Delayed *SCN1A* Diagnosis: A Case Series of Three Families

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Introduction

- The *SCN1A* gene encodes the alpha 1 subunit of the sodium channel.[1]
- Variants in *SCN1A* have been well-described and are related to a variety of epilepsy phenotypes ranging from genetic epilepsy with febrile seizures plus (GEFS+) to developmental and epileptic encephalopathies, such as Dravet Syndrome.[1]
- Recommendations for diagnosis and management of Dravet Syndrome are available and obtaining a genetic diagnosis can impact clinical management.[2]
- Although next generation sequencing has a high diagnostic yield[3], many children with early onset and childhood epilepsies do not undergo early diagnostic testing.

Objective

- To assess the reasons for, and potential clinical impact of, delayed genetic diagnosis of *SCN1A*-related epilepsy.

Methods

- We enrolled over 500 probands and their available, biological parents in the Children's Rare Disease Cohorts Initiative (CRDCI) at Boston Children's Hospital.[4]
- Proband inclusion criteria included having a diagnosis of epilepsy with unknown etiology and normal brain magnetic resonance imaging.
- Whole exome sequencing was completed for probands and their biological parents.
- Phenotypic data and clinical history notes were reviewed using the electronic medical record, and data was organized and managed using REDCap.

References

[1] Scheffer, I. E., & Nabbout, R. (2019). SCN1A-related phenotypes: Epilepsy and beyond. *Epilepsia, 60 Suppl 3*, S17–S24.
[2] Wirrell, E. C., et al. (2017). Optimizing the Diagnosis and Management of Dravet Syndrome: Recommendations From a North American Consensus Panel. *Pediatric neurology, 68*, 18–34.e3.
[3] Costain, G. et al. (2019). Clinical Application of Targeted Next-Generation Sequencing Panels and Whole Exome Sequencing in Childhood Epilepsy. Neuroscience, 418, 291–310.
[4] Rockowitz, S., et al. (2020). Children's rare disease cohorts: an integrative research and clinical genomics initiative. *Npj Genomic Medicine*, *5*(1), 29.

Table 1. Epilepsy diagnosis, age at seizure onset and genetic diagnosis, and total time passed from age at seizure onset to age at genetic diagnosis for each participant.

Participant	*Epilepsy Diagnosis*	*Age at Seizure Onset*	*Age at Genetic Diagnosis*	*Time Elapsed*
1	Dravet	9 months	4 years	3.4 years
2	Dravet	6 months	10 years	8.3 years
3	Dravet	6 months	11 years	9.8 years
4	Benign Occipital Lobe Epilepsy	4 years	7 years	3.9 years

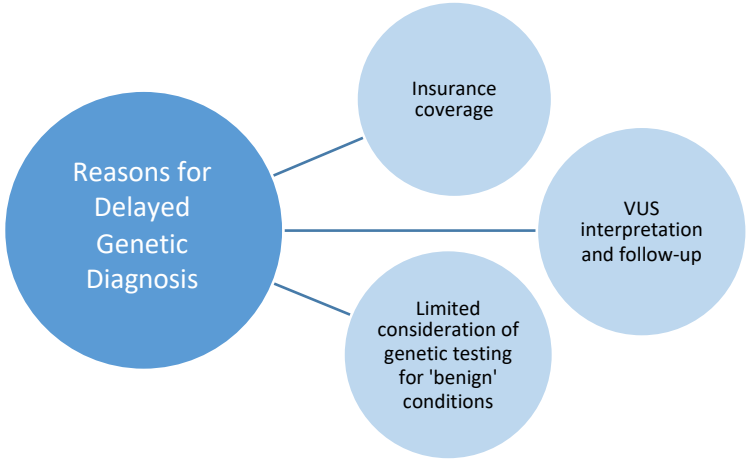

Figure 1. Three factors contributing to delayed genetic diagnosis for the four participants.

Table 2. Genotypic information and ACMG classification for participant variants in *SCN1A*.

Participant	*Variant*	*Protein Change*	*Classification*	*Inheritance*
1	c.664C>T	p.R222X	Pathogenic	De novo
2	c.5495C>A	p.A1832E	Likely Pathogenic	Maternal (mosaic)
3	c.5495C>A	p.A1832E	Likely Pathogenic	Maternal (mosaic)
4	c.5066T>C	p.M1689T	Likely Pathogenic	De novo

Results

- We identified pathogenic or likely pathogenic *SCN1A* variants in 4 children with epilepsy (Table 2).
- Time elapsed between age at seizure onset and age at genetic diagnosis of *SCN1A* variants ranged from 3.4 to 9.8 years (Table 1).
- Genetic testing was attempted clinically for Participants 1, 2, and 3 prior to enrollment in the CRDCI.
  - For Participant 1, despite clinical suspicion of a *SCN1A*-related etiology, clinical testing was not obtained due to insurance coverage.
  - Participants 2 and 3 are biological brothers. A clinical gene panel was pursued for Participant 3 (the older sibling) and a variant of uncertain significance (VUS) was identified in *SCN1A*. Segregation analysis was not pursued at the time.
  - Clinical genetic testing was not pursued for Participant 4 as the healthcare provider did not consider his relatively benign phenotype to be suggestive of a genetic etiology.
- Reasons for delayed diagnosis for this cohort include: 1) insurance coverage, 2) lack of provider familiarity with variant classification, VUS interpretation, and the need for re-analysis, and 3) limited clinical consideration for genetic testing for relatively 'benign' epilepsy phenotypes (Figure 1).

Conclusions

- Definitive diagnosis of *SCN1A*-related epilepsy varied considerably in the 4 cases identified through this institutional sequencing initiative.
- Delayed diagnosis can impact an individual and family's ability to participate in research and clinical trials, receive counseling regarding risk recurrence, and engage with advocacy groups and community resources.
- Recommendations include early consideration of genetic testing for patients with unexplained epilepsy, and routine re-analysis of VUS and additional testing strategies for those who remain 'unsolved' after initial evaluation.

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