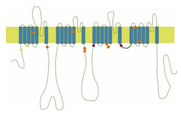
Disease Impact and Burden in Patients with *SCN2A*-Related Developmental and Epileptic Encephalopathy

Kelley Dalby[1], Ted Snyder[1], Lillian G Matthews[1], Elise Brimble[2], Geoffrey Beek[2], Alexa Berk[2], Michael Oldham[1]

[1]Praxis Precision Medicines, Boston, MA 02110 USA; [2]Ciitizen, a wholly owned subsidiary of Invitae Corporation, San Francisco, CA USA

Background

- The *SCN2A* gene encodes the voltage-gated sodium channel alpha subunit $Na_v1.2$; pathogenic variants of this gene result in *SCN2A*-related developmental and epileptic encephalopathy (DEE) characterized by a broad epilepsy phenotype, intellectual disability, and/or autism.[1,2,3]
- Uncontrolled seizures or status epilepticus are key risk factors associated with increased morbidity and mortality in affected infants and children, including sudden unexpected death in epilepsy (SUDEP).[4,5]
- As a rare neurological condition with significant phenotypic heterogeneity,[6] comprehensive understanding of disease impact and progression in *SCN2A* remains limited.
- Patient-centered data mining approaches can provide unprecedented insight into disease impact in affected patients and their caregivers.
- Ciitizen,[7] 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 from patients with *SCN2A*-related disorders generated using the Invitae Ciitizen platform were analyzed to investigate disease progression and impact.



$Na_v1.2$ mutations associated with SCN2A-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 using internal patient databases and through partnership with SCN2A Australia and the FamiliesSCN2A Foundation.
- 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.
- Participants were required to have written documentation of a pathogenic, likely pathogenic, or uncertain variant in *SCN2A*.
- 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.
- Data standardization was achieved through a curated ontology that supports mapping of data to standard codes derived from internationally recognized terminologies.
- Extracted data (seizure history, medication use, comorbidities, developmental milestones) were classified by phenotype based on age at seizure onset, type of seizure at initial presentation, variant type, and variant functional characterization using dynamic action potential clamp analysis.
- *SCN2A* variants producing increased or decreased action potential relative to wild type were classified as probable gain-of-function (GOF) or loss-of-function (LOF), respectively.

Clinical Spectrum of *SCN2A* Disorders

- Functional assays demonstrate strong correlation between genotype and phenotype in *SCN2A*.[1,8]
- Gain-of-function and loss-of-function variants underlie a spectrum of phenotypes, that can be further classified based on seizure presence, pattern and age of onset, mutation type, and treatment response.
- Findings from this study are presented according to the following four emergent phenotypes (***Table 1***).

Table 1. Clinical spectrum of SCN2A disorders

	Early Onset	Late Onset		Autism with Epilepsy
	Early Onset (EO)	**Late Onset with Infantile Spasms (LOIS)**	**Late Onset (LO)**	**Autism Only (AO)**
Variant Functional Characterization	GOF	LOF	LOF	LOF
Mutation Type	Missense	Missense	Nonsense Frameshift Missense	Nonsense Frameshift Missense
Age of Seizure Onset	Typically presents in the first few days of life, up to 3 months of life	Typically presents between 6 to 12 months of life	Typically presents between 18 months to 4 years of life	n/a
First Seizure Type	Seizures other than infantile spasms	Infantile spasms always first seizure presentation	Seizures other than infantile spasms	n/a
Other Characteristics	-	-	Autism typically presents prior to seizures	Developmental delay and autism

Participant Demographics and Seizure History

Phenotypes and Demographics

- Of 49 enrolled patients, 45 had data available for analyses (***Table 2***).
- 33.3% of patients were classified as early onset (EO); 42.2% as late onset (LO); 24.4% as autism without epilepsy (AO).
- The LO group comprised two distinct phenotypes based on age and type of seizure at onset
  - Half of whom were characterized by initial seizure presentation with infantile spasms (LOIS, 20% of all patients)
  - The other half characterized by seizures other than infantile spasms and presenting later in life (LO, 22.2% of all patients)
- The EO phenotype was associated with probable GOF variants whereas other phenotypes were associated with probable LOF variants.
- Mean patient age at records end across cohorts was 8 years.
- Mean age at *SCN2A* diagnosis across cohorts was 3.7 years, with similar percentages of male and females.

Table 2. Participant demographics by SCN2A phenotype

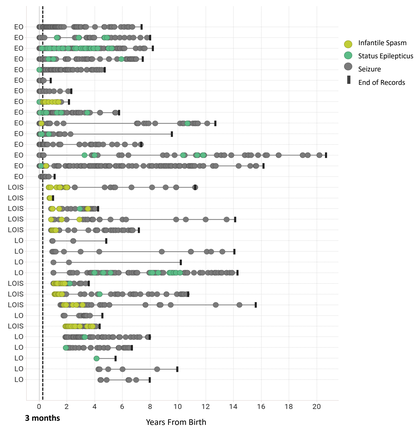
	EO (n=15)	LOIS (n=9)	LO (n=10)	AO (n=11)	Total (n=45)
Age at *SCN2A* diagnosis, *years*	3.0 (0, 19)	3.3 (0, 11)	3.5 (1, 8)	5.1 (1, 21)	3.7 (0, 21)
Female, *n (%)*	7 (47)	3 (33)	6 (60)	6 (55)	22 (49)
Male, *n (%)*	8 (53)	6 (67)	4 (40)	5 (45)	23 (51)
Age at seizure onset, *days*	5.1 (1, 44)	380.8 (243, 680)	807 (334, 1603)	N/A	340.4 (1, 1603)
Age at records end, *years* (derived)[a]	7.6 (0.8, 20.6)	8.0 (1, 15.6)	8.6 (4.5, 14.3)	7.9 (2.4, 23.3)	8.0 (0.8, 23.3)

[a]All but one patient had a records end date within 6 months of data being available for analysis.
Mean (min, max) presented unless otherwise specified.

Seizure timeline

- While seizure frequency appeared variable, patients continued to have seizures for years (***Fig. 1***).
- Seizures did not subside over time for most patients.
- 53% of patients with seizures experienced status epilepticus at least once.
- Date of seizure onset was inversely related to time to genetic diagnosis, with those patients experiencing seizure onset in later years (post-2014 when SCN2A was added to genetic epilepsy panels) demonstrating shorter time to diagnosis, likely reflecting the change in era of genetic testing.

Figure 1. Participant phenotypes and seizure history as timeline from birth to end of records

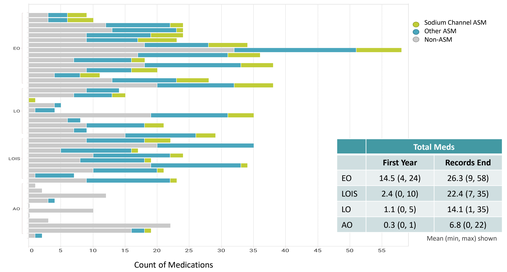


Medications, Procedures and Comorbidities

Medications and Procedures

- Mean number of medications prescribed by records end across phenotypes was 18.1 (range 0-58), with nearly a half of medications started in the first year of life for patients classified as EO (***Fig. 2***).
- 41 (91%) patients across all cohorts underwent ≥1 EEG; 26 (76%) patients across epilepsy phenotypes required >10 EEGs.

Figure 2. Medication use at records end by patient with ASM classification



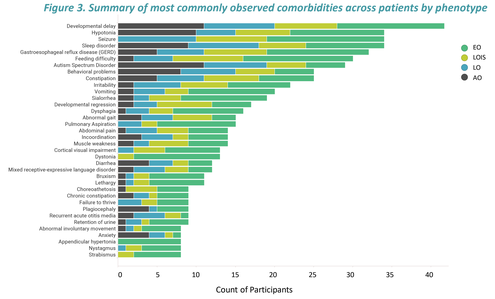
	Total Meds	
	First Year	Records End
EO	14.5 (4, 24)	26.3 (9, 58)
LOIS	2.4 (0, 10)	22.4 (7, 35)
LO	1.1 (0, 5)	14.1 (1, 35)
AO	0.3 (0, 1)	6.8 (0, 22)

Mean (min, max) shown

Comorbidities

- Most commonly reported comorbidities are shown in ***Fig. 3.***
- Participants across all cohorts experienced multiple comorbidities, with developmental delay reported in all patients with developmental assessment data.
- Other common comorbidities (>50%) included hypotonia, reflux, gastrointestinal and sleep disturbances.

Figure 3. Summary of most commonly observed comorbidities across patients by phenotype



Developmental Impairment

Developmental Assessments

- 42 (93.3%) patients had developmental assessment data available for analysis (***Table 3***).

Global Domains

- All patients did not meet at least one global developmental domain.
- Across all phenotypes, gross motor and language development were the most impacted
  - >90% in EO group; 100% LOIS; 70-80% LO; 90-100% AO
- Participants in the EO cohort had persisting impairment in at least 1 global developmental domain through a median of 5.5 years, with some demonstrating impairment through to 19 years of age.

Critical Milestones

- Further exploration of critical developmental milestones as a proxy for the extent of patients' developmental impairment and associated impact on quality-of-life revealed persisting impairment in at least 1 critical milestone across all cohorts.

Participants across epilepsy phenotypes (EO, LOIS, LO) demonstrated ~2-fold delay in the ability to meet age-appropriate development relative to patients without an epilepsy phenotype (AO); with the greatest developmental delays observed in EO and LOIS groups.

Table 3. Global developmental domain and milestone achievement by phenotype

	EO (n=14)		LOIS (n=8)		LO (n=10)		AO (n=10)	
Global Developmental Domain Not Achieved								
	Frequency n (%)	**Age (years)**	**Frequency n (%)**	**Age (years)**	**Frequency n (%)**	**Age (years)**	**Frequency n (%)**	**Age (years)**
Academic performance	1 (7.1)	3.8 (3.8, 3.8)	1 (12.5)	7.5 (7.5, 7.5)	3 (30.0)	6.9 (4.2, 7.1)	0 (0)	N/A
Fine motor development	12 (85.7)	1.7 (0.4, 6.6)	6 (75.0)	3.9 (0.9, 7.5)	3 (30.0)	2.7 (1.1, 4.1)	3 (30.0)	1.5 (0.3, 2.0)
Gross motor development	14 (93.3)	5.2 (0.6, 19.0)	8 (100.0)	3.7 (1.9, 7.6)	8 (80.0)	3.1 (1.0, 5.1)	9 (90.0)	1.6 (1.1, 4.5)
Language development	13 (92.9)	7.5 (0.4,19.0)	8 (100.0)	7.9 (2.6, 14.7)	7 (70.0)	6.4 (3.0, 7.9)	10 (100.0)	3.6 (1.0, 6.3)
Any domain	14 (100.0)	5.5 (0.4, 19.0)	8 (100.0)	4.1 (0.9, 14.7)	10 (100.0)	3.9 (1.0, 7.9)	10 (100.0)	2.1 (0.3, 6.3)
Critical Developmental Milestone Not Achieved								
	Frequency n (%)	**Age (years)**	**Frequency n (%)**	**Age (years)**	**Frequency n (%)**	**Age (years)**	**Frequency n (%)**	**Age (years)**
Holding head independently	10 (71.4)	0.6 (0.4, 10.1)	2 (25.0)	2.7 (1.9, 3.5)	0 (0)	N/A	2 (20.0)	0.1 (0.1, 0.2)
Sitting unassisted	11 (78.6)	4.2 (0.6, 18.7)	8 (100.0)	1.8 (0.5, 3.5)	1 (10.0)	2.0 (2.0, 2.0)	3 (30.0)	1.1 (0.9, 1.2)
Walking unassisted	10 (71.4)	5.7 (1.2, 19.0)	8 (100.0)	3.1 (1.7, 7.6)	6 (60.0)	3.2 (2.1, 5.1)	7 (70.0)	1.6 (1.4, 4.5)
Communicating independently using ≥1 word	11 (78.6)	7.5 (3.3, 19.0)	8 (100.0)	7.9 (2.6, 14.7)	7 (70.0)	6.4 (3.0, 7.9)	10 (100)	2.7 (1.0, 6.3)
Performing purposeful hand movements	12 (85.7)	3.3 (0.4, 6.6)	6 (75.0)	4.0 (0.9, 7.5)	4 (40.0)	4.1 (1.1, 7.1)	3 (30.0)	1.5 (0.3, 2.0)
Any milestone	14 (100.0)	3.8 (0.4, 19.0)	8 (100.0)	4.0 (0.5, 14.7)	10 (100.0)	4.1 (1.0, 7.9)	10 (100.0)	1.6 (0.1, 6.3)

Frequencies of patients with impaired developmental performance assessed by inability to meet global domains and key developmental milestones. Corresponding median (minimum, maximum) ages at which developmental performance was still impaired are also shown.

Conclusions

- **Using a novel real-world data platform and functional variant characterization, we provide unprecedented insight into clinical phenotypes, disease burden and treatment patterns in *SCN2A*-related disorders.**
- **We demonstrate that symptoms are diverse and extend beyond seizures, with patient burden compounded by multiple factors including comorbidities, high treatment use and procedural interventions, as well as profound developmental impairment extending through to early adulthood.**
- **Thus, our findings provide novel insights into the broad, longitudinal impact of disease, with the potential to inform trial endpoints beyond seizure symptomatology.**
- **Importantly, by allowing an unprecedented perspective into the clinical phenotypes and treatment patterns of *SCN2A*-related disorders, our findings are anticipated to aid development of more effective and targeted therapies for better outcomes in *SCN2A*-related disorders.**

References

1. Sanders et al. 2018 *Trends Neurosci*
2. Howell et al. 2015 *Neurology*
3. Oliva, Berkovic & Petrou 2012 *Epilepsia*
4. Berg et al. 2013 *Paediatrics*
5. Bagnall, Crompton & Semsarian 2017 *Front Neurol*
6. Wolff et al. 2017 *Brain*
7. www.ciitizen.com
8. Wolf, Brunklaus & Zuberi 2019 *Epilepsia*

Acknowledgments We thank the patients and their families, SCN2A Australia and the FamiliesSCN2A Foundation, as well as our collaborators at Invitae Ciitizen for their contributions to this work.

Funding All work was funded by Praxis Precision Medicines. Medical writing and editorial assistance were provided by Kathleen P. Hopf in accordance with Good Publication Practice (GPP3) guidelines.

Disclosures KD, TS, LGM and MO are current or former employees/consultants of Praxis Precision Medicines and may be Praxis stockholders.

@PraxisMedicines
Praxismedicines.com
kdalby@praxismedicines.com

Presented at:
2022 AES Annual Meeting
December 2-6
Nashville, TN