**Supplemental Method**

**Subject ascertainment**

Individuals underwent extensive pre-surgical evaluation with video electroencephalography (EEG) monitoring, high-resolution MRI, fluorodeoxyglucose (FDG)-PET, and subtraction ictal single photon emission computed tomography (SPECT) co-registered to MRI (SISCOM) to localize anatomic lesions. All subjects enrolled in this study showed no specific abnormal findings or subtle structural changes in MRI scan. The presurgical and surgical protocols were published previously in detail.1 The resection margin for epilepsy of neocortical origin was defined by 1) the presence of a massive and exclusive ictal-onset zone confirmed by intracranial EEG; 2) various interictal intracranial EEG findings, including repetitive spikes >3/s, runs of repetitive spikes, slow wave discharges, localized- or spindle shaped- fast activities, and electrodecremental fast activities; and 3) the absence of the eloquent cortex. Complete resection was defined by resection of all areas with seizure-onset and irritative zones on intracranial EEG. The pathological diagnoses of studied individuals were reconfirmed for this study according to the recent consensus classification developed by the International League Against Epilepsy (ILAE) Diagnostic Methods Commission and according to histopathological findings as proposed by the European Epilepsy Brain Bank (EEBB) Consortium.2, 3 The study was performed and all human tissues were obtained with informed consent in accordance with protocols approved by Severance Hospital and the KAIST Institutional Review Board and Committee on Human Research

**DNA extraction from tissue samples**

Genomic DNA was extracted from freshly frozen brain tissues and blood. The QIAamp mini DNA kit (Qiagen, USA) for freshly frozen brain tissues and the Flexigene DNA kit (Qiagen, USA) for blood were used according to the manufacturers’ protocols.

**Deep whole-exome sequencing for 13 NLFE patients**

Each sample was prepared according to the Agilent library preparation protocols (Agilent Human All Exon 50 Mb kit). Libraries underwent paired-end sequencing on an Illumina HiSeq 2500 instrument according to the manufacturer’s protocol. To evenly increase the average read depth of WES to more than 800×.

**Targeted amplicon sequencing for 18 NLFE or mMCD patients**

We performed targeted amplicon sequencing (mean depth, 1,230X) with 12 primers designed from Primer 34, 5. Human *SLC35A2* gene has 5 exons. Exon 1,3,5 were covered by 1 primer (~220 bp) and Exon 2,4 were covered by multiple primers which were overlapped at least ten bp. All designed primers overhung same 6 bp index sequences. Target sequences were PCR-amplified using PrimeSTAR DNA polymerase (Takara). For a second PCR amplification, 20 ng of purified PCR products from the first amplification were annealed with both Illumina adaptor and barcode sequences. To verify fragment sizes and the quality of the amplified libraries, individual aliquots were run on a 2100 Bioanalyzer (Agilent, USA). Libraries were pooled and sequenced on a HiSeq 2500 sequencer (Illumina, USA).

**Targeted hybrid capture sequencing**

We designed hybrid capture probes including 10 known MTOR pathway genes: *AKT3, DEPDC5, MTOR, PIK3CA, PIK3R2, PTEN, STRADA,TBC1D7, TSC1* and *TSC2* by using SureDesign online tools (Agilent Technologies). We performed library preparation according to the manufacturers’ protocol. The final libraries of hybrid capture were sequenced on a HiSeq 2500 sequencer (Illumina, USA).

**Validation sequencing for candidate somatic mutations**

Validation sequencing was performed in the same protocol as in targeted amplicon sequencing. We designed region-specific primers including 6 bp index sequences. Two cycle of PCR amplification for annealing both illumina adaptor and barcode sequences were performed. Amplified library were sequenced on a HiSeq 2500 sequencer (Illumina, USA).

**Bioinformatics analysis**

To generate analysis-ready bam files from Fastq files, we used the “Best Practices” workflow suggested by the Broad Institute. We aligned raw sequences from Fastq files to the GRCh37 assembly of the human genome reference sequence using BWA-MEM. For somatic mutation analysis, we utilized MuTect and Strelka for analyzing matched brain and peripheral sample sequencing data sets6, 7. All identified mutations were annotated using the snpEFF program. We applied in-house filtering criteria to exclude 1) read depth < 100, 2) registered mutations in a public database (common dbSNP147); 3) mutations with a putative low snpEFF impact score; 4) mutations with a PolyPhen & SIFT ≠ Damaging, phastCons score <0.9; 5) mutations with an allele frequency in the ExAC database for minor allele frequency (MAF) and East Asian populations > 0.01%; and 6) EB score < 5.0998, 9. To determine the cutoff value for the EBfilter (EB score), we used an in-house sequencing dataset as a normal control sample and previously reported validation results for somatic mutations as an positive call set10, 11. Then, to reduce false positive calls, we applied a cutoff value (EB score =5.099) showing the highest precision/recall value. After filtering process, we manually investigated mutations using Integrative Genomics Viewer (IGV) according to the following exclusion criteria; 1) adjacent alterations, not germline mutation, were found only in reads with target mutation; 2) target mutation detected in the read in one direction; 3) one or more biological similar sequence regions calculated by BLAST (https://blast.ncbi.nlm.nih.gov/Blast.cgi)12. All filtered variants were considered as true positive if site-specific amplicon sequencing revealed over 1 % of variant supporting read13. In case of amplicon sequencing data from control peripheral tissue DNA, we estimated the probability value for true positive calls using previously described method14. For germline analysis, we used GATK haplotypecaller. After initial calling process, we extracted variants called from 33 genes potentially linked to intractable focal epilepsy. All extracted variants were applied same in-house filtering criteria described previously.

**Histopathologic images**

The surgical specimens were fixed with 20% buffered formalin and embedded in paraffin. 4 µm thick coronal slices of specimens were prepared using a microtome (Leica RM 2135). FFPE slides were deparaffinized and rehydrated for the removal of paraffin. For H & E stating, acquired brain sections were stained with hematoxylin and eosin. For Immunohistochemical staining, deparaffinized FFPE slides were used in a heat-induced retrieval process with citrate buffer (sodium citrate 10mM[pH 6.0]) for enhancing the staining intensity of antibodies. Processed slides were blocked in 0.3% H2O2 solution in PBS for 10 minute at room temperature and stained with the NeuN (clone A60; Millipore, Billerica, USA; dilution 1:3000) using a Ventana Discovery XT automated staining system (Ventana Medical System, Tucson, AZ, USA). For immunohistochemistry, freshly frozen samples were fixed in freshly prepared phosphate-buffered 4% paraformaldehyde for overnight, cryo-protected in 30% buffered sucrose. 16 µm thick coronal cryostat-cut sections were prepared and blocked in PBS-GT (0.2% gelatin and 0.2% Triton X-100 in PBS) for 1h at room temperature and stained with the following antibodies: rabbit antibody to phosphorylated S6 ribosomal protein (Ser240/Ser244) (1:500 dilution; 5364, Cell Signaling Technology) and mouse antibody to NeuN (1:500 dillution; MAB377, Milipore). Sample were then washed in PBS and stained with the following secondary antibodies: Alexa Fluor 594-conjugated goat antibody to rabbit (1:500 dilution; A11012, Invitrogen), Alexa Fluor 488-conjugated goat antibody to mouse (1:500 dilluion; A11001, Invitrogen). DAPI included in mounting solution (P36931, Life Technology) was used for nuclear staining. Images were acquired using a Zeiss LSM880 confocal microscope (Carl Zeiss). The number of cells positive for P-S6 was determined with the 10X objective lens; 3 fields were acquired per subject.

**Brain tissue N-glycan preparation**

N-glycans of human brain tissues were prepared through following steps: 1) membrane extraction; 2) enzymatic N-glycan release; 3) glycan enrichment. Briefly, each brain tissue put into a homogenization buffer composed of 20 mM HEPES-KOH, 0.25 M sucrose, and protease inhibitor mixture, and then was sonicated for tissue lysis. For membrane extraction, the lysates were centrifuged at 60,000 rpm for 45 mins, washed and resuspended in 0.2 M sodium carbonate (pH 11), and finally centrifuged once more. Each membrane pellet was solubilized in a buffer solution of ammonium bicarbonate and dithiothreitol, and then thermally denatured in hot water at 100 degrees Celsius. For enzymatic release of N-glycans, 2 µl of peptide N-glycosidase F was loaded into sample solution and incubated in a water bath at 37 degrees Celsius for 16 h. The chilled ethanol was added to the mixture, and stayed at -80 degrees Celsius for 1h. After centrifuging it, the glycan-rich supernatant was collected and vacuum-dried. Released N-glycans were purified and enriched by porous graphitized carbon based solid phase extraction (PGC-SPE), which performed according to previously optimized steps15. After washing and conditioning of PGC cartridges, each N-glycan solution was loaded and pure-water was added to remove detergents such as remained chemicals. N-glycans were eluted in sequence with 10%, 20% acetonitrile in water (v/v), and 40% acetonitrile with 0.05% trifluoroacetic acid in water (v/v). All eluents were dried in vacuum prior to MS analysis.

**NanoLC/MS and CID MS/MS Analysis**

N-glycans of all tissues were analyzed by nanoLC chip/Q-TOF MS (Agilent Technologies). Briefly, each aqueous glycan solution was injected into a PGC chip composed of a 9 x 0.075 mm i.d. trapping column and a 43 x 0.075 mm i.d. analytical column. N-glycan mixtures were pre-concentrated and purified using 3.0% acetonitrile (ACN) and 0.1% formic acid (FA) (v/v) in water at 4 µl/min. The separation of enriched glycans was performed by binary system consisting of (A) 3.0% ACN in 0.5% FA solution and (B) 90.0% ACN in 0.5% FA solution at 0.4 µl/min. They were eluted with the gradient: 2.5-20 min, 0-16% B; 20-40 min, 16-44% B; 40-45 min, 44-100% B. MS spectra were obtained in positive ionization mode at a mass range of m/z 500-2500. For CID MS/MS, different collision energies were applied according to m/z values of the precursor ions. Raw LC/MS and MS/MS data were processed using MassHunter Qualitative Analysis software (Agilent Technologies).

**Supplementary reference**

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