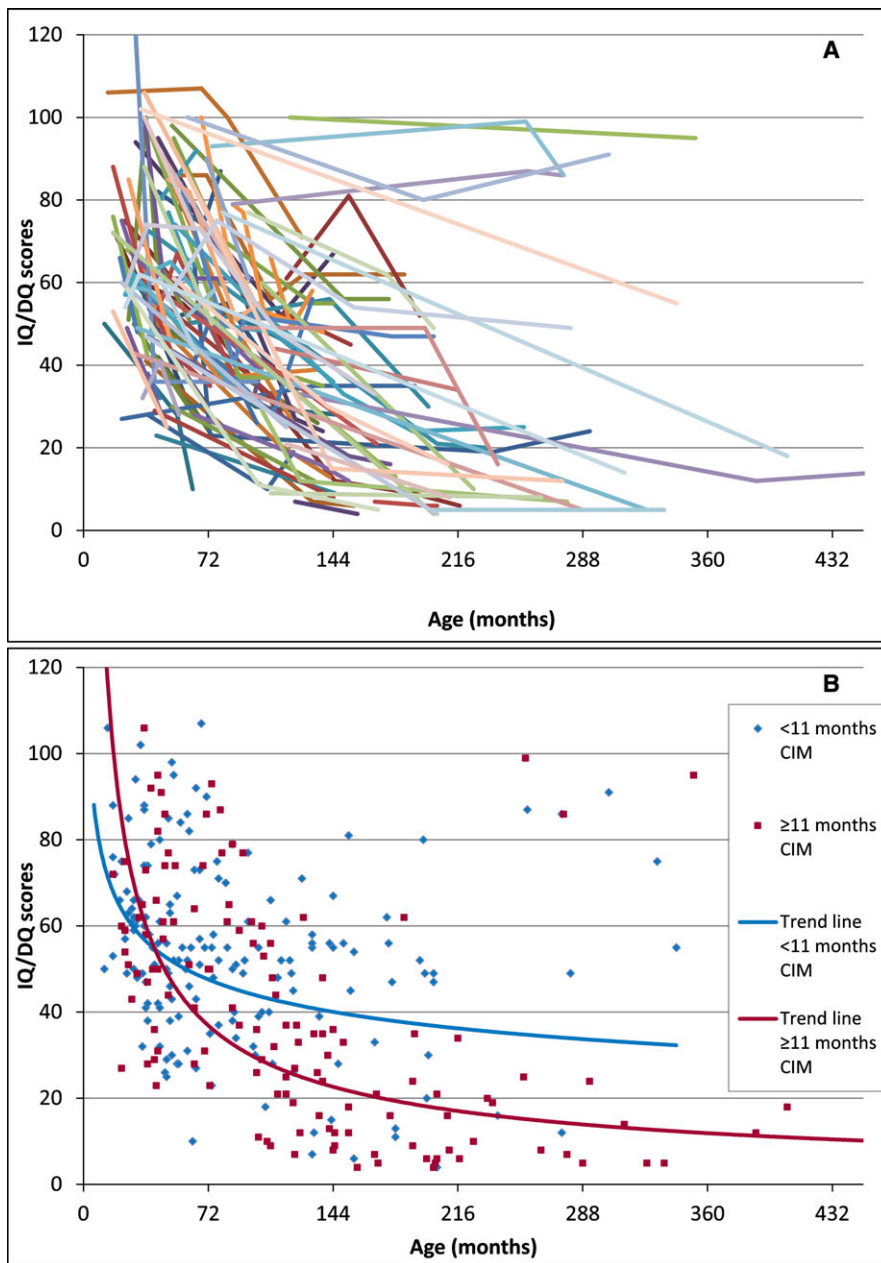


FIGURE 1 A, Decline of cognitive capacities of Dravet syndrome patients during their disease course, measured by interpolated intelligence quotient (IQ)/developmental quotient (DQ) scores. B, All measured IQ/DQ scores of the Dravet syndrome patients, divided into shorter and longer duration of contraindicated medication (CIM) use in the first 5 years of disease (blue, <11 months CIM; red, ≥11 months CIM). Trend lines were fitted for both groups

Ordinal logistic regression analysis, corrected for age at inclusion, age at first observation of developmental delay, and age at first afebrile seizure, showed a significantly higher chance of a worse cognitive outcome category score with a longer duration of CIM use ($P = .001$; Table 3c, Figure 2). Linear regression analysis, corrected for age at first observation of developmental delay and age at first afebrile seizure, showed that a longer duration of CIM use was also a significant predictor for a lower interpolated IQ/DQ score 5 years after disease onset ($B = -0.267$, $P = .010$; Table 3d, Figures 1B and 3). Repeated analyses, to investigate whether the use of estimated data for the interpolated IQ/DQ scores may have influenced our results, yielded very similar results:

$B = -0.237$, $P = .05$ without the 29 patients for whom estimated IQ/DQ scores were used, and $B = -0.244$, $P = .011$ when the IQ/DQ scores before the first notice of delay were estimated to be 85 instead of 100. We furthermore found the strongest effect for the second year of disease when analyzing the first 5 years separately ($B = 1.961$, $P = .002$; Table S2).

4 | DISCUSSION

We studied several clinical variables in patients with pathogenic *SCN1A* variants to determine those that can be used as predictors for the development of Dravet syndrome and its

TABLE 3 Regression analyses

Variable	3a. Outcome: Dravet syndrome vs non-Dravet; binomial regression, all non-Dravet patients (Nagelkerke $R^2 = 0.831$)			3b. Outcome: "mild" vs "severe" cognitive dysfunction; binomial regression, Dravet syndrome patients with disease onset >5 years ago (Nagelkerke $R^2 = 0.647$)			3c. Outcome: cognition scores at inclusion (1-5) ^a ; ordinal regression, Dravet syndrome patients with disease onset >5 years ago ($\chi^2 = 51.84$)			3d. Outcome: interpolated IQ/DQ scores after 5 years of disease; linear regression, Dravet syndrome patients with disease onset >5 years ago ($R^2 = 0.386$)		
	Odds ratio	95% CI	P	Odds ratio	95% CI	P	Odds ratio	95% CI	P	B	95% CI	P
Age at inclusion	1.074	0.992-1.162	.077	1.250	1.050-1.488	.012	1.105	1.036-1.179	.002			
Age at first seizure	0.956	0.824-1.110	.558	0.919	0.657-1.284	.620						
Age at first afebrile seizure ^b	0.101	0.035-0.287	< .0005	0.341	0.139-0.835	.019	0.644	0.380-1.093	.103	3.658	-0.920 to 8.236	.116
ICU admittance	6.044	1.097-33.294	.039									
Secondary seizure types at <12 months ^c	5.450	0.655-45.354	.117	0.275	0.056-1.358	.113						
Variant type, truncating/splice-site vs missense	16.591	2.253-122.178	.006									
Age at first observation of developmental delay				0.238	0.089-0.636	.004	0.394	0.255-0.607	< .0005	9.510	6.104-12.917	< .0005
Mosaicism				1.981	0.110-35.552	.643						
Duration of CIM use in first 5 years of disease				1.091	1.012-1.175	.022	1.057	1.022-1.092	.001	-0.267	-0.469 to -0.065	.010

Significant P-values are in boldface. CI, confidence interval; CIM, contraindicated medication (sodium channel blockers: lamotrigine, phenytoin, carbamazepine, oxcarbazepine, vigabatrin); DQ, developmental quotient; ICU, intensive care unit; ID, intellectual disability; IQ, intelligence quotient.

^aBased on available data on IQ and developmental level, adjusted for age at assessment (1 = no ID [IQ or DQ > 85], 2 = borderline ID [IQ or DQ = 70-85], 3 = mild ID [IQ or DQ = 50-70], 4 = moderate ID [IQ or DQ = 30-50], 5 = severe or profound ID [IQ or DQ < 30]). When no (recent) IQ or DQ was available, the assessment was made based on function in school, communication, and adaptive behavior.

^bDefined as seizures with a body temperature < 38°C or seizures for which medical records reported "no fever" without mentioning the exact temperature.

^cAbsences, myoclonias, focal seizures, and focal seizures with impaired awareness.

severity. The most novel finding of our study is negative influence of longer CIM use on cognition in Dravet syndrome patients. Previous studies have suggested that appropriate treatment may have a positive effect on long-term cognitive outcomes in Dravet syndrome.^{10,16,29,30} To our knowledge, only one study tried to correlate CIM to cognitive outcomes and found no effect²⁵; however, only 17 participants (25%) had used CIM and none of them had taken it for >3 months. In our current study, 86% of Dravet syndrome patients had used CIM and the median duration of use in the first 5 years of disease was 11 months. We identify a significantly higher probability of a worse cognitive outcome, as well as a more severe cognitive decline in the first 5 years of the disease, when CIM was used for longer periods of time. Although reliable data on seizure frequency during CIM use are not available for our cohort, increases in seizure frequency due to sodium channel blocker use have been reported previously.^{6,27,28} High seizure frequency has been associated with a worse cognitive outcome in Dravet syndrome patients,^{26,37} and similar findings have recently been shown in *SCN1A*+ mice.³⁸ Furthermore, if CIM is used, indicated medication is less likely to be prescribed, and therefore the negative effects of CIM can also partly be due to the deprivation of optimal treatment. It is therefore likely that an increased seizure severity, at least to some extent, explains the worse cognitive outcome associated with longer CIM use, in accordance with the epileptic encephalopathy disease model. However, because we did not observe an association between longer CIM use and ICU admittances (data not shown), the worse cognitive

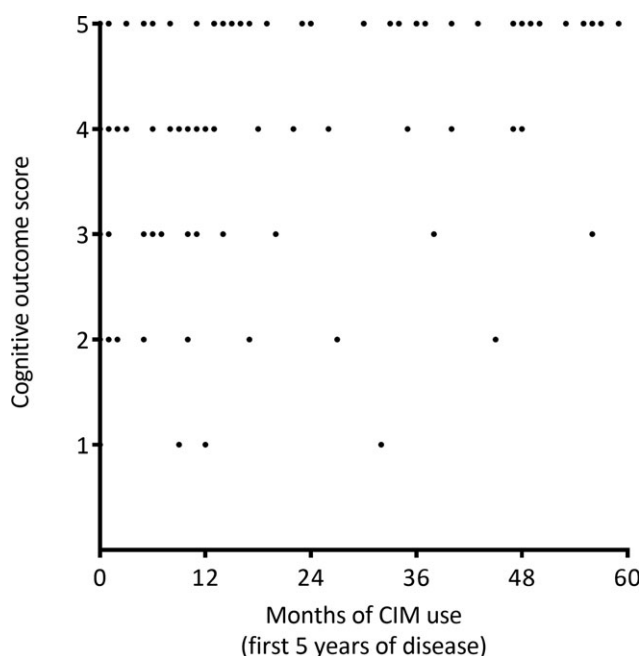


FIGURE 2 Duration of contraindicated medication (CIM) use by Dravet syndrome patients during the first 5 years of disease, divided into cognitive outcome categories

outcome is probably not due to an increase in status epilepticus. Furthermore, multiple authors have suggested that cognition in Dravet syndrome patients declines independent of seizures due to the direct impact of sodium channel dysfunction on cognitive processes,^{25,39} which may also explain the negative effects of CIM use on cognition. We specifically observed the largest effect of CIM use in the second year of disease, indicating that the developing brain might be particularly sensitive to CIM during this time frame. This finding emphasizes the importance of an early diagnosis and correct clinical management as soon as possible in the disease course. We suggest that *SCN1A* analysis should be considered in every child with atypical febrile seizures at the moment that maintenance treatment is indicated. Not surprisingly, older patients were more likely to be diagnosed at a later age and to have used CIM for a longer period of time, likely due to the upcoming availability of *SCN1A* genetic testing and evolving insights regarding best treatments. Better cognitive outcomes and a shorter duration of CIM use are to be expected if a younger and more recent cohort would be studied. Future research could therefore also focus on the effects of indicated treatment in this patient group.

There are a few limitations to our strategy of IQ/DQ interpolation. Different testing methods have been used, and IQ scores are not necessarily completely comparable to DQ scores. Furthermore, interpolated values become less reliable as the difference between the ages at which the tests are performed increases, as deterioration might not have been linear but might have fluctuated or was logarithmic instead. This can especially be a problem when a first assessment is performed a long time after a period of steep decline. Most importantly, it is likely that development had already begun to decrease before it was first observed by parents or clinicians, and although the assumption of an IQ/DQ of 100 before this moment might be correct for the group as a whole, in reality individual scores will differ. However, the same estimation was made for patients with longer and shorter CIM use and it therefore has probably not affected our results; repeated analyses without the 29 patients for whom estimated IQ/DQ scores were used and analyses in which the IQ/DQ scores before the first observation of delay were estimated to be 85 instead of 100 yielded very similar results. Ideally, CIM use should be tested in a prospective cohort with regular IQ/DQ assessments at similar ages for all participants, including an assessment before developmental delay is present. However, because of the known negative effects of CIM use, this is not ethically responsible. Our method, although probably not completely accurate, seems to lead to a close approximation of the real situation, as all different approaches, including our main analysis, show the same effect of CIM use on cognition.

A previous study has suggested that older patients respond differently to CIM use than younger patients.⁴⁰

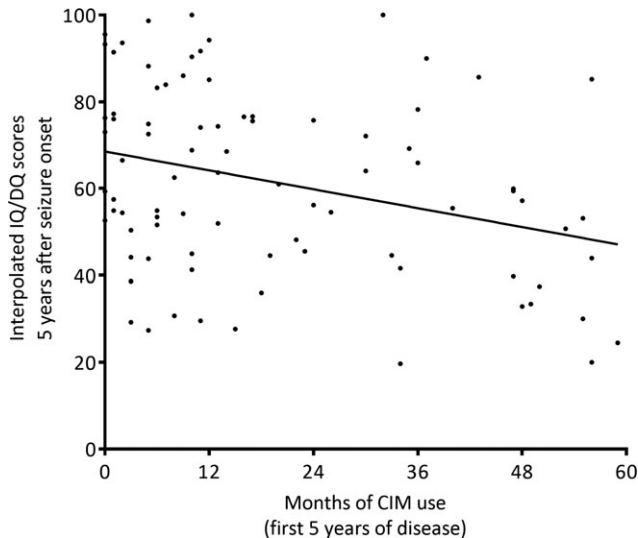


FIGURE 3 Relationship of interpolated intelligence quotient (IQ)/developmental quotient (DQ) scores and duration of contraindicated medication (CIM) use by Dravet syndrome patients after 5 years of disease

Although there is anecdotal evidence for improved cognition after withdrawal of CIM following long-term use in adults,³⁷ there are also adult patients in whom CIM discontinuation cannot be established because of increased seizure severity.⁴⁰ It is hypothesized that this could be due to secondary lesions or compensatory mechanisms after a long disease course, leading to seizures that respond to sodium channel blockers.⁴⁰ Eighty-one percent of adults in our cohort have a severe or profound intellectual disability (score = 4-5), and only one patient had never used CIM. The small group of mildly affected participants (score = 1-3, $n = 8$) gives us little power to show an effect of CIM use in adulthood. We can therefore not state whether continued CIM use at higher ages results in further cognitive deterioration. Ideally, a cohort of adults would be analyzed prospectively, with functional assessment before and after withdrawal. If discontinuing CIM in adult patients is shown to have a positive effect on function or reduces further decline, this would advocate for changing medication even in patients who have acceptable seizure control at the moment of diagnosis.

Although CIM seems to be able to influence cognitive outcomes, it only explains a small part of the differences in cognitive capabilities; adding duration of CIM use to the multivariate binomial regression model increased the explained variance by 14% (Nagelkerke R^2 : from 0.498 to 0.647). There are many patients who have used CIM for only short periods of time and still have a severe cognitive outcome, and IQ/DQ scores after 5 years of disease ranged over 60 IQ/DQ points for participants who had used CIM for almost the complete duration of that period. It is very likely that other genetic factors have a substantial influence

on cognitive outcomes and also on responses to CIM, as multiple genetic modifiers have already been implicated to influence *SCN1A* phenotypes^{18-20,33} and responses to antiepileptic medication in general.⁴¹ Further research investigating the role of other genetic modifiers and pharmacogenetics is needed. However, even if CIM use is responsible for only a small part of cognitive decline, it should still be avoided to optimize disease courses in individual patients. An early diagnosis is crucial in achieving this result.

We have also studied several other clinical variables in patients with pathogenic *SCN1A* variants. We identified that having a first afebrile seizure at a young age is the most significant predictor for seizures to evolve into Dravet syndrome; 96% of patients experiencing afebrile seizures before age 24 months developed Dravet syndrome, in contrast to 20% of patients who did not. Age at the first afebrile seizure was shown to be a better predictor than age at seizure onset, a variable that was previously mentioned as the most relevant parameter associated with Dravet syndrome.²¹ Having a truncating or splice-site variant, a well-known predictor,¹³ added significant predictive value to the regression model, as was expected. ICU admittances were also significantly associated with the outcome. Interestingly, 6 non-Dravet syndrome patients (13%) also experienced ICU admittances. These patients were not classified as having Dravet syndrome because of their readily achieved seizure control and absence of intellectual disability at the time of inclusion. Having secondary seizure types at a young age, previously described as having predictive value,^{16,22} was in our cohort only significant in univariate analysis.

A younger age at first afebrile seizure was also shown to be a significant predictor in analyses of the cognitive outcome in Dravet syndrome, together with a longer duration of CIM use and an earlier onset of developmental delay. Although age at the start of developmental delay was already identified as a significant prognostic factor,⁶ age at first afebrile seizure was not mentioned in previous studies. That age at the first afebrile seizure is a significant predictor for distinguishing between Dravet syndrome and non-Dravet syndrome, as well as for the severity of Dravet syndrome itself, provides support for the theory that febrile seizures, GEFS+, and Dravet syndrome are all part of the same disease spectrum, as previously proposed.^{16,42} Having secondary seizure types at an early age, another variable that was found to be significant in other studies,^{6,23,25} was again only significant in a univariate analysis.

5 | CONCLUSION

Our data suggest that longer use of CIM in the first 5 years of disease may have negative effects on cognitive outcomes in Dravet syndrome patients and should therefore be

avoided. An early diagnosis is essential to achieve this result. The negative effect of CIM might be mediated through a direct impact on cognitive processes and/or an increased seizure frequency, caused by the medication itself or by deprivation of indicated treatment. We furthermore identified age at first afebrile seizure as an important predictor for evolution of seizures into Dravet syndrome, as well as for the severity of Dravet syndrome, which can be used to counsel parents of young patients with *SCN1A*-related seizures.

ACKNOWLEDGMENT

This study was supported by Stichting Vrienden WKZ (project 1614054) on behalf of Stichting Panta Rhei, and the Dutch Epilepsy Foundation (project 2017-01).

DISCLOSURE OF CONFLICTS OF INTEREST

B.G. has served on an advisory board for GW Pharmaceuticals (Pan-EU Advisory Board on Dravet Syndrome, on Epidiolex) and an advisory board for Zogenix (Belgium/Netherlands advisory board, on fenfluramine). None of the other authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

ORCID

Iris M. de Lange  <http://orcid.org/0000-0003-2107-9224>

REFERENCES

- Claes L, Ceulemans B, Audenaert D, et al. De novo *SCN1A* mutations are a major cause of severe myoclonic epilepsy of infancy. *Hum Mutat.* 2003;21:615–21.
- Mulley JC, Scheffer IE, Petrou S, et al. *SCN1A* mutations and epilepsy. *Hum Mutat.* 2005;25:535–42.
- Escayg A, MacDonald BT, Meisler MH, et al. Mutations of *SCN1A*, encoding a neuronal sodium channel, in two families with GEFS+2. *Nat Genet.* 2000;24:343–5.
- Sadleir LG, Mountier EI, Gill D, et al. Not all *SCN1A* epileptic encephalopathies are Dravet syndrome. *Neurology.* 2017;89:1035–42.
- Dravet C. Les epilepsies graves de l'enfant. *Vie Med.* 1978;8:543–8.
- Brunklaus A, Ellis R, Reavey E, et al. Prognostic, clinical and demographic features in *SCN1A* mutation-positive Dravet syndrome. *Brain.* 2012;135:2329–36.
- Rilstone JJ, Coelho FM, Minassian BA, et al. Dravet syndrome: seizure control and gait in adults with different *SCN1A* mutations. *Epilepsia.* 2012;53:1421–8.
- Gitiaux C, Chemaly N, Quijano-Roy S, et al. Motor neuropathy contributes to crouching in patients with Dravet syndrome. *Neurology.* 2016;87:277–81.
- Catterall WA, Kalume F, Oakley JC. Na^v 1.1 channels and epilepsy. *J Physiol.* 2010;588:1849–59.
- Akiyama M, Kobayashi K, Yoshinaga H, et al. A long-term follow-up study of Dravet syndrome up to adulthood. *Epilepsia.* 2010;51:1043–52.
- Harkin LA, McMahon JM, Iona X, et al. The spectrum of *SCN1A*-related infantile epileptic encephalopathies. *Brain.* 2007;130:843–52.
- Jansen F, Sadleir L, Harkin L, et al. Severe myoclonic epilepsy of infancy (Dravet syndrome): recognition and diagnosis in adults. *Neurology.* 2006;67:2224–6.
- Meng H, Xu HQ, Yu L, et al. The *SCN1A* mutation database: updating information and analysis of the relationships among genotype, functional alteration, and phenotype. *Hum Mutat.* 2015;36:573–80.
- Rhodes TH, Lossin C, Vanoye CG, et al. Noninactivating voltage-gated sodium channels in severe myoclonic epilepsy of infancy. *Proc Natl Acad Sci U S A.* 2004;101:11147–52.
- Zuberi SM, Brunklaus A, Birch R, et al. Genotype-phenotype associations in *SCN1A*-related epilepsies. *Neurology.* 2011;76:594–600.
- Ceulemans BPGM, Claes LRF, Lagae LG. Clinical correlations of mutations in the *SCN1A* gene: from febrile seizures to severe myoclonic epilepsy in infancy. *Pediatr Neurol.* 2004;30:236–43.
- Kanai K, Yoshida S, Hirose S, et al. Physicochemical property changes of amino acid residues that accompany missense mutations in *SCN1A* affect epilepsy phenotype severity. *J Med Genet.* 2009;46:671–9.
- Ohmori I, Ouchida M, Kobayashi K, et al. *CACNA1A* variants may modify the epileptic phenotype of Dravet syndrome. *Neurobiol Dis.* 2013;50:209–17.
- Singh NA, Pappas C, Dahle EJ, et al. A role of *SCN9A* in human epilepsies, as a cause of febrile seizures and as a potential modifier of Dravet syndrome. *PLoS Genet.* 2009;5:1–12.
- Long YS, Zhao QH, Su T, et al. Identification of the promoter region and the 5'-untranslated exons of the human voltage-gated sodium channel Nav1.1 gene (*SCN1A*) and enhancement of gene expression by the 5'-untranslated exons. *J Neurosci Res.* 2008;86:3375–81.
- Cetica V, Chiari S, Mei D, et al. Clinical and genetic factors predicting Dravet in syndrome in infants with *SCN1A* mutations. *Neurology.* 2017;88:1–8.
- Hattori J, Ouchida M, Ono J, et al. A screening test for the prediction of Dravet syndrome before one year of age. *Epilepsia.* 2008;49:626–33.
- Ragona F. Cognitive development in children with Dravet syndrome. *Epilepsia.* 2011;52:39–43.
- Takayama R, Fujiwara T, Shigematsu H, et al. Long-term course of Dravet syndrome: a study from an epilepsy center in Japan. *Epilepsia.* 2014;55:528–38.
- Nabbout R, Chemaly N, Chipaux M, et al. Encephalopathy in children with Dravet syndrome is not a pure consequence of epilepsy. *Orphanet J Rare Dis.* 2013;8:176.
- Wolff M, Cassé-Perrot C, Dravet C. Severe myoclonic epilepsy of infants (Dravet syndrome): natural history and neuropsychological findings. *Epilepsia.* 2006;47:45–8.

27. Guerrini R, Dravet C, Genton P, et al. Lamotrigine and seizure aggravation in severe myoclonic epilepsy. *Epilepsia*. 1998;39:508–12.
28. Ceulemans B. Overall management of patients with Dravet syndrome. *Dev Med Child Neurol*. 2011;53:19–23.
29. Guerrini R, Falchi M. Dravet syndrome and SCN1A gene mutation related-epilepsies: cognitive impairment and its determinants. *Dev Med Child Neurol*. 2011;53:11–5.
30. Brunklaus A, Dorris L, Ellis R, et al. The clinical utility of an SCN1A genetic diagnosis in infantile-onset epilepsy. *Dev Med Child Neurol*. 2013;55:154–61.
31. Bremer A, Lossius MI, Nakken KO. Dravet syndrome—considerable delay in making the diagnosis. *Acta Neurol Scand*. 2012;125:359–62.
32. Lagae L, Brambilla I, Mingorance A, et al. Quality of life and comorbidities associated with Dravet syndrome severity: a multinational cohort survey. *Dev Med Child Neurol*. 2018;60:63–72.
33. de Lange IM, Koudijs MJ, van't Slot R, et al. Mosaicism of de novo pathogenic *SCN1A* variants in epilepsy is a frequent phenomenon that correlates with variable phenotypes. *Epilepsia*. 2018;59:690–703.
34. Richards S, Azi N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American college of medical genetics and genomics and the association for molecular pathology. *Genet Med*. 2015;17:405–24.
35. Verbeek NE, Van Der Maas NAT, Jansen FE, et al. Prevalence of SCN1A-related Dravet syndrome among children reported with seizures following vaccination: a population-based ten-year cohort study. *PLoS One* 2013;8:e65758.
36. Wirrell EC, Laux L, Donner E, et al. Optimizing the diagnosis and management of Dravet syndrome: recommendations from a North American consensus panel. *Pediatr Neurol* 2017;68:18–34.e3.
37. Catarino CB, Liu JYW, Liagkouras I, et al. Dravet syndrome as epileptic encephalopathy: evidence from long-term course and neuropathology. *Brain*. 2011;134:2982–3010.
38. Dutton SBB, Dutt K, Papale LA, et al. Early-life febrile seizures worsen adult phenotypes in *Scn1a* mutants. *Exp Neurol*. 2017;293:159–71.
39. Brunklaus A, Zuberi SM. Dravet syndrome—from epileptic encephalopathy to channelopathy. *Epilepsia*. 2014;55:979–84.
40. Snoeijen-Schouwenaars FM, Veendrick MJB, Van Mierlo P, et al. Carbamazepine and oxcarbazepine in adult patients with Dravet syndrome: friend or foe? *Seizure*. 2015;29:114–8.
41. Balestrini S, Sisodiya SM. Pharmacogenomics in epilepsy. *Neurosci Lett* 2018;667:27–39.
42. Singh R, Andermann E, Whitehouse WPA, et al. Severe myoclonic epilepsy of infancy: extended spectrum of GEFS+? *Epilepsia*. 2001;42:837–44.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

How to cite this article: de Lange IM, Gunning B, Sonsma ACM, et al. Influence of contraindicated medication use on cognitive outcome in Dravet syndrome and age at first afebrile seizure as a clinical predictor in *SCN1A*-related seizure phenotypes. *Epilepsia*. 2018;59:1154–1165. <https://doi.org/10.1111/epi.14191>