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RESEARCH ARTICLE

Deep whole genome sequencing of epileptogenic brain lesions

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Abstract

Objective: Malformations of cortical development and low-grade epilepsy-associated tumors often cause drug-resistant lesional focal epilepsy (LFE) amenable to surgical treatment. Genetic testing of resected brain tissue can provide diagnostic and mechanistic information and may eventually support personalized treatment approaches. However, systematic >300× whole genome sequencing (GS) of bulk epileptogenic lesions, particularly after nondiagnostic deep exome sequencing and array-based genotyping, has not been evaluated.

Methods: Here, we performed deep GS (>300× coverage) on 33 epileptogenic brain lesions from individuals with LFE, selected for lesions with a high prior probability of a genetic finding, all of whom had negative results for candidate germline or somatic variants in previous deep exome sequencing (ES; >350× coverage) and array-based genotyping.

Results: We identified candidate somatic variants in known LFE-associated genes in seven of 33 participants (21%). Two participants had two candidate variants each. In total, three of 33 participants (9%) had variants that could only be detected by GS: two deletions in *TSC2*, two deletions in *NPRL3*, and an exonic inversion in *FGFR1*. Three individuals had germline polymorphisms that may represent modulators or risk factors. Exploratory mutational signature analysis revealed clocklike signatures and a correlation between mutational signatures, age at seizure onset, and histopathology, indicating an age-related mechanism of mutation.

Significance: Deep GS establishes the feasibility of genome-wide profiling at a depth relevant to low-variant allelic frequency mosaicism and reveals candidate

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variants missed by ES, particularly complex structural variants. As sequencing costs decrease, GS may complement other technologies in somatic variant detection, enabling more widespread clinical implementation of tissue sequencing in epilepsy surgery. Further studies are needed to address the remaining conceptual and technological challenges in somatic variant detection.

KEYWORDS

deep sequencing, epilepsy genetics, next generation sequencing, somatic variant

1 | INTRODUCTION

More than 30% of individuals with epilepsy, which affects an estimated 3.4 million Americans (1.2% of the population), continue to experience seizures despite optimal medical treatment.[1,2] Treatment failure is particularly common (up to 50%) in lesional focal epilepsy (LFE), where epileptogenic brain lesions are the cause of seizures.[3] These epileptogenic brain lesions, including malformations of cortical development (MCD) and low-grade epilepsy-associated tumors (LEAT), may be amenable to epilepsy surgery, a safe and effective treatment option. Surgical outcome is influenced by the underlying genetic etiology.[4] Overall, genetic testing from resected brain tissue may improve histopathological accuracy, inform postoperative prognosis, and potentially enable precision therapies.[5–7]

To date, LFE has been associated with brain-specific somatic variants in more than 20 genes.[8,9] Still, ~65% (15%–85%) of all cases currently remain unsolved,[5,8] likely partially related to technological limitations, as panel sequencing represents the current standard. Recent studies have improved upon this by using exome sequencing (ES) to investigate the genetic causes of LFE.[8–10] However, even this approach remains subject to two key technical limitations compared to the most comprehensive testing, genome sequencing (GS). First, quality of sequencing (i.e., depth distribution, genotype quality, and minor read ratio) is generally higher in GS, which results in more true-positive variants and fewer false-positive variants compared to ES.[11] Second, ES cannot capture the entire spectrum of genetic variants, including structural variants (SVs), large deletions, and noncoding single nucleotide polymorphisms (SNPs) or indels, which are known to occur in a large proportion of LFE cases.[12] This makes GS a promising diagnostic approach to facilitate the clinical use of genetic biomarkers.[13]

In germline disorders, including other forms of epilepsy, GS can identify genetic causes in individuals who remained undiagnosed after ES.[14] The systematic application of deep GS to bulk epileptogenic brain tissue, particularly after nondiagnostic deep ES and array-based genotyping, remains largely unexplored. This is not a routine substitution; the >300× coverage evaluated here extends deep sequencing to the entire genome and generates approximately an order of magnitude more sequence data than conventional ~30× research GS, a depth difference that is central to reliable interrogation of low-variant allelic frequency (VAF) somatic mosaicism. We therefore aimed to evaluate a comprehensive approach for detecting somatic variants in brain tissue using deep GS (>300× coverage), following nondiagnostic deep ES (>350× coverage) and array-based genotyping in our previous study.[10] Our primary objective was to demonstrate feasibility and, through our implementation, highlight areas in somatic variant detection that represent ongoing technological and conceptual challenges.[5] We therefore report "candidate variants" but do not claim diagnostic yield.

Key points

- Deep (>300×) GS enables genome-wide interrogation of epileptogenic brain lesions at a depth relevant to low-VAF mosaicism but remains subject to conceptual and technological challenges.
- Deep GS reveals candidate variants and exploratory mutational signatures that may be associated with electroclinical and histopathological phenotypes.
- Adoption of brain tissue sequencing will require equitable access, standardized variant assessment, and broader sample availability.

2 | MATERIALS AND METHODS

The study protocol was approved by the institutional review boards (IRBs) of the Cleveland Clinic Epilepsy Center (IRB approval ID 20–151) and the University of Erlangen, Germany (IRB approval ID 193_18B). All participants provided written informed consent for study

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participation. In total, we identified 33 participants with LFE from the European Epilepsy Brain Bank. Brain tissue samples were previously sequenced with deep (>350×) ES and genotyped with Illumina OmniExpress SNP arrays without identifying a candidate germline or somatic variant, including copy number variants.[10] Samples were selected for deep GS if they had a lesion associated with a high diagnostic probability of a genetic finding: focal cortical dysplasia type IIB (FCD IIB), dysembryoplastic neuroepithelial tumor (DNET), ganglioglioma, or mild malformation of cortical development with oligodendroglial hyperplasia in epilepsy (MOGHE).

We repeated DNA extraction from fresh-frozen bulk brain tissue following microscopic analysis of frozen sections and performed deep (>300×) GS (Supplementary Methods). Germline and somatic single nucleotide variants (SNVs) and SVs were detected using a custom in-house computational pipeline (Supplementary Methods). The DNA extraction method and sequencing platform were the same across both studies; however, DNA was re-extracted from the source tissue for GS, which limits direct platform comparison.[10] Each sample with candidate variants received independent histopathological review to confirm the original lesion diagnosis, including additional immunohistochemistry where required, as previously described.[8] The sample and analysis workflows are shown in the Supplementary Methods.

Each candidate variant was reviewed by a multidisciplinary panel consisting of an epileptologist (C.M.B.), neuropathologists (I.B. and L.H.), and genetics researchers (D.L. and C.L.). Unlike in cancer,[15] there are no comprehensive classification guidelines for somatic variants in nonmalignant diseases such as lesional focal epilepsy, beyond formal initial efforts (*AKT3, MTOR, PIK3CA*, and *PIK3R2*).[16] In several cases, gene–disease associations have been supported by large-scale sequencing studies,[8] but the underlying disease mechanism remains to be resolved (e.g., *SLC35A2, DYRK1A, EGFR*). Therefore, we consider variants that passed the variant calling and filtering (Supplementary Methods) to be candidate variants that cannot claim (likely) pathogenicity in the absence of direct experimental evidence. Furthermore, this study was not powered for gene discovery, and we therefore only considered variants in genes with established LFE disease validity (*MTOR, SLC35A2, AKT3, PIK3CA, RHEB, TSC1, TSC2, NPRL2, NPRL3, DEPDC5, PTEN, BRAF, FGFR1, MYB, MYBL1, PTPN11, NRAS, KRAS, NF1, DYRK1A*, and *EGFR*).[8]

Candidate variants were considered to be specific to genome sequencing if they fulfilled one of the following criteria: (1) noncoding variants; (2) deletions not covered by the ES enrichment kit SureSelect Human All Exon V7, or within the size interval that cannot reliably be detected by ES[9,17]; or (3) other SVs. Specifically, we did not consider SNVs not previously called on ES for the calculation of GS-specific yield of candidate variants. These SNVs may be hard to sequence, but they may also be explained by the repeated extraction of DNA from the source tissue.[18]

Somatic SNVs were further filtered using DeepMosaic, a deep-learning model for postcalling quality control that enables highly accurate validation of somatic variants in noncancer samples without matched controls.[19] This filtered subset was used for mutational signature assignment with the SigProfiler suite, reporting the COSMIC SBS96, ID83, and SV decomposed solutions.[20] Detection of putative local hypermutational events (kataegis) was done with unsupervised changepoint analysis via the Katdetectr R package at default parameters.[21]

3 | RESULTS

3.1 | Deep GS from 33 resected epileptogenic human brain lesions

Here, we report results from deep GS of 33 resected epileptogenic human brain lesions (MCD, $n = 24$; LEAT, $n = 9$) from 21 (64%) male and 12 (36%) female participants. Overall, participants had seizure onset and epilepsy surgery early in life (median age at seizure onset = 4 years, interquartile range [IQR] = 2–7 years, range = 0–28 years; median age at surgery = 16 years, IQR = 8–26 years, range = .3–45 years), with a median length of follow-up of 2 years (IQR = 24–24 months, range = 6–228 months). Postoperative outcomes for seizure freedom were excellent (Engel I, i.e., "free of disabling seizures": 30/33, 91%; Engel I–II, i.e., including "rare disabling seizures": 32/33, 97%). Each participant had previously received nondiagnostic deep ES and array-based genotyping as part of a previous cohort study.[10] Deep GS achieved an average per-target depth of 294× (SD = 39×) and was superior to ES for global, exon-level, and target-level coverage (Figure S1).

Overall, we identified candidate somatic variants in known LFE-associated genes in seven of 33 (21%) selected individuals with MCD or LEAT. Two participants had two candidate variants each. In total, three of 33 participants (9%) had variants that could only be detected by GS (Figure 1): two deletions in *TSC2*, two deletions in *NPRL3*, and an exonic inversion in *FGFR1* (Table 1). Across all participants, we identified a total of two known and seven novel candidate somatic variants. All novel variants were absent in large population databases (gnomAD, gnomAD-SV, TOPMed, DiscovEHR, UKBB) and databases of somatic variation (COSMIC). One case with ganglioglioma carried BRAF V600E, an established oncogenic variant.[22] The *RHEB* doublet variant, c.(A104T, C105A):p.Y35L, was

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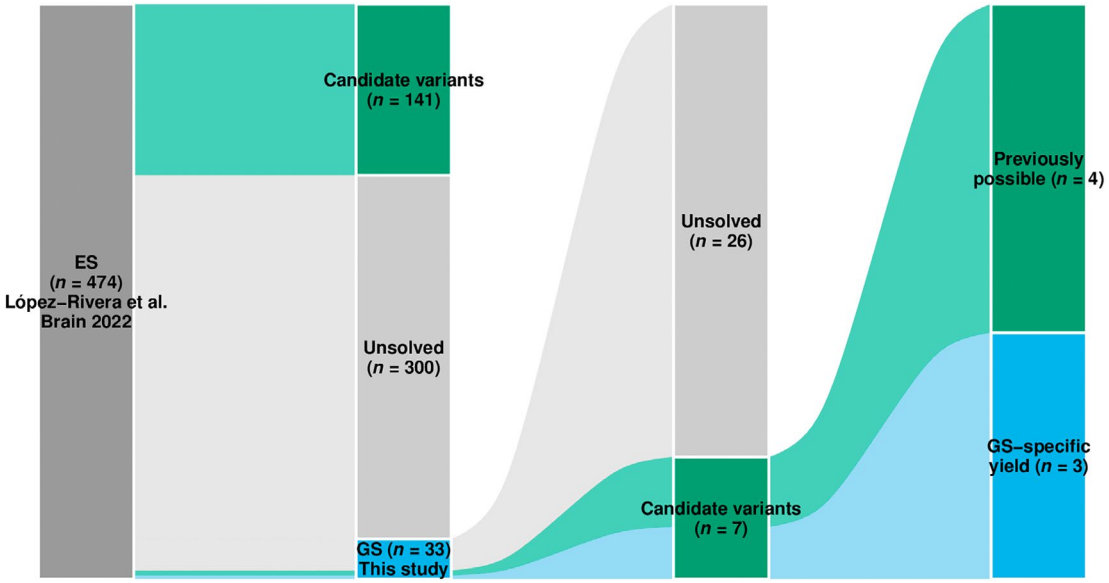

FIGURE 1 Deep genome sequencing (GS; coverage > 300×) after nondiagnostic deep exome sequencing (ES; coverage > 350×). Alluvial plot shows patient flow from the previous ES cohort ($n = 474$) through the GS follow-up ($n = 33$) presented in this study to final outcome.

previously described in another case of FCD II, where it was demonstrated to act as a strong activator of mTOR signaling.[23] One case with MOGHE carried a novel missense variant in *SLC35A2* that was predicted to be deleterious in silico (REVEL, .912; AlphaMissense, .996),[24,25] with prior experimental evidence of a similar variant at the same position (G178I) demonstrating loss of membrane trafficking.[26] Furthermore, we retained two deletions in *NPRL3* as candidate variants based on very high genomic constraint (JARVIS score > .9998, 99th percentile)[27] and the known functional relevance of the 5′ untranslated region of *NPRL3*.[28,29] Meanwhile, the exonic inversion in *FGFR1* is expected to fall within the kinase domain (breakpoints around p.Leu557 and p.Arg576), which is under high regional constraint (exome-wide missense tolerance ratio, 1st percentile) and has known biological relevance in DNET.[30–32]

We inspected all candidate variants in the Integrative Genomics Viewer[33] to evaluate for mapping quality and strand bias (Figure S2). For each variant, we also inspected the BAM files from our deep ES study to determine whether any of the reads supported the variant identified by GS, without surpassing the necessary thresholds leading to a variant call. One variant, *TSC2* p.L204Afs*30 in sample 156409 with an FCD IIB, was seen in ES data but was not called likely due to low VAF (4/353, .01). All other variants were absent from ES data. Illustrative examples are shown in Figure S3. We did not detect candidate germline SNVs or SVs. Sample 156415, an FCD type IIB with a candidate somatic variant in *TSC2*, was heterozygous for two common polymorphisms in related genes, *TSC1* (rs1073123) and *PTEN* (rs12573787). Similarly, samples 156393 and 156413 carried one of rs1073123 and rs12573787, respectively.

Knowledge of an underlying genetic etiology can improve the diagnostic accuracy of histopathology.[6] Therefore, we repeated the histopathological assessment for each case, including additional immunohistochemical staining where required. The initial histopathological diagnosis was confirmed in each case, and representative histopathological findings are shown in Figure 2. This match between histopathology and the expected genetic etiology serves as additional support for the genetic results. The clinical and histopathological characteristics of the entire study cohort are shown in Table S1.

3.2 | Exploratory analysis of mutational signatures and changepoint detection

Next, we explored whether deep GS could provide additional biological insight into the etiology and clinical characteristics of epileptogenic lesions. We assigned mutational signatures based on the COSMIC decomposed solutions using the SigProfiler[20] suite, after additional post-calling somatic variant quality control with DeepMosaic.[19] Of 79 COSMICv3.3 SBS signatures, each sample carried two clocklike mutational signatures of single-base substitutions (SBS: SBS1, SBS5; Figure S4), which are generally indicative of an endogenous mutational process that correlates with patient age. The same clocklike behavior was observed for indel signatures (Figure S5), whereas SV signatures were ubiquitous and nonspecific (Figure S6). Sample-level assignment statistics are shown

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TABLE 1 Clinical characteristics and key findings of the cases presented in this study.

ID	Variant(s)	Effect	VAF (alt/all)	Pathology	Sex	Age at onset/surgery, years	Outcome (Engel)
156415[a]	NM_000548 (***TSC2***):c.4006_4483del:p.S1337Tfs*80	Frameshift deletion	.03 (18/716)	FCD IIB	M	17/27	IA
156393	NM_005660 (***SLC35A2***):c.G533T:p.G178V	nsSNV	.294 (45/153)	MOGHE	M	.17/2.42	IA
156409	NM_021055 (***TSC2***):c.609_610del:p.L204Afs*30	Frameshift deletion	.02 (5/298)	FCD IIB	M	2/16	IA
156413	NM_005614 (***RHEB***):c.104_105delinsTA:p.Y35L	Nonframeshift substitution	.03 (8/288)	FCD IIB	M	5/5	IA
205933	NM_001354609 (***BRAF***):c.T1799A:p.V600E	nsSNV	.03 (9/266)	GG	F	.67/31	IA
156390[a]	NM_023110 (***FGFR1***):g.38273518_38273577inv NM_001077350 (***NPRL3***):g.188319_188541del	Inversion 223-bp 5′ UTR deletion	.007 (3/442) .03 (5/154)	DNET	M	5/6	IA
156421[a]	NM_001077350 (***NPRL3***):g.188319_188573del NM_021055 (***TSC2***):c.1840_2097del:p.A614_Q699del	255-bp 5′ UTR deletion Nonframeshift deletion	.18 (11/61) .005 (3/562)	FCD IIB	M	7/8	IA

Abbreviations: DNET, dysembryoplastic neuroepithelial tumor; F, female; FCD, focal cortical dysplasia; GG, ganglioglioma; M, male; MOGHE, mild malformation of cortical development with oligodendroglial hyperplasia in epilepsy; nsSNV, nonsynonymous single nucleotide variant; UTR, untranslated region; VAF, variant allelic frequency (with alt reads and total reads shown in brackets).

[a]Samples had variants that cannot be identified with exome sequencing and require genome sequencing.

in Tables S2–S4, and the tumor mutational burden plot is shown as Figure S7A. We found that the mutational signature SBS1, but not SBS5, correlated with age at seizure onset (Figure S7B). Importantly, we found no evidence of exogenous mutagenic processes or patterns related to defective DNA repair, which are common in other cancers. Regarding clinical correlations, total mutational burden was not different for cases with an unfavorable surgical outcome compared to cases with a favorable surgical outcome (Figure S7C). For SBS1, but not for SBS5, LEAT had a higher mutational signature burden compared to MCD (SBS1: median = .646, IQR = 1.720 vs. median = −.467, IQR = .400; Wilcoxon unpaired two-sample test, $W = 32.5$, $p = .0024$; SBS5: median = .428, IQR = .568 vs. median = −.399, IQR = 1.120; Wilcoxon unpaired two-sample test, $W = 79.5$, $p = .258$; Figure S7D). The lack of association with other mutational signatures suggests that this effect is not simply based on total mutational burden. Pending further validation in larger and independent cohorts, mutational signatures from deep GS may eventually provide additional diagnostic information beyond the detection of single candidate somatic variants.

Lastly, we investigated whether epileptogenic lesions showed evidence of localized hypermutations that colocalize with somatic genome rearrangements, so-called kataegis, which have recently been identified as key prognostic markers in cancers.[34] Unsupervised changepoint analysis did not yield any putative foci. Thus, we found no evidence of hypermutation phenomena or large-scale somatic genome rearrangement in our samples.

4 | DISCUSSION

4.1 | Deep genome sequencing identifies candidate variants in exome- and array-negative cases of LFE

Here, we show that using deep GS in individuals with LFE may detect candidate somatic variants. Even though all participants had previously undergone deep ES and array genotyping, we achieved a candidate variant yield of seven of 33 (21%), which is comparable to the results of recent studies analyzing tissues that had not been sequenced before.[5,8] Two individuals had two candidate variants each, a phenomenon that has been observed in previous studies.[35] In the absence of comprehensive somatic variant pathogenicity classification guidelines, their respective contribution to the participants' phenotypes cannot be fully resolved, and different mechanisms remain possible (e.g., dual etiology, phenotype modulation).[36] We identified GS-specific variants in three of 33 (9%) of our samples, highlighting the

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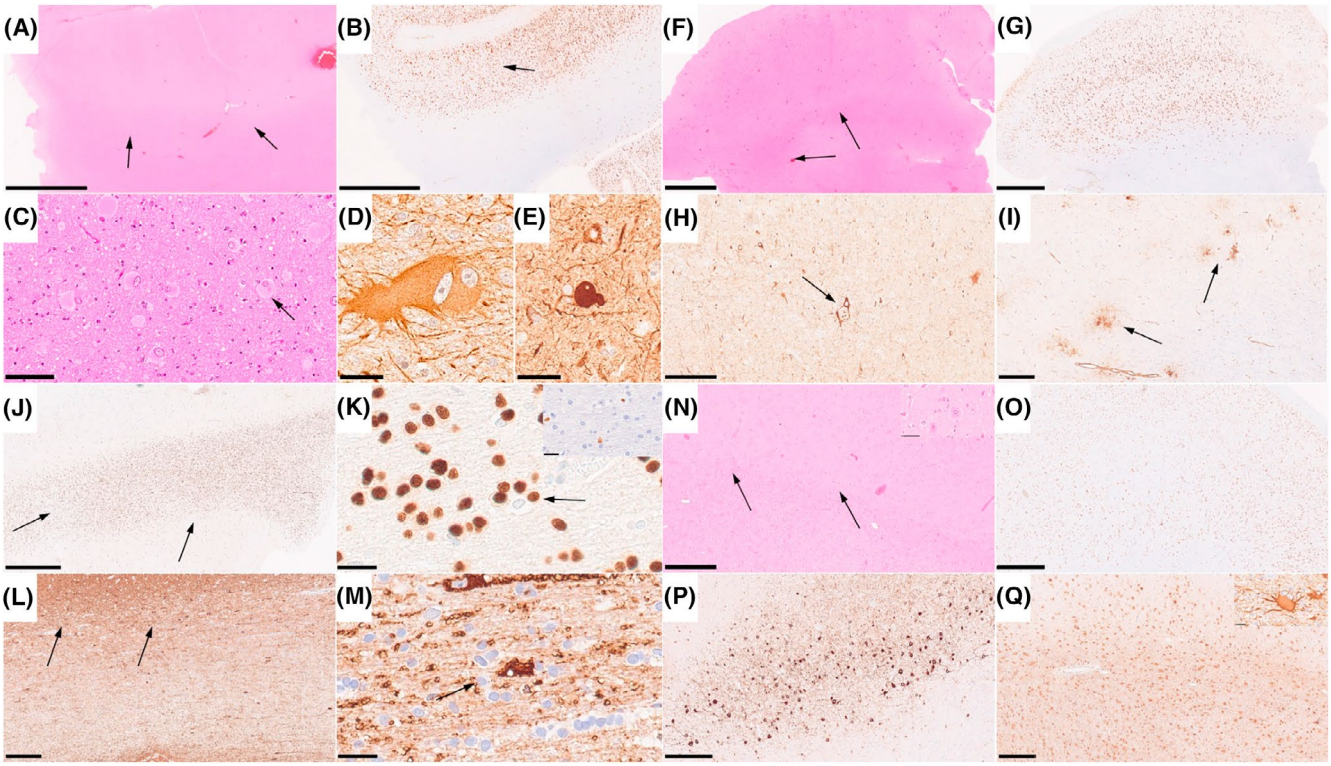

FIGURE 2 Representative histopathological findings for four cases presented in this study. Sample 156415 was a focal cortical dysplasia type IIB (FCD IIB) with sparse dysmorphic neurons. (A) In hematoxylin and eosin (H&E), gray–white matter boundary blurring can be detected. (B) NeuN immunohistochemistry indicated an area with large brown dysmorphic neurons accumulating neurofilament. (C–E) Frequent balloon cells were seen in the white matter (C; H&E; representative magnification in panels D and E), with strong vimentin positivity. Scalebars: A, B, 2.5 mm; C, 100 µm; D, 25 µm; E, 50 µm). (F–I) Sample 156409 was a FCD IIB with sparse balloon cells and sparse dysmorphic neurons. (F) In H&E, gray–white matter boundary blurring could be seen in overview. (G) Immunohistochemistry against NeuN indicated loss of the six-layered cortical lamination. (H) Within the cortex, singular dysmorphic neurons with neurofilament accumulation were found (arrow). (I) Sparse nests of balloon cells were marked with vimentin (arrows). Scalebars: F, G, 1 mm; H, I, 250 µm. (J–M) Sample 156393 was a MOGHE (mild malformation of cortical development with oligodendroglial hyperplasia in epilepsy) in a small proportion of the white matter. Typical high oligodendrocytic density (J, arrows) is shown with oligodendrocytic clusters (K, arrow, brown nuclei; Olig2 immunohistochemistry) surrounding neurons (M, arrow, brown nucleus with surrounding blue oligodendrocytes; Map2 immunohistochemistry). Very low proliferative activity was detected with Ki67 staining (K, inset). (L) Gray–white matter blurring and heterotopic neurons (dark brown nuclei below arrows) in white matter were illustrated with Map2 immunohistochemistry (arrows indicating gray matter). Scalebars: J, 1 mm; K (and inset), L, 25 µm; M, 250 µm. (N–Q) Sample 156413 was a large FCD IIB. In H&E, gray–white matter boundary blurring can be detected in overview (N, arrows). Dysmorphic neurons were readily visible in H&E (N, inset). There was complete loss of six-layered cortical lamination and dysmorphic neurons were enriched at lesion site (O, NeuN staining, neurons in brown; P neurofilament staining, dysmorphic neurons in dark brown). Concordant balloon cells (inset in Q) in large quantity could be spotted in white matter (Q, vimentin immunohistochemistry, balloon cells in brown, darker/lower proportion) and partially in gray matter (Q, lighter/upper proportion). Scalebars: N, P, 500 µm; N, inset, 50 µm; O, 1 mm; Q, 250 µm.

advantages of deep GS over less comprehensive technologies. Because this yield is calculated based on already established LFE-associated genes, this represents only the initial lower bound of a comprehensive whole genome approach. These findings are in line with the yield of GS after nondiagnostic ES in germline variant studies in epilepsy (7/125, 5.6%)[14] and other rare genetic disorders (9%–60%),[37] but behind the added yield seen in cancer sequencing studies (GS vs. ES: 89% vs. 62%).[38] We identified variants at low (<10%) and ultralow (<2%) VAFs, in line with previous evidence.[12] Accordingly, this study should not be interpreted as a routine comparison of standard-coverage GS with ES; the technical advance lies in extending >300× sequencing to the entire genome in bulk lesion tissue. This depth is required for reliable interrogation of low-level somatic variation, a major established genetic mechanism in LFE.[5]

We have shown that deep GS is advantageous in this particular scenario. However, at >300× coverage, the approach generates approximately 10-fold more sequence data than conventional ~30× research GS and currently costs ~US$10 000 per sample. This resource

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intensity has led to recent research into alternative approaches for the detection of rare somatic variants, including target enrichment by fluorescence-activated cell sorting and whole genome amplification to increase VAF,[12] and RNA sequencing to detect somatic structural variation and gene fusions, which can contribute significantly to yield.[18] Target enrichment is feasible but technically challenging and thus likely less feasible at the large scale required by gene discovery studies or future clinical applications. RNA sequencing will first require further GS studies to more clearly describe the genomic landscape of structural variation in LFE. Each of these methods shares the same potential benefit; through somatic variant detection, we may further our understanding of neurodevelopmental disease mechanisms, inform histopathological diagnoses, and guide precision treatment for affected individuals.[17,39,40] At present, somatic variant detection in resected tissue is primarily of diagnostic value and mechanistic interest. Its direct impact on treatment selection or postoperative management remains limited and requires prospective studies. As sequencing costs decrease, deep GS may complement or extend existing technologies in somatic variant detection. This approach may facilitate the clinical implementation of tissue sequencing in the care of individuals receiving epilepsy surgery.

Interestingly, we identified common germline polymorphisms in three of our samples. None of these polymorphisms can be considered candidate variants by themselves, but they may represent modulators or risk factors. Previously, these polymorphisms, rs1073123 (*TSC1*) and rs12573787 (*PTEN*), have been associated with genetic risk for specific cancers and the likelihood of progression-free survival after chemotherapy.[41,42] Although their role in LFE remains to be clarified, we hypothesize that common variants may influence disease risk and phenotype in a manner analogous to that observed in germline monogenic epilepsy syndromes and other neurodevelopmental disorders.[43,44] Further exploratory analyses—enabled by the comprehensive profiling provided by deep GS—revealed evidence of mutational signatures with known clocklike behavior. We observed correlations with histopathology (LEAT vs. MCD) and age at seizure onset, in line with their known accumulation with age related to an interplay of DNA damage and repair.[45] These clinical correlations may eventually provide clinically informative signals, that is, if reported and molecularly estimated age at disease onset do not match (which is key information for postoperative prognosis[46]) or if the reported histopathology does not match the molecular profile, possibly prompting reassessment as in a previous iterative agreement trial.[6] Importantly, this concept of mutational signatures in nonmalignant neurological disease is not yet established and requires validation in independent cohorts. Larger follow-up studies may also reach the power required for de novo mutational signature extraction.[20]

4.2 | Limitations

Several limitations apply. We deliberately selected lesions with a high prior probability of an underlying genetic etiology. This may introduce selection bias, and the estimated additional yield of deep GS shown here likely does not apply to other less specific epileptogenic lesions (e.g., FCD I or III). Furthermore, we note that deep GS from bulk tissue requires a relatively large amount of genomic DNA. We therefore were not able to conduct GS from the same DNA that was previously used for ES in the discovery cohort, as the derived material was previously exhausted, and instead had to repeat DNA extraction from the same sample. We acknowledge that re-extraction of DNA may have contributed to some of the additional yield of candidate variants and may confound direct platform comparison.[18] Due to the retrospective biobank-based design of this study, paired blood samples were not available, and all analyses were done on unpaired brain samples. We therefore cannot fully exclude misclassification of germline variants, comment on multitissue versus brain-specific variant distribution, or extend our lower credible VAF threshold to include potentially disease-related ultralow-frequency variants.

Experimental validation (e.g., droplet digital polymerase chain reaction) would have strengthened this study but was not feasible due to the retrospective design and regulatory constraints governing sample use. We mitigated the risk of sequencing artifacts by visual analysis of all candidate variants, the use of advanced postcalling quality control algorithms (DeepMosaic), and through independent biological evidence from histopathology (i.e., only considering variants that follow known genotype–phenotype correlations) but acknowledge that using paired samples would have been more robust.[5] In particular, distinguishing germline variants relies on VAF cutoffs from credible intervals derived from sequencing studies that did not use GS. Furthermore, lesion-only samples cannot be used to distinguish broadly spread versus brain-specific somatic events. In addition, the interpretation of complex structural variants remains challenging. We therefore report high-confidence structural variants that cover known LFE genes. Future studies may benefit from prospective recruitment of paired samples and the use of DNA biobanking in addition to tissue storage, facilitating reanalysis and validation. The yield of somatic variant detection with GS will likely continue to increase as additional gene–disease associations for LFE are discovered.[8]

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5 | CONCLUSIONS

Deep GS may complement or extend existing technologies in somatic variant detection from bulk brain tissue while establishing a technical benchmark for future tissue-sequencing studies in epilepsy surgery. Fully realizing the potential of this diagnostic approach will depend on decreasing sequencing costs, as deep GS is currently prohibitively expensive for widespread clinical implementation.[5] This cost has to be carefully considered, as the potential clinical benefits of somatic variant detection remain to be further investigated, and studies on cost-effectiveness will be needed. Accessibility of this method will depend on multiple stakeholders including national reimbursement structures, as in standard depth GS for germline disorders, and may worsen inequality in genomic testing in low- and middle-income countries.[47] Accurate and standardized interpretation of somatic variants will require continued efforts toward variant classification guidelines.[16]

AUTHOR CONTRIBUTIONS

Conceptualization: Christian M. Boßelmann, Costin Leu, and Dennis Lal. *Investigation & data curation*: All authors. *Writing—original draft*: Christian M. Boßelmann and Dennis Lal. *Writing—review & editing*: All authors. *Supervision*: Dennis Lal.

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CONFLICT OF INTEREST STATEMENT

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

DATA AVAILABILITY STATEMENT

VCF (Variant Call Format) files supporting the findings of this study are publicly available on Zenodo (DOI

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10.5281/zenodo.20742591). Additional deidentified participant data will be made available on request to the corresponding author. Raw sequencing data are not openly available due to informed consent limitations, which did not include specific language permitting public raw data sharing. These data are securely stored in controlled access data storage at the Cleveland Clinic Epilepsy Biorepository and Data Registry, Cleveland Clinic, Ohio, USA. To access the raw sequencing data, requests should be directed to the corresponding author. Requests will be reviewed promptly, with a response provided within 1 month of receipt. Data sharing will be contingent upon an institutional data use agreement, which will not impose prior restrictions on the use of the data.

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