Introduction

Epilepsy is a common disorder that is increasingly known to result from genetic causes, particularly when it occurs in early childhood. Understanding the genetic etiology can inform treatment strategies, prognosis, and recurrence risk.

- 2,267 unrelated individuals were analyzed using a multi-gene panel with 189 genes associated with epilepsy for sequence and exonic copy number variants.
- Exome data from 3 different exome methods was analyzed for coverage (<20X) to extrapolate variants that would likely be missed (false negatives in exome).
- We present our observation of panel-based diagnostic yield, mutation spectrum including CNVs and compare results for panel testing to exome studies.

Results

Clinical yield of 3,694 variants across 1,693 individuals

Spectrum of variants identified

- Includes rare hard to detect variants
  - Small and large indels
  - ARX trinucleotide expansions
  - Exon-level CNVs and cytogenetic changes
  - Mosaics
- Majority of pathogenic variants are not missense changes in contrast to VUS

Distribution of variants of uncertain significance

- Majority of VUS are in a single genes with AR and likely not resolvable
- Small fraction of VUS are likely resolvable with additional data
- Family variant testing in 116 cases provided resolution in 54 cases (46.5%)

Comparison to exome sequencing

- Epilepsy variants from 3 exome methods
  - ~1.6% of variants at low coverage (<20X)
  - Comparable to recent publication (PMID: 28152038)
- Most variants in genes found on panels
  - 65-80% of exome variants are in genes covered in panels depending on source of exome data

Conclusions

- Multi-gene panels have a high yield for epilepsy and cover the most medically-relevant genes at low cost with a fast turnaround time
  - 16-24% of patients had a positive molecular diagnosis (depending on panel)
  - 3 patients had dual diagnoses
- Important for NGS tests to include analysis of CNVs, large indels, and complex variants
  - In this cohort, 16.4% of positive finding were of these types
- Results with treatment implications are a significant proportion
  - 21% of molecular diagnosis in this cohort
- Some genetic causes of epilepsy are more common than anticipated
  - Pathogenic variants observed in PCDH19, SYNGAP1, PRRT2, DEPDC5
- Exome sequencing yields positive results in genes mostly found on panels, but has technical limitations for hard-to-detect variants