# Clinical Signature and Longitudinal Seizure Pattern of *SLC6A1*-Related Neurodevelopmental Disorder

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December 4, 2025

# Outline

Overview of *SLC6A1* and project aims

Clinical characteristics of our cohort

Seizure characteristics of our cohort

Anti-seizure medication use

Conclusions

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# Introduction

- *SLC6A1*-related Neurodevelopmental Disorder (NDD) involves:
  - Early onset epilepsy
  - Hypotonia (low muscle tone)
  - Variety of neurodevelopmental and behavioral disorders
  - Movement disorders, gastrointestinal symptoms, sleep disturbances

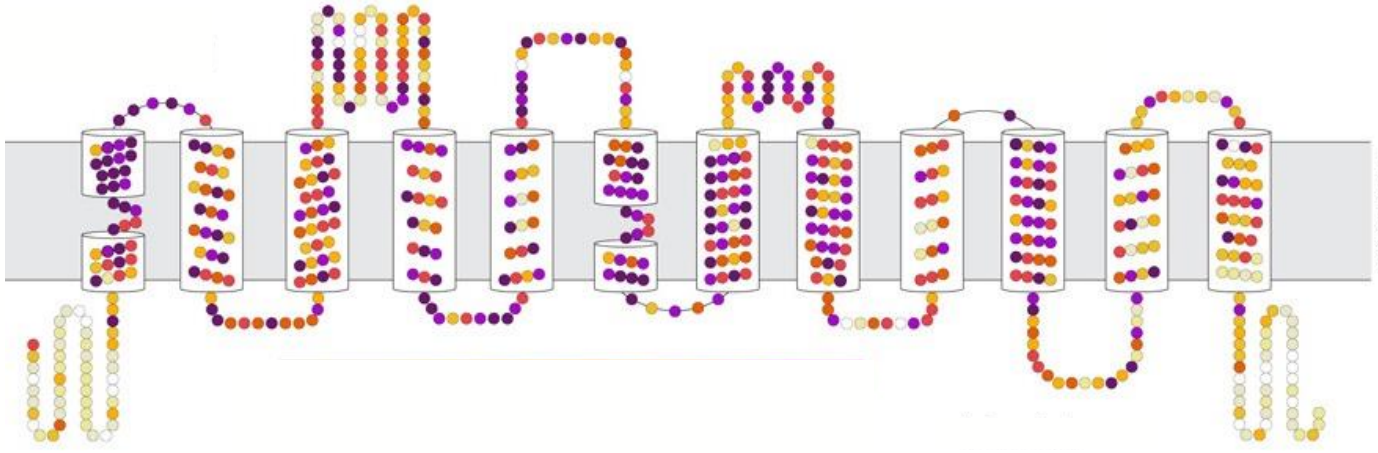

Figure: Silva et al. (2024), AJHG

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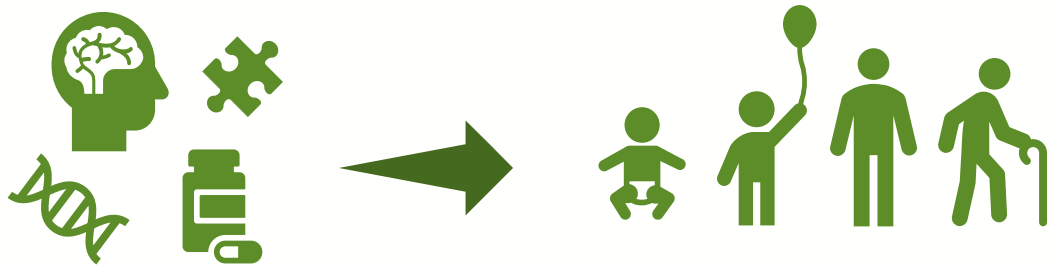
# Goals

- While seizure onset and types are documented, data on natural history, medication response, and long-term prognosis are limited
- **Our goals:**
  - Characterize the features of *SLC6A1*-related NDD
  - Elucidate the natural history of seizures through childhood and into adulthood
- **Ultimate aim:** increase clinical trial readiness and highlight potential outcome measures



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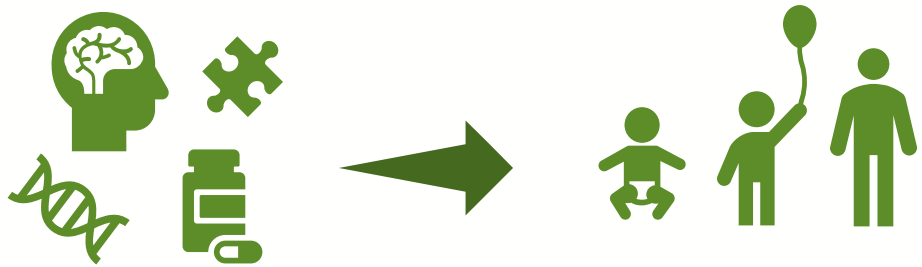
# Methods

- Longitudinal disease reconstruction:
  - CHOP patients with confirmed *SLC6A1*-related NDD
  - All documented clinical diagnoses
  - Developmental milestones
  - Seizure types + frequencies mapped for each month
  - Anti-seizure medications (ASMs) mapped for each month



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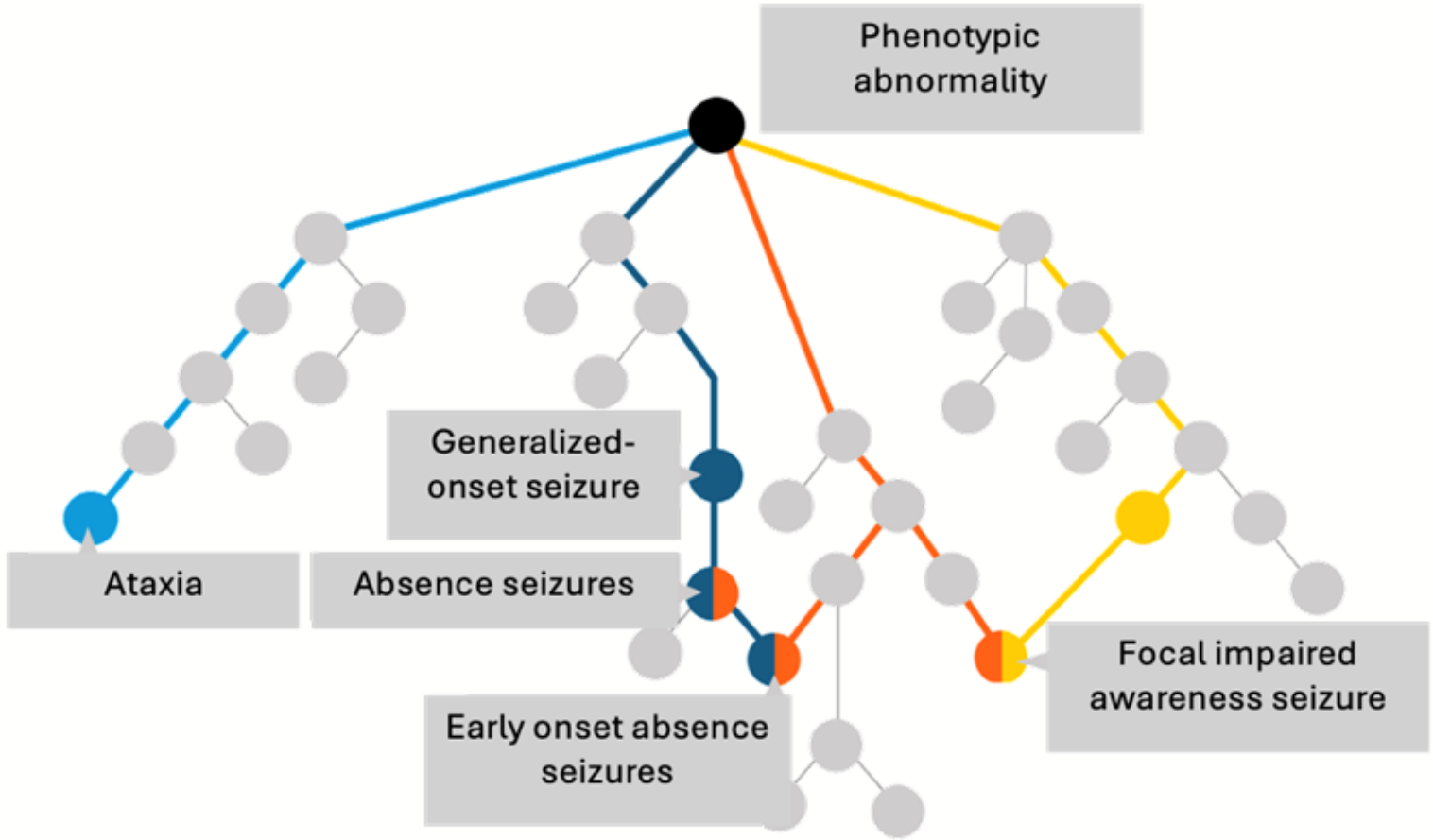
# Methods

- Phenotypic traits standardized using the Human Phenotype Ontology (HPO)

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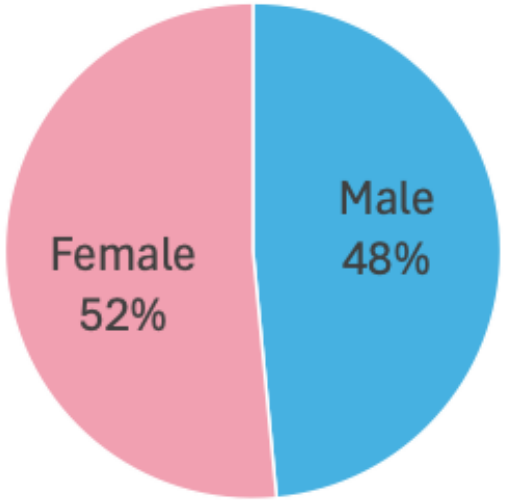
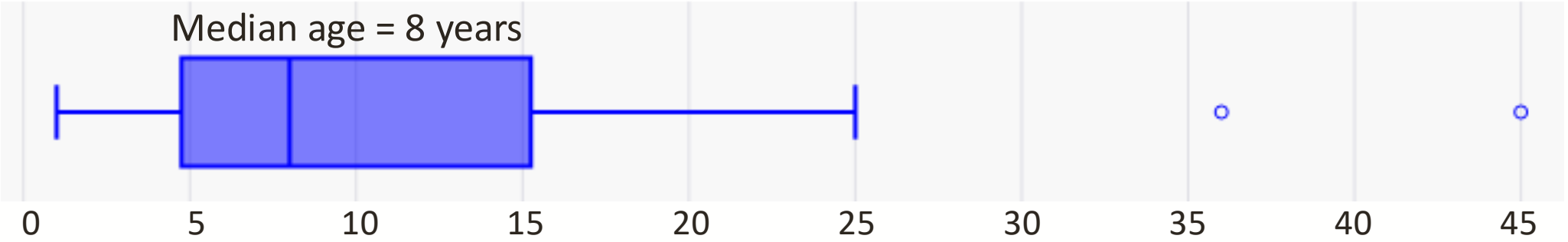
# Results: cohort description

- 33 individuals
  - 17 female, 16 male
  - Age range of 1-45 years
  - Total of 3476 patient-months (289.7 patient-years)

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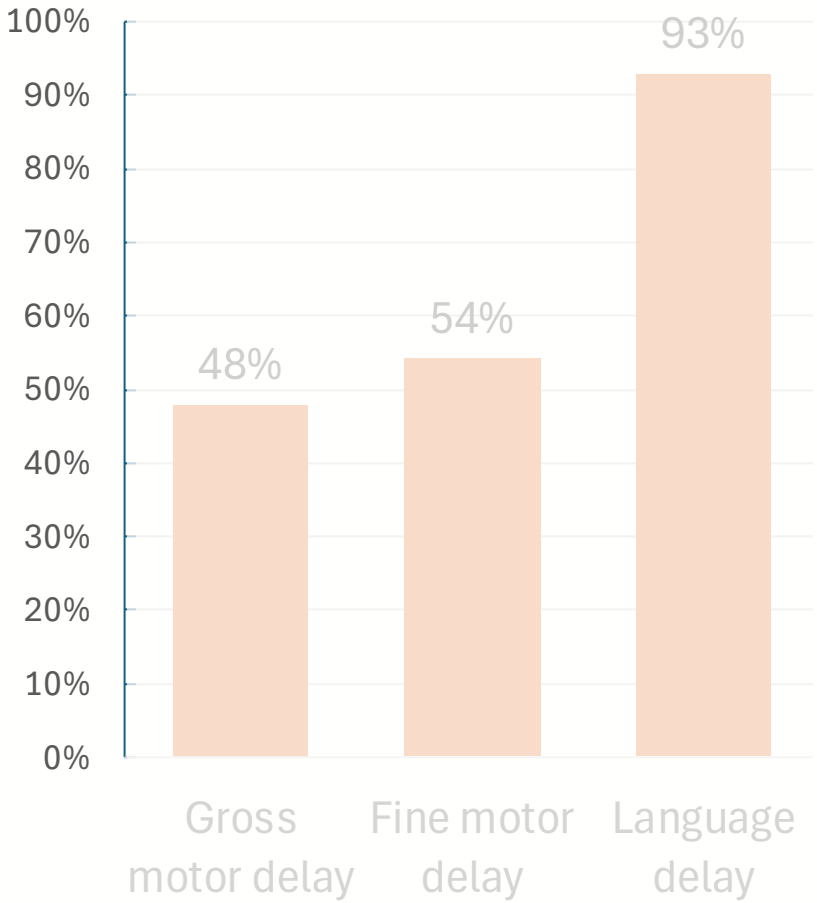
# Clinical features

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# Seizure data

- Median age of **onset was 29 months** (4-89 months)
- **55% (12/22)** achieved ≥ 24 mos **seizure freedom**
  - Last seizure at a median age of **7.4 years** (4-12 years)
- Among the 5 adults with epilepsy history data, **60% (3/5) were seizure free** with/without ASM

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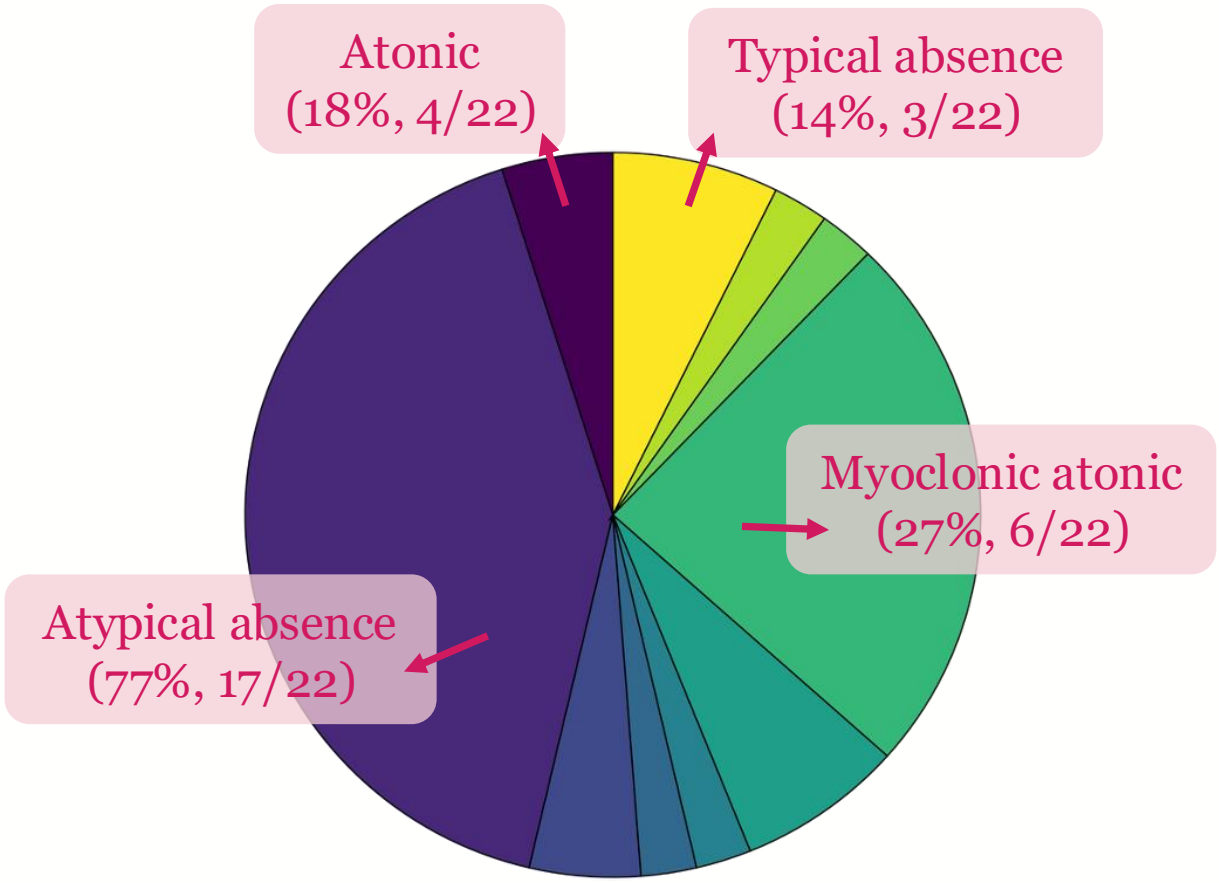
# Seizure types




**Seizure Type**

- Atonic Seizure
- Atypical Absence Seizure
- Bilateral tonic-clonic with generalized onset
- Complex febrile seizure
- Focal clonic seizure
- Generalized atonic seizure
- Myoclonic-atonic seizure
- Generalized onset seizure (not otherwise specified)
- Myoclonic seizure
- Typical absence seizure

All seizure types reported amongst 22/33 participants in our cohort

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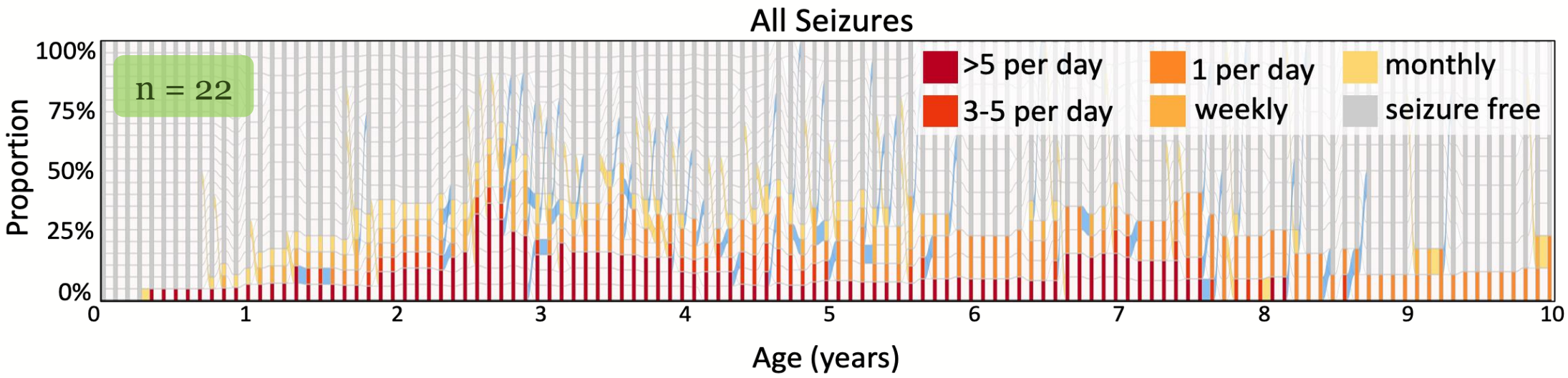
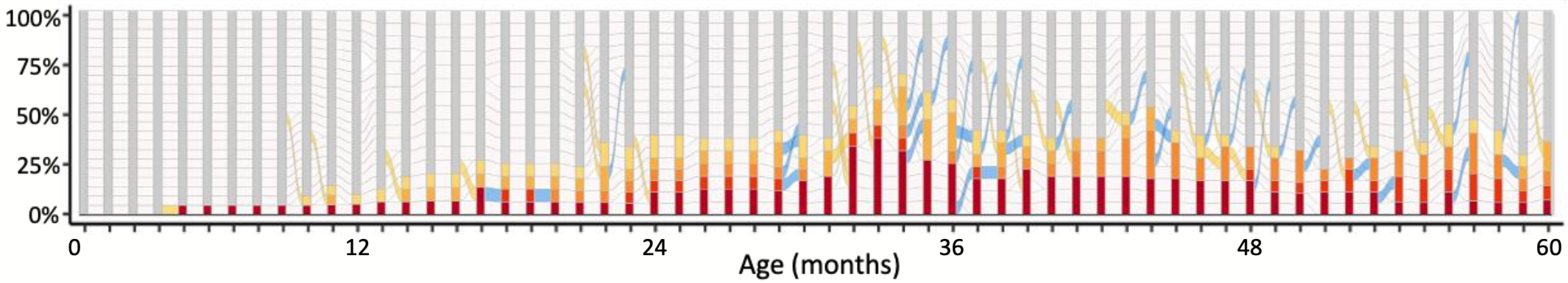

All Seizures
n = 22
>5 per day
3-5 per day
1 per day
weekly
monthly
seizure free
Proportion
100%
75%
50%
25%
0%
0
1
2
3
4
5
6
7
8
9
10
Age (years)

# Comparison of seizure trajectories

***SLC6A1***




McKee et al., Genet Med. 2025 Jun; 27(6):101419.

# ASM effectiveness across participants with seizures

Valproic acid (n = 13, 59%)

Levetiracetam (n = 13, 59%)

Lamotrigine (n = 11, 50%)

Ethosuximide (n = 10, 45%)

Clobazam (n = 9, 41%)

**Valproic acid: OR = 1.3 ($p < 0.001$)**

**Clobazam: OR = 1.4 ($p < 0.001$)**

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# Summary

Psychiatric diagnoses are common

Seizures show a unique longitudinal pattern

Seizure frequencies are dynamic over time, rather than a stable proportion with seizures

Valproic acid and clobazam were more effective, while lamotrigine had a less clear benefit

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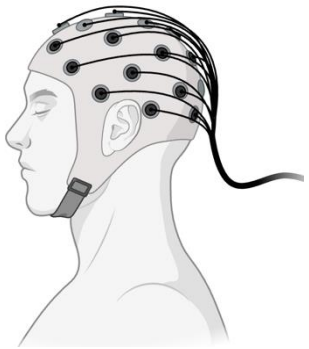
# Next steps

- Leverage our large dataset as basis for prospective natural history
  - Standardized measures, tracked over time
  - Assess cognitive abilities, motor functions, and psychiatric features
  - qEEG data available
  - Brain Gene Registry Project collaboration

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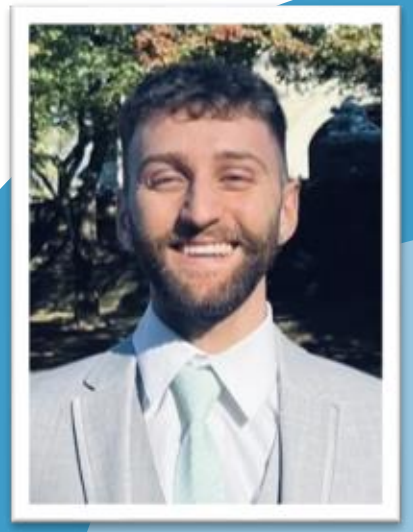
# Thank you!



**Special thanks to:**

- Samuel Miller, MS - GC thesis student
- Michael Kaufman, MS; Jillian McKee, MD PhD
- Helbig lab
- ENGIN team at CHOP
- All of our patients and families!

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