**Supplemental** **Data**



figure e-1. **Overview of epilepsy research study workflow.** As a NAEC Level 4 epilepsy center, our institution offers advanced epilepsy surgery services, including evaluation using intracranial electrodes and surgical excision of epileptogenic tissue. These neurosurgical procedures provide an opportunity to evaluate brain tissue for genomic alterations. We recently initiated an Institutional Review Board (IRB)-approved research protocol that compares high depth next generation sequencing of DNA extracted from brain tissue plus normal (blood) samples to identify somatic mosaicism in cases of intractable epilepsy. After sequencing and variant identification, we discuss results in an informal, collaborative meeting setting, which comprises neurosurgeons, pathologists, pediatric neurologists, bioinformaticians, genetic counselors and genomic scientists. We clinically confirm any candidate genomic alterations in our Clinical Laboratory Improvement Amendments (CLIA)-approved laboratory using validated assays, in order to record results in the patient’s electronic medical chart. CNV, copy number variation; SNV, single nucleotide variant; WES, whole exome sequencing



figure e-2. ***SLC35A2* expression in patient brain vs. other epilepsy brain tissues.** DESeq2 normalized SLC35A2 expression values for six brain tissues from our patient, compared to expression of SLC35A2 in brain tissues from other epilepsy patients. Fold-change in patient relative to other is -1.5 (p < 0.0001). Six brain tissues from our patient include A1, A2, B, C, D1, and D2.



figure e-3. **Plot of pathogenic and likely pathogenic sequence variants previously reported in *SLC35A2*.** Lollipop-style variant diagram displaying all pathogenic and likely pathogenic variants previously reported in ClinVar or peer-reviewed literature (as of July 7, 2019). The protein changes relative to NP\_001035963.1 and origin of each variant are listed along with diagnosis of the patient in which the alteration was detected. CGD, congenital disorder of glycosylation; EE, epileptic encephalopathy; EOEE, early-onset epileptic encephalopathy; FE, focal epilepsy; LGS, Lennox-Gastaut syndrome; WS, west syndrome

|  |  |  |  |
| --- | --- | --- | --- |
| ID | Tissue Source | Histology | Sample Type |
| Normal | Blood | N/A | Frozen |
| A1 | Left Temporal Lobe | Cortical dyslamination | Frozen |
| A2 | Left Temporal Lobe | Cortical dyslamination | Frozen |
| B | Left Amygdala | Fragment of gray and white matter with gliosis | Frozen |
| C | Left Hippocampus | Fragment of gray and white matter with gliosis | Frozen |
| D1 | Left Occipital Lobe and Pole | Cortical dyslamination | Frozen |
| D2 | Left Occipital Lobe and Pole | Cortical dyslamination | Frozen |
| E | Left Superior Temporal Gyrus | Cortical dyslamination | FFPE |
| F | Left Inferior Occipital Lobe | Cortical dyslamination | FFPE |
| G1 | Left Medial Occipital Lobe | Cortical dyslamination | FFPE |
| G2 | Left Medial Occipital Lobe | Cortical dyslamination | FFPE |
| H1 | Left Inferior Parietal Cortex | Cortical dyslamination | FFPE |
| H2 | Left Inferior Parietal Cortex | Cortical dyslamination | FFPE |

table e-1. **Description of all tissues used for analysis.** Details listed for each specimen include internally assigned ID (ID), anatomical origin (Tissue Source), histopathological assessment as determined by a board-certified neuropathologist (Histology), and preparation method used to preserve specimens (Sample Type). FFPE, formalin-fixed paraffin embedded

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| ID | Tissue Source | Sample Type | Total Reads | Mapped Reads | Mean Coverage | Bases Covered >= 20X  | Duplicate Reads |
| Comparator | Blood | Frozen | 254,978,958 | 56.3% | 222x | 98.5% | 30.4% |
| A1 | Temporal Lobe | Frozen | 281,534,278 | 63.1% | 282x | 98.6% | 23.7% |
| A2 | Temporal Lobe | Frozen | 338,558,622 | 63.5% | 342x | 98.7% | 24.0% |
| B | Amygdala | Frozen | 334,317,104 | 64.9% | 347x | 98.8% | 22.1% |
| C | Hippocampus | Frozen | 372,460,026 | 64.5% | 384x | 98.8% | 22.9% |
| D1 | Occipital Lobe  | Frozen | 312,807,558 | 64.7% | 323x | 98.7% | 21.8% |
| D2 | Occipital Lobe | Frozen | 311,161,848 | 62.5% | 309x | 98.7% | 25.2% |

table e-2. **Exome sequencing metrics for matched blood and affected brain tissues.**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Genomic location (GRCh37) | Gene | HGVS cDNA | HGVS protein | Zygosity | Origin | Interpretation |
| 14:102452850 | *DYNC1H1* | NM\_001376.4:c.2288C>T | p.Ala763Val | Heterozygous | Maternal | VUS |
| 11:125831607 | *CDON* | NM\_001243597.1:c.3643A>C | p.Met1215Leu | Heterozygous | Unknown | Poor phenotype fit |
| X:53223805 | *KDM5C* | NM\_004187.3:c.3554C>T | p.Thr1185Ile | Hemizygous | Unknown | Poor phenotype fit |

table e-3. **Filtered list of inherited germline variants identified in exome sequencing.** VUS, variant of unknown significance

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Genomic location (GRCh37)  | X:48762550 | 12:124970991 | 4:177605120 | 2:190584473 | 12:111886014 |
| Gene | *SLC35A2* | *NCOR2* | *VEGFC* | *ANKAR* | *SH2B3* |
| HGVS cDNA | NM\_005660.2:c.634\_635del | \*NM\_006312.5:c.229G>A | \*NM\_005429.4:c.1220G>A | \*NM\_144708.3:c.2400C>A | \*NM\_005475.2:c.1636C>A |
| HGVS protein | p.Ser212LeufsTer9 | p.Glu77Lys | p.Arg407His | p.His800Gln | p.Pro546Thr |
| Interpretation | Pathogenic | VUS | VUS | VUS | VUS |
| **Variant allele fractionAlt/Total reads (VAF%)** |   |   |   |   |   |
| Temporal lobe (A1) | 4/135 (3.0%) | 2/408 (0.5%) | 1/219 (0.5%) | 0 | 0 |
| Temporal lobe (A2) | 6/184 (3.3%) | 2/532 (0.4%) | 0 | 4/228 (1.8%) | 0 |
| Amygdala (B) | 23/184 (12.5%) | 11/513 (2.1%) | 5/237 (2.1%) | 0 | 4/343 (1.2%) |
| Hippocampus (C) | 57/206 (27.7%) | 1/536 (0.2%) | 5/279 (1.8%) | 0 | 0 |
| Occipital lobe (D1) | 15/153 (9.8%) | 2/408 (0.5%) | 2/229 (0.9%) | 0 | 0 |
| Occipital lobe (D2) | 1/166 (0.6%) | 1/414 (0.2%) | 0 | 0 | 0 |

table e-4. **Filtered list of somatic variants identified in exome sequencing.** VUS, variant of unknown significance; \*these variants were not validated using a secondary sequencing method