



Time Is Brain: The Importance of an Accurate SCN1A Prediction Score in the Era of Precision Medicine

Epilepsy Currents
2022, Vol. 22(4) 231-233
© The Author(s) 2022
Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/15357597221096017
journals.sagepub.com/home/epi



Danielle M. Andrade, MD¹ 

Development and Validation of a Prediction Model for Early Diagnosis of SCN1A-Related Epilepsies

Brunklaus A, Pérez-Palma E, Ghanty I, et al. *Neurology*. 2022;98(11):e1163-e1174. doi:10.1212/WNL.0000000000200028.

Background and objectives: Pathogenic variants in the neuronal sodium channel $\alpha 1$ -subunit gene (SCN1A) are the most frequent monogenic cause of epilepsy. Phenotypes comprise a wide clinical spectrum including the severe childhood epilepsy, Dravet syndrome, characterized by drug-resistant seizures, intellectual disability and high mortality, and the milder genetic epilepsy with febrile seizures plus (GEFS+), characterized by normal cognition. Early recognition of a child's risk for developing Dravet syndrome versus GEFS+ is key for implementing disease-modifying therapies when available before cognitive impairment emerges. Our objective was to develop and validate a prediction model using clinical and genetic biomarkers for early diagnosis of SCN1A-related epilepsies. **Methods:** Retrospective multicenter cohort study comprising data from SCN1A-positive Dravet syndrome and GEFS+ patients consecutively referred for genetic testing (March 2001-June 2020) including age of seizure onset and a newly-developed SCN1A genetic score. A training cohort was used to develop multiple prediction models that were validated using two independent blinded cohorts. Primary outcome was the discriminative accuracy of the model predicting Dravet syndrome versus other GEFS+ phenotypes. **Results:** 1018 participants were included. The frequency of Dravet syndrome was 616/743 (83%) in the training cohort, 147/203 (72%) in validation cohort 1 and 60/72 (83%) in validation cohort 2. A high SCN1A genetic score 133.4 (SD, 78.5) versus 52.0 (SD, 57.5; $p < 0.001$) and young age of onset 6.0 (SD, 3.0) months versus 14.8 (SD, 11.8; $p < 0.001$) months, were each associated with Dravet syndrome versus GEFS+. A combined "SCN1A genetic score and seizure onset" model separated Dravet syndrome from GEFS+ more effectively (area under the curve [AUC], 0.89 [95% CI, 0.86-0.92]) and outperformed all other models (AUC, 0.79-0.85; $p < 0.001$). Model performance was replicated in both validation cohorts 1 (AUC, 0.94 [95% CI, 0.91-0.97]) and 2 (AUC, 0.92 [95% CI, 0.82-1.00]). **Discussion:** The prediction model allows objective estimation at disease onset whether a child will develop Dravet syndrome versus GEFS+, assisting clinicians with prognostic counseling and decisions on early institution of precision therapies (<http://scn1a-prediction-model.broadinstitute.org/>). **Classification of evidence:** This study provides Class II evidence that a combined "SCN1A genetic score and seizure onset" model distinguishes Dravet syndrome from other GEFS+ phenotypes.

Commentary

Developmental and epileptic encephalopathies (DEEs) are severe, treatment-resistant epilepsies, often associated with comorbidities such as intellectual disability (ID), autism, motor and speech abnormalities. Several DEEs are monogenic epilepsies, and as such, lend themselves very well to precision medicine (PM) approaches. Based on some positive results of PM in other neurological disorders,¹ the general sense is that PM should be started very early, when the first symptoms appear, or even before symptoms are apparent. However, for early PM intervention in DEEs, more accurate genotype-phenotype correlations are urgently needed.

Dravet Syndrome (DS), the prototype of DEEs, is caused by abnormalities in the *SCN1A* gene in over 80% of cases.² However, having a pathogenic *SCN1A* mutation alone is not enough to predict whether the outcome will be DS, genetic epilepsy with febrile seizures plus (GEFS+), or another form of epilepsy, since pathogenic variants in this gene are associated with a spectrum of epilepsies with very different severities.^{3,4} Patients with DS are born without neurological deficits, and have an early normal development. Usually, in the first

¹ Adult Genetic Epilepsy Program, Division of Neurology, Faculty of Medicine, University of Toronto, Toronto, ON, Canada





6-12 months of life they start having febrile seizures, and soon they also develop afebrile seizures, of several types, often resistant to treatment with antiseizure medication (ASM). It is only months to years after the onset of seizures that other comorbidities such as ID and autism become evident, and the typical DS phenotype is recognized. On the other hand, patients with GEFS+ have febrile and afebrile seizures in the first decade of life, many outgrow those seizures and they often have a normal intelligence or only mild ID. It had been previously demonstrated that in patients with *SCN1A* variants, the risk of developing DS was higher if seizure onset was in the first 12 months of life, whereas the risk of GEFS+ was higher if seizure onset happened after the first 12 months.⁵

Today, patients presenting with a first prolonged or atypical febrile seizure often have a genetic test. But even when a pathogenic *SCN1A* variant is found, one cannot predict if the phenotype will be DS or GEFS+. It is the clinical evolution, that is, the response to treatment and the appearance of neurodevelopmental delay over the next few years that will reveal the phenotype associated with that genetic abnormality. And why it is important to determine the phenotype as soon as the genetic variant is found? Because some forms of PM (such as antisense oligonucleotides (ASOs)) are not just antiseizure treatments, but are disease-modifying therapies that can potentially decrease the risk of premature mortality, and the earlier the treatment starts, the better the results.⁶

In the work of Brunklaus and colleagues a prediction model of *SCN1A*-related epilepsies has been created.⁷ Such a prediction model may be useful in clinical practice to determine who should receive ASM and even PM intervention as early as at the time of the first seizure.

In this retrospective, multicenter study, the authors collected genetic and clinical information in 1018 patients with pathogenic variants in *SCN1A*. They then developed a *SCN1A* genetic scoring system that, when combined with age of onset of seizures, could predict whether a particular patient was likely to develop a DS or GEFS+ phenotype.

To develop the genetic score, Brunklaus and colleagues analyzed *SCN1A* pathogenic variants in a large group of patients with DS and GEFS+. Missense and protein truncating variants (PTVs) were prioritized. Patients who carried variants that could not be predicted to be pathogenic (such as splice variants, in-frame small deletions/insertions and synonymous variants) were excluded. The score was generated based on: (A) the paralog conservation of the mutated amino acid position, using 10 aligned genes encoding sodium channel alpha 1-11 subunits *SCN1A* to *SCN11A*; and (B) the physicochemical properties of the amino acid substitution (Grantham score). Higher scores were seen in genes with both variants in positions that were most conserved throughout the 11 genes coding sodium channel alpha subunits, and where the amino acid substitution was more likely to cause protein damage. The genetic score was then combined with the age of seizure onset (in months).

The “*SCN1A* score & Onset” model was applied to a training cohort of 743 patients, 83% of whom had DS. It was then applied to a blinded validation cohort 1 (203 patients, 72% with

DS) and to a blinded validation cohort 2 (72 patients, 83% with DS). Results showed that “A high *SCN1A* genetic score 133.4 (SD, 78.5) vs 52.0 (SD, 57.5; $P < .001$) and young age of onset 6.0 (SD, 3.0) months vs 14.8 (SD, 11.8; $P < .001$) months, were each associated with Dravet syndrome vs GEFS+.”

This is a very robust study with a large initial number of patients (1018) from Europe and Australia, who were clinically diagnosed as having DS or GEFS+ by experts in the field. It is very important to note that the present model outperformed other models based on genetic pathogenicity scores.^{8,9} This study also showed, through dominance analysis, that “the age of seizure onset was 2.06 times more important than the *SCN1A* genetic score to the overall model.”

However, there are still some gaps. As the clinical manifestations of *SCN1A* pathogenic variants represent a spectrum of symptoms, some patients who had a phenotype milder than classic DS, but more severe than typical GEFS+ might not have been included in this study. In addition, 14% of patients in the training cohort carried variations that were not clearly pathogenic, and had to be excluded. No patients with DS had PTV beyond amino acid position 1930, suggesting that terminal truncating variants are not subjected to nonsense mediated decay. The cohort was predominantly Caucasian, and it is unclear if the model can be translated to other ethnicities. In addition, the cohort was more heavily weighted toward patients with DS than GEFS+. Other unknown variables such as the genetic background (which might increase or lower seizure and ID threshold) could not be evaluated. Epigenetic and environmental factors such as diet, increased developmental stimulation/therapies, or use of contraindicated drugs such as sodium channel blockers were also not evaluated.

Despite the shortcomings mentioned above, the creation of this “*SCN1A* score & onset” model is a significant advancement in our knowledge of who may or may not develop DS. Furthermore, this model stands to have a significant impact in clinical decision making: moving from “should I start an ASM in this patient?” to “should I start a PM, disease-modifier treatment, before all symptoms are apparent?”

Since time is brain, having objective and quantifiable data at an earlier age may have significant clinical impact. For instance, it is known that seizures in a young, developing brain may contribute to the ID observed in DS. However, it is possible that *SCN1A* haploinsufficiency alone may contribute to the cognitive and behavioral problems seen in these patients.¹⁰ Therefore, simply controlling the seizures would not avoid the ID phenotype. A prediction score like the one presented here could be the tool that will lead to the early initiation of PM and ultimately lead to important changes in the disease trajectory. More prediction scores need to be developed for the other forms of monogenic DEEs so that more patients will have a better chance at a better life.

ORCID iD

Danielle M. Andrade  <https://orcid.org/0000-0003-0953-2698>



References

1. Finkel RS, Chiriboga CA, Vajsar J, et al. Treatment of infantile-onset spinal muscular atrophy with nusinersen: a phase 2, open-label, dose-escalation study. *Lancet*. 2016;388(10063):3017-3026.
2. Marini C, Scheffer IE, Nabbout R, et al. The genetics of Dravet syndrome. *Epilepsia*. 2011;52:24-29.
3. 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(4):343-345.
4. Claes L, Del-Favero J, Ceulemans B, Lagae L, Van Broeckhoven C, De Jonghe P. De novo mutations in the sodium-channel gene SCN1A cause severe myoclonic epilepsy of infancy. *Am J Hum Genet*. 2001;68(6):1327-1332.
5. Cetica V, Chiari S, Mei D, et al. Clinical and genetic factors predicting Dravet syndrome in infants with SCN1A mutations. *Neurology*. 2017;88(11):1037-1044.
6. Han Z, Chen C, Christiansen A, et al. Antisense oligonucleotides increase Scn1a expression and reduce seizures and SUDEP incidence in a mouse model of Dravet syndrome. *Sci Transl Med*. 2020;12(558):eaaz6100.
7. Brunklaus A, Pérez-Palma E, Ghanty I, et al. Development and Validation of a Prediction Model for Early Diagnosis of SCN1A-Related Epilepsies. *Neurology*. 2022;98:e1163-e1174.
8. Rentzsch P, Witten D, Cooper GM, Shendure J, Kircher M. CADD: predicting the deleteriousness of variants throughout the human genome. *Nucleic acids research*. 2019;47(D1):D886-D894.
9. Ioannidis NM, Rothstein JH, Pejaver V, et al. REVEL: an ensemble method for predicting the pathogenicity of rare missense variants. *Am J Hum Genet*. 2016;99(4):877-885.
10. Guerrini R, Falchi M. Dravet syndrome and SCN1A gene mutation related-epilepsies: cognitive impairment and its determinants. *Dev Med Child Neurol*. 2011;53:11-15.