# The Role of Genetic Factors in Electroclinic and Therapeutic Effectiveness in Children with Dravet Syndrome: A Multi-Center Cohort Study

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## INTRODUCTION

Dravet Syndrome (DS) also known as Severe Myoclonic Epilepsy of Infants is an early-onset encephalopathy accounting for 1.4% of pediatric epilepsy cases. Incidence of approximately 1 in 12,200 to 1 in 40,900 live-births. DS typically manifests around the first year of life with prolonged, febrile & afebrile seizures, developmental delay becomes apparent from around the second year of life and severe intellectual disability in most adults. The disease is also linked with increased mortality mainly due to sudden unexpected death in epilepsy. Over 80% of cases are due to a de novo mutation in one allele of the SCN1A gene, which encodes the α-subunit of the voltage-gated ion channel NaV1.1.

## OBJECTIVES

Although pharmacological and dietary treatment modalities exist for patients with DS who are the prototype of drug-resistant developmental epileptic encephalopathies, they are often inadequate. The association of DS with genetics and approaches to it have led to new developments in recent years. We aimed to determine the electroclinical features and neurodevelopmental comorbidities and the effectiveness of first and second-generation anti-seizure medication (ASM) in treatment success in cases with genetic mutations.

## MATERIALS METHODS

- After the approval of the ethics committee, a total of 70 patients aged between 1 month and 18 years from 5 centers were included between January 1, 2010 and January 1, 2022.
- Demographic characteristics of patients, neuromotor developmental stages, neurological examination findings, comorbidities, seizure semiology, electroencephalography and magnetic resonance findings, genetic mutations, anti-seizure drugs, relationship between genetic mutation and treatment response, seizure freedom and SUDEP rates examined.
- Patients in the appropriate age range, who met the clinical diagnostic criteria of DS and who were found to be genetically positive for DS were included in the study. Patients under the age of one month and over 18 years of age and those who did not have sufficient clinical and laboratory information in their files were not included in the study.
- Analysis of data: SPSS 26.0 was used for statistical analysis. Descriptive statistics of evaluation results; numbers and percentages were given for categorical variables, mean, standard deviation, minimum and maximum were given for numerical variables. The conformity of the data to the normal distribution was determined by Kolmogorov-Smirnov and Shapiro-Wilk. Pearson Chi-square or Fisher's Exact Test was used to compare categorical variables, and Mann-Whitney U test was used to compare numerical variables. McNemar-Bowker Test was used to determine the difference between seizure frequency before medication and seizure frequency after medication. In all statistical analyses, the significance value was taken as $p<0.05$.

## RESULTS

- Mean age 13.52 ± 0.51 (1-24), 58.6% (n:41) female gender
- Average follow-up time 42 months (3 to 190 months)
- Clinical staging: Stage 1 22.9% (n:16) Stage 2 22.9% (n:16) Stage 3 54.3% (n:38)
- Neurological examination of 48 patients (68.6%) was normal at first admission.
- The mean duration of the first seizure was 9.2 months and the history of febrile seizure was 95.7% (n:67).
- The most commonly used anti-seizure drug was clobazam with 70% (n:49).
- EEG deterioration time: 11.6 months ± 13.9.
- While the most common mutation was 82.6% (n:66) SCN1A, the least frequent mutations were HCN1, GABRA1, PCDH19 and STXBP1.
- The frequency of status epilepticus was 48.6 % (n: 34).
- SUDEP occurs at a rate of 4.3% (n:3).
- Table 1: Comparison of the data before and after initiation of ASMs shown.
- Table 2: ASMs effective on seizure frequency and duration shown.
- Table 3: Seizure frequency rates with ASMs shown.

## CONCLUSIONS

- It was observed that anti-seizure drugs started in cases with SCN1A mutation did not reduce the frequency of seizures.
- New drugs and new treatment modalities are needed to be developed in DS.
- Clinicians; In a patient presenting with a single, prolonged, febrile seizure and a confirmed mutation in SCN1A, treatment should be started immediately with an approved drug for Dravet syndrome.
- New treatment options should focus not only on reducing the frequency of seizures but also on the long-term effects of these comorbidities, such as intellectual disability and motor and sleep problems.

## REFERENCES

1. Chilcott, E., Díaz, J. A., Bertram, C., Berti, M., & Karda, R. (2022). Genetic therapeutic advancements for Dravet Syndrome. *Epilepsy & Behavior*, *132*, 108741.
2. Ding, J., Li, X., Tian, H., Wang, L., Guo, B., Wang, Y., ... & Sun, T. (2021). SCN1A Mutation—Beyond Dravet Syndrome: A Systematic Review and Narrative Synthesis. *Frontiers in neurology*, *12*.
3. Dravet, C. (2011). The core Dravet syndrome phenotype. Epilepsia, 52, 3-9.
4. Brunklaus, A., Pérez-Palma, E., Ghanty, I., Xinge, J., Brilstra, E., Ceulemans, B., ... & Lal, D. (2022). Development and validation of a prediction model for early diagnosis of SCN1A-related epilepsies. Neurology, 98(11), e1163-e1174.