Using a Large Control Cohort to Benchmark EEG Spectral Abnormalities in *SCN2A* Developmental And Epileptic Encephalopathy

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SCN2A-DEE disrupts the expected pattern of healthy EEG spectral development. Background spectral features could serve as an EEG biomarker of *SCN2A* when normalized to controls.

Background

- Variants in the *SCN2A* gene are a common cause of a wide range of human neuropathology, including devastating developmental and epileptic encephalopathy (DEE).
- The EEG background spectral content is a function of many factors, including age-dependent functional and anatomic network architecture, state of vigilance, epileptic activity, and medication effects. Deviation from expected content could be used to monitor disease severity and treatment effects.
- Interpreting background spectral patterns requires an understanding of both disease-specific changes and expected developmental changes in background EEG rhythms.
- In the first years of life, the dominant EEG rhythm is expected to increase in frequency, shifting from the delta to theta and finally settling into a posterior-dominant rhythm in the alpha band.

Dataset

- *SCN2A* cohort (Ciitizen® platform)
  - 230 recordings from 11 subjects with gain-of-function (GoF) variants
  - 195 recordings from 15 subjects with loss-of-function (LoF) variants
  - Ages 1 day to 16 years
- Normative data (Beacon Biosignals' clinico-EEG real-world evidence database)
  - 1670 recordings from 1206 children without an epilepsy diagnosis or epileptiform features based on neurologists' review
  - Ages 0 days to 16 years

Methods

- *SCN2A* variants were computationally classified as presumably GoF or LoF using a multi-stage consensus framework developed by the Lal lab.
- Interical epileptiform discharges (IEDs) were identified using Beacon's neural network-based detection algorithm SpikeML™ and seizures were manually labeled by experts. Periods with IEDs and seizures were excluded from analyses.
- Relative spectral power was computed across EEG segments determined to be free of artifact and epileptiform activity via the multitaper method within four frequency bands (delta = 1-4Hz, theta=4-8Hz, alpha=8-13Hz, beta=13-30Hz) and averaged across all channels.
- To capture differences from age-matched controls, median relative power was computed across all control recordings, for each band and within age bins. Z-scores were then computed for *SCN2A* spectral feature values using age-matched control median and median absolute deviation.
- Gross motor developmental delay status was assigned to recordings by comparing reported milestones to published expected normal ages for the milestones.
- Mixed effects logistic regression models were used to estimate the relationship between z-scored relative power and reported gross motor developmental delay.

Results

- The expected shift in the dominant rhythm can be seen in the controls, as exhibited by the gradual decline in relative delta power with age, increase and plateau of relative theta with age, and increase of relative alpha and beta with age.
- These patterns were less well developed in the *SCN2A* subjects, and most notably so in LoF subjects, who exhibit elevated relative delta power across all ages.
- Mixed-effects logistic regression models including z-scored relative power and functional variant classification revealed a positive association between z-scored relative delta power and the probability of reporting gross motor developmental delay, and the opposite relationship (a negative correlation) for z-scored relative alpha power.

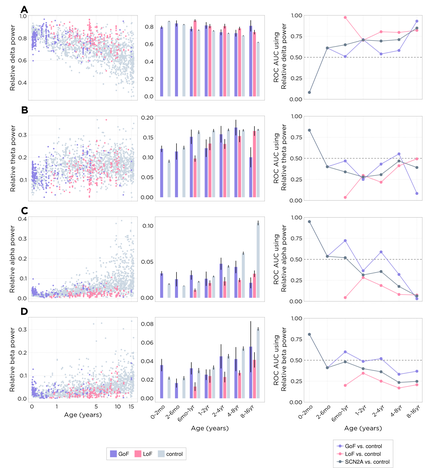

Figure 1. Relative band-wise spectral power by age for *SCN2A* and control subjects. (A-D) Relative delta, theta, alpha, beta power, respectively; Column 1: Per-recording scatter plots; Column 2: Bar plots representing per-subject values within each variant characterization / age bin; Column 3: ROC-AUC curves showing predictive power of each EEG feature.

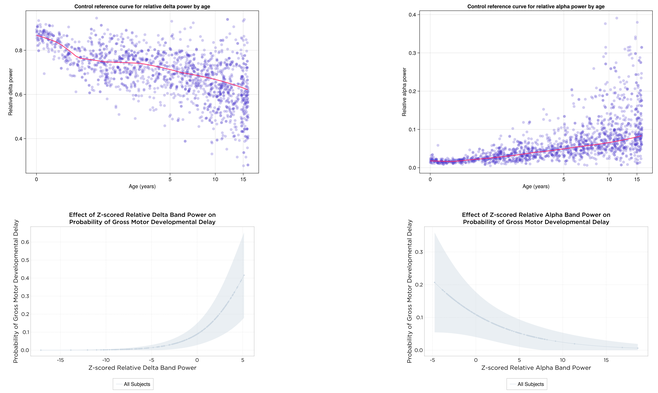

Figure 2. Effect of z-scored relative power on probability of gross motor delay. Top: Relative delta (left) and alpha (right) distribution and reference curve for control recordings. Bottom: Effect of z-scored relative delta (left) and alpha (right) on gross motor delay for *SCN2A* recordings. Lines represent model predictions and shaded bars represent model uncertainty.

Conclusions

- Relative delta is persistently elevated in subjects with LoF variants- this could represent persistent slowing which would be consistent with delayed development of normal brain rhythms.
- Abnormally elevated delta power and suppressed alpha power signify encephalopathy, although must be considered in the context of age and medication. Here we find that elevated delta and suppressed alpha, when normalized to age-matched normative values, are correlated with gross motor developmental delay.
- These findings suggest (though more investigation is required) that greater deviation from age-adjusted normal background frequencies implies greater disability.

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