A Novel Approach to Assess the Impact of Disease in Patients with *SCN8A*-Related Developmental and Epileptic Encephalopathy

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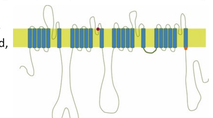
Background

- *SCN8A*-related developmental and epileptic encephalopathy (DEE) is a rare disease associated with pathogenic variants in the *SCN8A* gene encoding the voltage-gated sodium channel alpha subunit $Na_v1.6$, with devastating neurodevelopmental consequences.[1-3]
- The phenotypic spectrum is broad, involving seizures, movement disorders, intellectual disability, and feeding challenges including swallowing difficulty and lack of head control.[1]
- As a rare neurological condition with significant phenotypic heterogeneity, comprehensive understanding of disease impact and progression in *SCN8A* remains limited.
- Ciitizen[4], a novel, patient-centric, real-world data platform aims to improve and accelerate natural history data collection via unbiased, systematic extraction of clinical data from unstructured medical records.
- In this study, clinical data generated using Invitae's Ciitizen patient-consented, real-world data platform were used to explore disease burden in *SCN8A*-DEE.



$Na_v1.6$ mutations associated with SCN8A-related epilepsy (Oliva, Berkovic & Petrou 2012 Epilepsia)

Methods

- This data mining study captured data derived from unstructured data sources spanning ~10 years, with patients recruited through partnership with The Cute Syndrome Foundation and the SCN8A Alliance.
- Eligible patients or caregivers were required to complete a Ciitizen profile, list the name of at least one institution where they have received medical care, and provide informed consent to participate and share de-identified medical data for research purposes.
- Data were extracted via ingestion of medical records into Invitae's Ciitizen platform for preprocessing.
- Standard and unique data were extracted longitudinally from each source, including genotype, clinical phenotype, and therapeutic intervention, for up to 10 years.
- Data standardization was achieved through a curated ontology that supports mapping of data to standard codes derived from internationally recognized terminologies.
- Extracted data included seizure history, comorbidities, and therapeutic interventions.
- Data were analyzed according to age at seizure onset and seizure type at initial presentation.

Demographics

Demographics

- A total of 79 patients were enrolled and contributed data for analyses.
- Mean age was 8.3 years, with similar percentages of males and females (***Fig. 1, Table 1***).
- Participants were categorized based on age at seizure onset
  - Early seizures with onset ≤6 months (ES, 60.8%)
  - Later seizures with onset >6 months (LS, 34.2%)

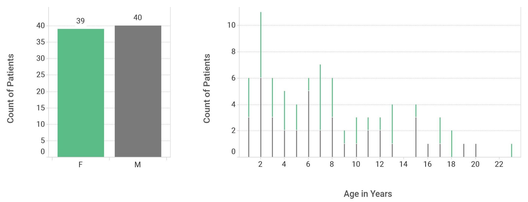


Figure 1. Patient age and sex distribution

Seizure History and Patterns

Table 1. Patient demographics by seizure classification

	Early Seizures (n=48)	Later Seizures (n=27)	No Seizures (n=4)	Total Sample (n=79)
Age at *SCN8A* diagnosis (years)	3.0 (0, 15)	5.7 (0, 19)	5.8 (1, 8)	4.0 (0, 19)
Female, *n (%)*	28 (58)	9 (33)	2 (50)	39 (49)
Male, *n (%)*	20 (42)	18 (67)	2 (50)	40 (51)
Age at seizure onset, *years*	0.2 (0, 0.5)	2.1 (0.6, 12.1)	n/a	0.9 (0, 12.1)
Age at records end, *years*	7.2 (1.1, 23.7)	10.1 (2.6, 20.6)	9.6 (3.9, 12.5)	8.3 (1.1, 23.7)

Mean (min, max) presented unless otherwise specified.

Seizure Timeline

- Mean age at seizure onset was 70.4 (1-175) days for patients with early seizures (onset ≤6 months), and 749.3 (224-4409) days for those with later seizures (onset >6 months).
- While seizure frequency was variable, most patients continued to experience seizures over time (***Fig. 2***).
- Seizures did not subside over time for most patients.

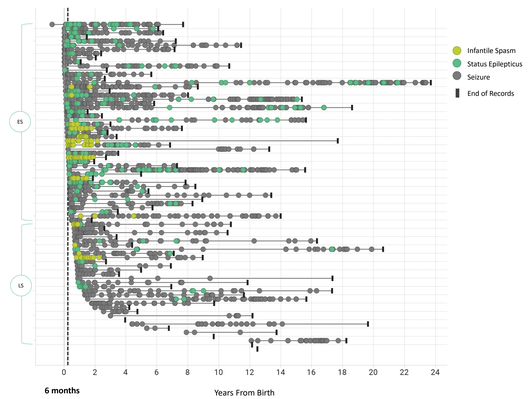


Figure 2. Participant phenotypes and seizure history as timeline from birth to end of records.
ES=early seizures (onset ≤6 months); LS=later seizures (onset >6 months)

Seizure Patterns and Genetic Testing

- Date of seizure onset was inversely related to time to genetic diagnosis, with those patients experiencing seizure onset in later years (post-2014 when *SCN8A* was added to genetic epilepsy panels) demonstrating shorter time to diagnostic confirmation (***Fig. 3***), likely reflecting the change in era of genetic testing.

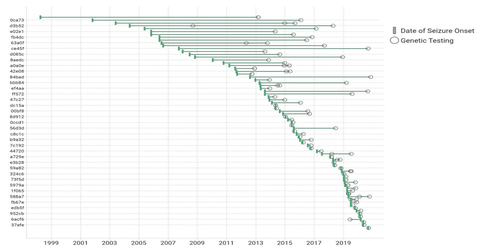
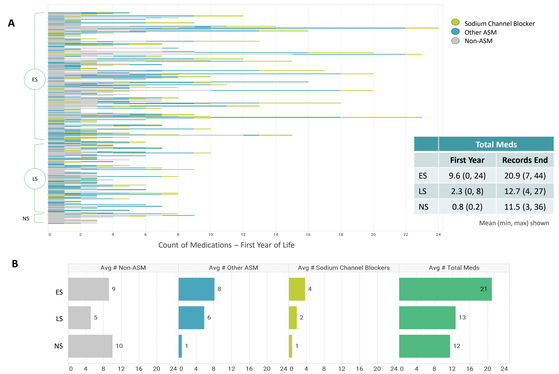


Figure 3. Time from seizure onset to genetic testing by patient

Medication Use

Medications

- The mean number of medications prescribed across patients by records end was 17.6 (3-44), half of which were started in the first year of life for patients with early seizures (***Fig. 4***).
- Most commonly prescribed medications by antiseizure medication (ASM) classification are shown in ***Fig. 5***.



	Total Meds	
	First Year	Records End
ES	9.6 (0, 24)	20.9 (7, 44)
LS	2.3 (0, 8)	12.7 (4, 27)
NS	0.8 (0.2)	11.5 (3, 36)

Mean (min, max) shown

Figure 4. Medication use by ASM classification for the first year of life (A) and at records end (B). Panel A shows number of medications by patient and ASM classification as started in the first year of life. Panel B shows the number of medications by seizure category and ASM classification at records end. Table inset summarizes mean medications by seizure category and ASM classification in the first year of life vs at records end. ES=early seizures (onset ≤6 months); LS=later seizures (onset >6 months); NS=no seizures

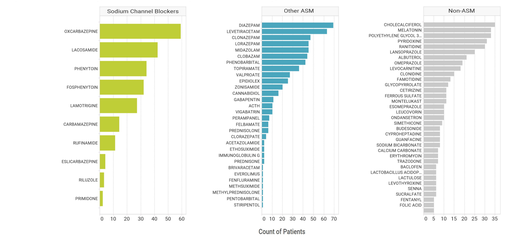


Figure 5. Most prescribed ASMs and other medications for all patients

Interventions, Admissions and Comorbidities

Interventions and Hospital Admissions

- Procedural interventions and hospitalization duration were high at records end (mean 8.3 years; range 1.1-23.7); with nearly a third of procedures occurring in the first year of life (***Fig. 6***).

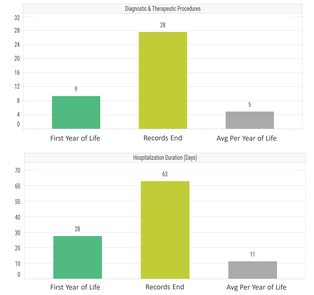


Figure 6. Mean count of procedures and duration of hospitalizations for the first year of life and at records end

Comorbidities

- Most commonly reported comorbidities other than seizures are shown in ***Fig. 7.***
- All patients experienced multiple comorbidities; developmental delay being the most common (81%), while sleep disorders, hypotonia, feeding difficulties and GERD were reported in >50% of patients.

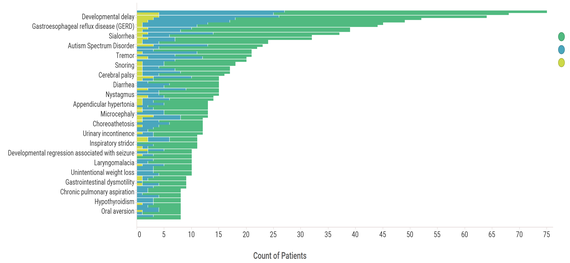


Figure 7. Summary of most commonly observed comorbidities in patients by seizure category.
ES=early seizures (onset ≤6 months); LS=later seizures (onset >6 months); NS=no seizures

Conclusions

- **This work represents a new generation of natural history study providing the most robust, longitudinal real-world dataset to date on disease burden and progression in *SCN8A*-DEE.**
- **Our findings highlight the severity and burden of disease in *SCN8A*-DEE, particularly in the first year of life for patients with seizures presenting earlier in life (≤6 months); further compounded by multiple factors including high medication usage, hospital duration and comorbidities.**
- **Together with ongoing efforts to better understand underlying genotype-phenotype relationships, our findings will guide development of targeted, innovative therapies that can benefit patients and their caregivers.**

References

1. Wagnon et al. 2015 *Annals Clin Transl Neurol*
2. Grayson et al. 2020 *AAN Annual Meeting*
3. Oliva, Berkovic & Petrou 2012 *Epilepsia*
4. www.ciitizen.com

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