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Surgical decision-making in adult patients with epilepsy related to germline mutations: A single-center study

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Abstract

Objectives: Genetic testing is not routinely performed during presurgical evaluation of adult patients with epilepsy.

Methods: In this retrospective observational study, we analyzed the diagnostic yield of an epilepsy multigene panel and patient characteristics in adult epilepsy surgery candidates from 2014 to 2024. We compared data collected from patients with GTPase-activating protein activity toward Rags 1 (GATOR1) and non-GATOR1 pathway mutations.

Results: In total, 31 of the 236 (13%) patients tested positive for monogenic epilepsy disorders. The epilepsy multigene panel diagnostic yield was 12% (28 of the 233 patients). Overall, 9 of the 31 patients had GATOR1 pathway mutations. Moreover, 15 of the 31 patients underwent invasive electroencephalography evaluations, with 6 exhibiting GATOR1 and 9 exhibiting non-GATOR1 pathway mutations. In the GATOR1 mutations group, three of the six (50%) patients had focal ictal onset. In the non-GATOR1 mutations group, two of the nine (22%) patients had focal ictal onset. Overall, 8 of the 31 patients underwent resection or laser ablation, with 4 exhibiting GATOR1 and 4 exhibiting non-GATOR1 pathway mutations. In the GATOR1 mutations group, four of the nine (44.4%) patients underwent resection or laser ablation, and all had favorable outcomes (Engel I–II). In the non-GATOR1 mutations group, 4 of the 22 (18.2%) patients underwent resection. One patient had a favorable outcome (Engel I).

Conclusions: Genetic testing may be helpful for selection of epilepsy surgery candidates and for counseling regarding expected epilepsy surgery outcome. These findings may be valuable for large multicenter studies with the goal to streamline the surgical journey of epilepsy patients with germline mutations.

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Introduction

Monogenic etiologies are related to numerous neurological diseases, and more than 900 monogenic "epilepsy genes" have been identified.[1–2] Although genetic testing has been recommended as useful for epilepsy patients undergoing presurgical evaluations, Boßelmann et al. demonstrated that clinicians have different opinions regarding how necessary epilepsy genetic tests are in clinical practice, including presurgical evaluations.[3–5] The role of genetic testing in epilepsy surgery decision-making is debated, and published reports have mostly focused on pediatric or combined pediatric and adult patient cohorts.[4,6–10] Several studies reported more favorable resective epilepsy surgery outcomes in patients with mTORopathies, disorders related to mutations affecting genes encoding regulators of mechanistic target of rapamycin complex 1 (mTOR), compared to non-mTOR pathway mutations.[6,9,11–15] The most frequently reported mTORopaties are tuberous sclerosis, caused by *TSC1* and *TSC2* gene mutations, and epilepsies related to mutations in GTPase activating protein activity toward Rags 1 (GATOR1) complex such as *DEPDC5*, *NPRL2*, and *NPRL3*.[16–21]

Here, we describe the real-world experience with genetic testing at a Level 4 epilepsy center treating adult epilepsy patients and surgical management of patients with pathogenic and likely pathogenic germline mutations. We provide a comparison of clinical variables and surgical data in patients with GATOR1 and non-GATOR1 germline mutations.

Methods

Patients

This is a retrospective observational study completed after institutional review board approval. We conducted our study in accordance with the Helsinki Declaration of 1975 as revised in 2024. The reporting of this study conforms to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[22] We performed a retrospective chart review of the consecutive patients who were on the surgical pathway in our adult Level 4 epilepsy center from 2014 to 2024. We included all patients with monogenic epilepsy disorders related to pathogenic or likely pathogenic germline mutations diagnosed via a multigene panel (MGP), whole exome sequencing (WES), or whole genome sequencing (WGS) from 2014 to 2024. Patients whose genetic testing only identified variant(s) of uncertain significance were excluded from the analysis. All patient details were deidentified. Genetic testing was not mandatorily performed for all patients undergoing surgical evaluation at our center during this time range. Because the assays have become more readily accessible, our center's practice has evolved such that genetic testing is increasingly performed when there is a clinical suspicion for a genetic etiology based on family history (FH), developmental history, age of seizure onset, semiology, electroencephalography (EEG), and imaging findings.

Clinical variables

We analyzed the diagnostic yield of genetic testing, patient demographics, epilepsy phenotype and received and recommended surgical treatment and outcome. We compared data collected from patients with GATOR1 and non-GATOR1 pathway mutations.

Epilepsy surgery outcomes

Surgical outcomes were classified according to the Engel classification system and were based on patient interview at the time of last clinic follow-up.[23] For patients treated with the palliative disconnection surgery and neuromodulation, we calculated their percentage of seizure frequency reduction.

Statistics

Statistical analysis was performed using Python 3.11.7 software. Group differences were compared using Fisher's exact test, and two-sided $p < 0.05$ was considered significant.

Results

Positive tests: monogenic epilepsy disorders

After screening, 236 patients who underwent genetic testing were identified. Of these, 234 underwent MGP testing (233 with epilepsy MGP and 1 with a comprehensive brain malformation panel (CBMP)), 1 underwent WES, and 1 underwent WGS. Overall, 31 of the 236 (13%) patients tested positive for monogenic epilepsy disorders related to pathogenic or likely pathogenic germline mutations (Figure 1(a)). The yield of the epilepsy MGP alone was 12% (28 of the 233 patients). In total, 30 of the 31 patients were heterozygous for autosomal dominant mutations, and 1 of the 31 patients was homozygous for an autosomal-recessive *PIGN* mutation. The most frequent were GATOR1 mutations, specifically *DEPDC5* (five patients) and *NPRL3* (four patients). Two patients each had *MECP2*, *SCN1A* (one with Dravet syndrome phenotype and one high-functioning patient), and *TSC1* mutations. All the other germline mutations related to monogenic epilepsy disorders (*CACNA1A*, *DHDDS*, *FLNA*, *GABRA1*, *HCN1*, *HNRNPU*, *NEXMIF*, *NSD1*, *PAFAH1B1*, *PCDH19*, *PIGN*, *PRRT2*, *SCN8A*, *TCF4*, *TSC2*, and *UBE3A*) were represented by one patient each. Mutation and epilepsy phenotype details are listed in Table 1 and Supplementary Table 1.

Comparison of phenotype, surgical interventions, and outcomes in patients with GATOR1 vs. non-GATOR1 mutations

The comparison of epilepsy phenotype, surgeries received, and surgical outcomes in patients with GATOR1 vs. non-GATOR1 mutations is described below and summarized in Table 2. No significant difference was noted in the phenotypic features and number of resective and ablative surgeries received between the two groups due to a small sample size.

Epilepsy onset and genetic testing age

In patients with GATOR1 mutations, average age at epilepsy onset was 10 years (range: 0.5–19 years) and average age at genetic testing was 27.8 years (range: 19–53 years). In patients with non-GATOR1 mutations, average age at epilepsy onset was 8 years (range: 0–20 years) and average age at genetic testing was 29.8 years (range: 16–49 years), Figure 1(b).

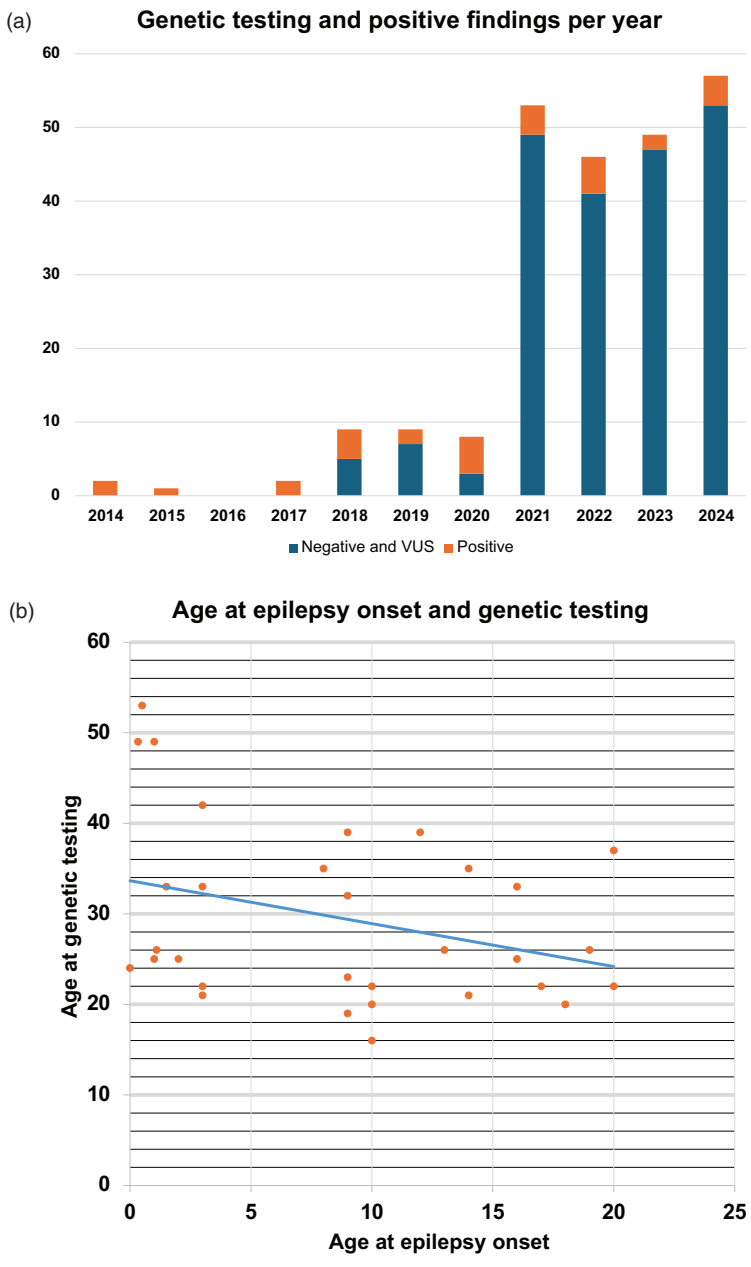

Figure 1. (a) Genetic testing and positive findings per year and (b) Age at epilepsy onset and genetic testing.

Race and ethnicity

In patients with GATOR1 mutations, six of the nine patients were White non-Hispanic, two were African American (*DEPDC5* and *NPRL3* mutations), and one was White Hispanic (*DEPDC5* mutation). In patients with non-GATOR1 mutations, 16 of the 22 patients were White non-Hispanic, 4 were

Table 1. Genetic diagnosis, demographics, images, and surgeries (see also Supplementary Tables 1 and 2).

Patient	Genetic diagnosis	Sex, age at epilepsy onset and genetic testing (years)	Brain MRI	Epilepsy surgeries/ Engel class outcome and follow-up for resection and LITT
	GATOR1 pathway mutations, n = 9			
1	*DEPDC5*, c.856C>T (p.Arg286*)	M,2; 25	Normal	VNS; SDE, MST/ n/a
2	*DEPDC5*, c.3485 + 1G>T (Splice donor)	M,18; 20	Normal	SEEG, RP resection/ II, 3 mo
3	*DEPDC5* c.484-2A>T (Splice acceptor)	F,3; 42	Normal	SEEG, LITTx2/ II, 5 mo
4	*DEPDC5*, c.1663C>T (p.Arg555*)	M,0.5; 53	Normal	VNS/ n/a
5	*DEPDC5*, c.4280_4289delinsAAGGGG (p.Pro1427Glnfs*146)	F,9; 19	Normal	SEEG pending/ n/a
6	*NPRL3* (deletion, Exons 6–7)	F,19; 26	Normal	SEEG, RF resection/ I, 6 mo
7	*NPRL3*, c.547 + 1G>A, splicing	F,10; 20	Normal	SEEG, LF resection/ II, 2 y 9 mo
8	*NPRL3* (deletion, Exon 2)	F,10; 22	Normal	None/ n/a
9	*NPRL3* (deletion, Exon 2)	F,9; 23	Normal	SEEG, DBS/ n/a
	Tuberous sclerosis complex, n = 3			
10	*TSC1*, c.2356C>T (p.Arg786*)	F,12; 39	Bilateral tubers	VNS, SEEG, DBS/ n/a
11	*TSC1*, c.107 − 1G>A (Splice variant)	F,9; 32	Bilateral tubers	SEEG pending/ n/a
12	*TSC2*	F,3; 33	Bilateral tubers	SEEG pending/ n/a
	Other lesion-associated, n = 2			
13	*FLNA*	F,16; 33	Bilateral PNH	SEEG/ n/a
14	*PAFAH1B1*, c.337C>T (p.Arg113*)	M,9; 39	Band heterotopia	VNS/ n/a
	Ion channels and neurotransmitter receptors, n = 6			
15	*CACNA1A*, c.4177G>A (p.Val1393Met)	F,1.1; 26	Normal	L ATL/ III, 28 y
16	*GABRA1*, c.335G>A (p.Arg112Gln)	F,8; 35	Normal	VNS, SEEG, DBS/ n/a
17	*HCN1*, c.1522G>A (p.Val508Met)	M,17; 22	R MTS	VNS, SEEG, LF res, DBS/IV, 4 y
18	*SCN1A*, c.2961del (p.Leu988Trpfs*5)	F,0.33; 49	Normal	VNS, DBS/ n/a
19	*SCN1A*, c.4943G>A (p.Arg1648His)	F,20; 37	Normal	SEEG, DBS/ n/a
20	*SCN8A*, c.2671G>A (p.Val891Met)	M,0; 24	Normal	VNS, SEEG, R ATL/III, 6 y
	Others, n = 11			
21	*DHDDS*, c.110G>A (p.Arg37His)	M,1.5; 33	Normal	None/ n/a
22	*HNRNPU*, c.523C>T (pQ175X)	F,10; 16	Normal	VNS/ n/a
23	*MECP2*, c.1267_1298del (p.Leu424*)	F,16; 25	Normal	VNS/ n/a
24	*MECP2*, c.925C>T (p.Arg309Trp)	F,20; 22	Normal	CC/ n/a
25	*NEXMIF*, c.2420_2421ins17 (p.Pro808Thrfs*4)	F,3; 22	Normal	VNS pending/ n/a
26	*NSD1*, c.5951G>A (p.Arg1984Gln)	M,14; 21	Polymicrogyria	None, lost f/u/ n/a
27	*PCDH19*, c.2147 + 1G>T	F,3; 21	Normal	SEEG/ n/a
28	*PIGN* pat c.932T>G (p.Leu311Trp), mat c.2283G>A (p.Lys761Lys)	F,1; 25	Normal	VNS or DBS pending/ n/a
29	*PRRT2*, c.649dup (p.Arg217Profs*8)	M,13; 26	Normal	None, lost f/u/ n/a
30	*TCF4*, c.329C>T (p.Ser110Leu)	F,1; 49	Normal	SEEG, LT resection/ I, 6 mo
31	*UBE3A*, Gain (Entire coding sequence), copy number = 4	M,14; 35	Normal	SEEG/ n/a

Abbreviations: ATL: anterior temporal lobectomy; CC: corpus callosotomy; DBS: deep brain stimulation; f/u: follow-up; L: left; LF: left frontal; LITT: laser interstitial thermal therapy; LT: left temporal; mo: months; MRI: magnetic resonance imaging; MST: multiple subpial transections; PNH: periventricular nodular heterotopia; R: right; RF: right frontal; RP: right parietal; RT: right temporal; SDE: subdural electrodes; SEEG: stereoelectroencephalography; VNS: vagus nerve stimulation; y: years.

Table 2. Phenotype and surgical interventions comparison in patients with *GATOR1* vs. non-*GATOR1* mutations.*

	GATOR1, n = 9	non-GATOR1, n = 22	*p*
Age at epilepsy onset, average (range), years	10 (0.5–19)	8 (0–20)	
No family history of epilepsy, n (%)	1 (11%)	7 (31.8%)	0.379
MRI lesion, n (%)	0	7 (31.8%)	0.068
Intellectual disability, n (%)	1 (11%)	11 (50%)	0.101
Focal epilepsy phenotype, n (%)	9 (100%)	14 (63.6%)	0.068
Focal ictal scalp EEG, n (%)	1 (11%)	7 (31.8%)	0.379
iEEG and post-iEEG surgeries			
iEEG (completed), n (%)	6 (66.7%)	9 (40.9%)	
Single seizure focus detected with iEEG	3 of the 6 (50%)	2 of the 9 (22%)	
Resection or MST only	3 of the 6 (50%)	2 of the 9 (22%)	
Resection or LITT plus neuromodulation	2 of the 6 (33.3%)	1 of the 9 (11%)	
Neuromodulation only recommended	1 of the 6 (16.7%)	6 of the 9 (67%)	
All completed surgeries			
Resection or LITT	4 (44.4%)	4 (18.2%)	0.105
MST	1 (11/1%)	0	
Corpus callosotomy	0	1 (4.5%)	
Neuromodulation total (VNS+DBS)	3 (33.3%)	13 (59.1%)	
VNS	2 (22.2%)	8 (36.4%)	
DBS	1 (11%)	5 (22.7%)	
Surgical outcomes			
Resection and LITT			
Engel I–II	4 of the 4 (100%)	1 of the 4 (25%)	
Engel III–IV	0	3 of the 4 (75%)	
Palliative surgery responders (>50% seizure frequency reduction)			
MST	1 of the 1	n/a	
Corpus callosotomy	n/a	1 of the 1	
Neuromodulation			
DBS	0 of the 1	4 of the 5 (80%)	
VNS	0 of the 2	1 of the 8 (12.5%)	
DBS after VNS	n/a	3 of the 4 (75%)	

Abbreviations: DBS: deep brain stimulation; *GATOR1*: GTPase-activating protein activity toward Rags 1; iEEG: intracranial electroencephalography; LITT: laser interstitial thermal therapy; MRI: magnetic resonance imaging; MST: multiple subpial transections; RNS: responsive neurostimulation; TSC: tuberous sclerosis complex; VNS: vagus nerve stimulation; y: years.
*Percentage provided in relation to subgroup size (patients with *GATOR1* and non-*GATOR1* mutations), unless otherwise specified.

White Hispanic (*HNRNPU*, *MECP2*, *TCF4*, *TSC1* mutations), and 2 were Asian (*MECP2* and *TSC2* mutations).

FH of epilepsy or neurodevelopmental disorders

In patients with GATOR1 mutations, only one of the nine patients (11%) did not have a positive FH of epilepsy. This patient had a *DEPDC5* mutation.

Among patients with non-GATOR1 mutations, 7 of the 22 (31.8%) patients did not have a FH of epilepsy or neurodevelopmental disorder (NDD). Seven patients without positive FH had mutations in the following genes: *DHDDS*, *FLNA*, *GABRA1*, *HCN1*,

NSD1, *SCN1A* (Dravet syndrome phenotype), and *TSC1*.

Full-Scale Intelligence Quotient

In the GATOR1 mutation patient group, seven of the nine patients had a numerical Full-Scale Intelligence Quotient (FSIQ) score available. The average FSIQ score was 83.4 (range: 62–105). Two of the nine patients had an FSIQ score within the average range per report but without an available score value. The lowest FSIQ was 62 (extremely low/impaired) in a patient with *DFEPDC5* mutation who had 14 years of education (completed high school and 2 years of college); his low FSIQ score was noted to possibly have been underestimated due to suboptimal performance during the neuropsychological evaluation.

A numerical FSIQ score was available for nine of 22 patients with non-GATOR1 mutations. The average FSIQ score was 81.7 (range: 70–98), and two additional patients had an FSIQ score within average range per report but without an available score value. Overall, 11 of the 22 patients (50%) were reported to have intellectual disability (but without FSIQ score available) and required special education (Figure 2(a)).

Brain magnetic resonance imaging

In patients with GATOR1 mutations, none had definitive magnetic resonance imaging (MRI) lesions.

In patients with non-GATOR1 mutations, 7 of the 22 (31.8%) had MRI lesion (s) and 1 of the 22 had postoperative changes (preoperative brain MRI was not available). MRI abnormalities corresponding to genotype were observed in patients with *FLNA*, *NSD1*, *PAFAH1B1*, *TSC1* (two patients), and *TSC2* mutations. A patient with *HCN1* mutation had right mesial temporal sclerosis and moderate generalized cerebral atrophy.

Focal vs. generalized epilepsy phenotype

In patients with GATOR1 mutations, all nine patients had focal epilepsy.

In patients with non-GATOR1 mutations, 5 of the 22 patients had generalized epilepsy phenotype based on seizure semiology and ictal and interictal scalp EEG (the mutations were *DNDDS*, *HNRNPU*, *MECP2*, *NEXMIF*, and *SCN1A* with Dravet syndrome phenotype). Overall, 3 of the 22 patients had generalized epilepsy with focal features (*GABRA1*, *MECP2*, and *PIGN* mutations). In total, 14 of the 22 patients had focal epilepsy (*CACNA1A*, *FLNA*, *HCN1*, *NSD1*, *PAFAH1B1*, *PCDH19*, *PRRT2*, *SCN1A*, *SCN8A*, *TCF4*, *TSC1* (two patients), *TSC2*, and *UBE3A* mutations).

Epilepsy surgery

Overall, 22 (6 exhibiting GATOR1 pathway mutations) of the 31 patients underwent one or more epilepsy surgeries. Furthermore, 5 (1 exhibiting GATOR1 pathway mutations) of the 31 patients were discussed for epilepsy surgery and the surgical procedure is pending. Moreover, 4 of the 31 patients did not have surgical recommendations in the chart: two (one exhibiting GATOR1 pathway mutations) of them due to good seizure control on anti-seizure medications and two (both exhibiting non-GATOR1 pathway mutations) were lost to follow-up at our institution. Overall, 13 (6 exhibiting GATOR1 pathway mutations) of the 31 patients had more than one epilepsy surgery (including invasive EEG electrode placement). Twelve patients (3 exhibiting GATOR1 pathway mutations) received neuromodulation, and 10 patients (5 exhibiting GATOR1 pathway mutations)

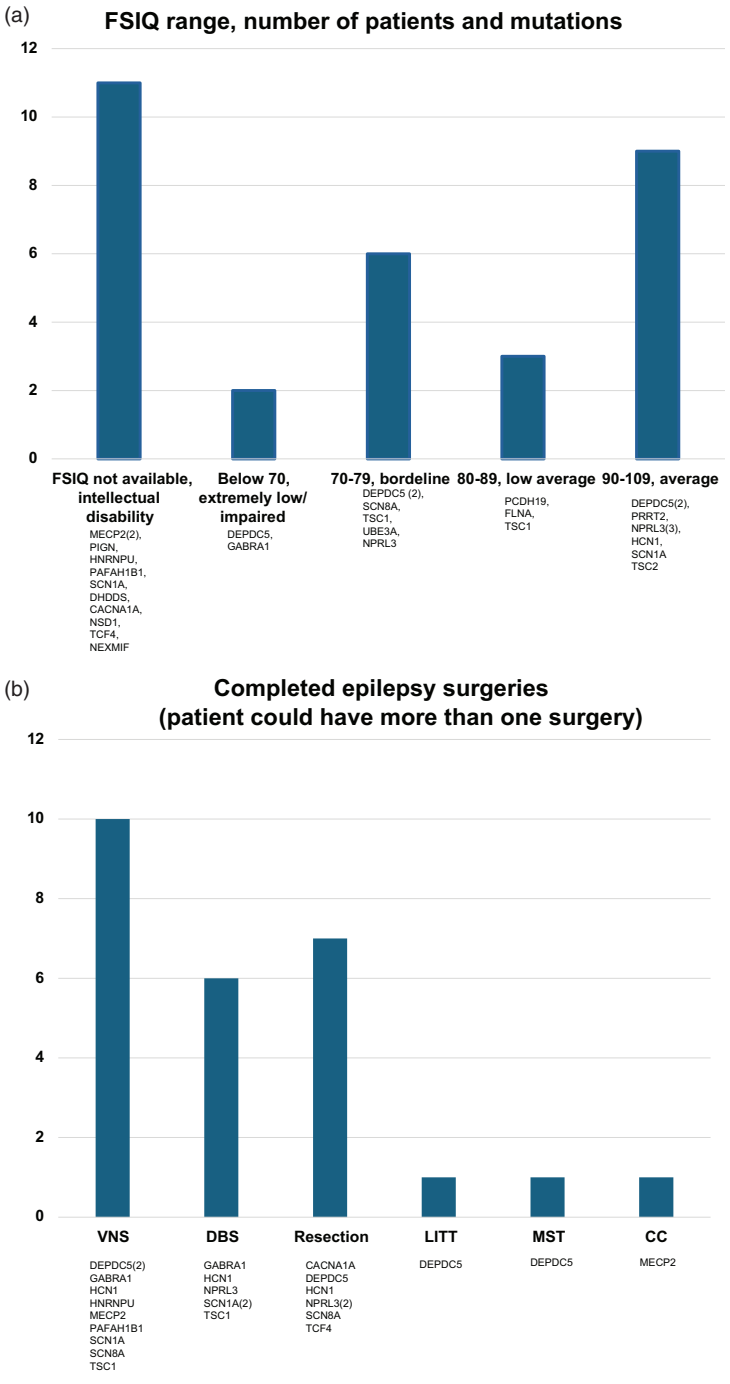

Figure 2. (a) FSIQ range, number of patients, and mutations and (b) completed epilepsy surgeries.

received resection, laser interstitial thermal therapy (LITT), or disconnection surgery. Three patients received both neuromodulation and resective surgery; one *DEPDC5* and one *SCN8A* patient had therapy with vagus nerve stimulation (VNS) before multiple subpial transections (MST) or resective surgery, respectively, and the *HCN1* patient had VNS, then resective surgery followed by deep brain stimulation (DBS) of bilateral centro-median (CM) nucleus of the thalamus. Overall, 15 patients (6 exhibiting GATOR1 pathway mutations) received invasive EEG evaluation (including 14 with stereoelectroencephalography (SEEG) and 1 with subdural electrodes (SDE) placement) before therapeutic surgery; in three of them (all exhibiting non-GATOR1 pathway mutations), post-SEEG therapeutic surgery (neuromodulation) is pending (Figure 2(b), Table 1, and Supplementary Table 2).

Invasive EEG evaluation and subsequent therapeutic surgery. In patients with GATOR1 mutations, six of the nine patients underwent invasive EEG evaluation (three with *DEPDC5* and three with *NPRL3* mutations). Overall, 3 of the 6 patients (50%, two *DEPDC5* and one *NPRL3* mutation) had focal ictal onset followed by resection or MST of the seizure focus. Furthermore, 2 of the 6 patients had multifocal ictal onset (one *DEPDC3* and one *NPRL3* mutation) and were treated by resection or LITT of the seizure foci plus additional neuromodulation was recommended. One patient with *NPRL3* mutation had SEEG evaluation outside of our institution; the ictal onset reportedly was broad bilateral frontal, and the patient was treated with research DBS.

Among patients with non-GATOR1 mutations, 9 of the 22 patients underwent invasive EEG evaluation. Only two of the nine (22%) patients had focal ictal onset followed by destructive surgery. A patient with *SCN8A* mutation had ictal onset from the right hippocampus, and a patient with *TCF4* mutation had ictal onset from the left entorhinal cortex and temporal pole. Both patients underwent ipsilateral temporal lobectomies. The other invasive EEG patients in non-GATOR1 mutations group (seven of the nine patients) had bilateral broad or multifocal ictal onsets. These were treated with neuromodulation only (two with CM DBS and one with anterior nucleus of thalamus (ANT) DBS), palliative resective surgery followed by neuromodulation (one of the seven patients, left frontal resection followed by ANT DBS), and three of the seven patients have so far deferred recommended neuromodulation modality (thalamic DBS, thalamic responsive neurostimulation (RNS), or VNS).

Invasive EEG and scalp EEG ictal onset comparison. All nine patients with GATOR1 mutations had focal epilepsy, yet the scalp EEG was localized to a single region in one patient and was poorly localized in the others. Invasive EEG was performed in six of these nine patients, and a solitary seizure-onset zone was identified in three of the six (50%) patients.

In the 22 patients with non-GATOR1 mutations, 14 patients had focal epilepsy. Scalp EEG demonstrated a single regional focus in seven of these patients. However, of the nine patients with non-GATOR1 mutations who underwent invasive EEG, a solitary seizure-onset zone was identified in only two of the nine (22%) patients.

Resective, ablative, and disconnection surgery. In patients with GATOR1 mutations, four of the nine (44.4%) patients had resection (three patients) or LITT (one patient) of the cortex where the seizure onset zone was localized with SEEG evaluation. The surgical pathology was normal in all patients who underwent resective surgery. In one patient (*DEPDC5* mutation), VNS

was placed one year before subsequent SDE followed by perirolandic MST.

Among patients with non-GATOR1 mutations, 4 of the 22 (18.2%) patients had resection and 1 of the 22 patients had corpus callosotomy. Patients with *CACNA1A*, *SCN8A*, and *TCF4* mutations had temporal lobectomy preceded by SEEG in two patients (*SCN8A* and *TCF4* mutations). The patient with *HCN1* mutation had a palliative left frontal cortex resection after SEEG followed by CM DBS. The surgical pathology was normal in three of the four patients who underwent resective surgery and was not available in a patient who underwent left anterior temporal lobectomy (ATL) 28 years ago. The patient with *MECP2* mutation had corpus callosotomy. In two of the five patients (*HCN1* and *SCN8A* mutations), VNS was placed 3 and 6 years, respectively, before subsequent resective surgery.

Neuromodulation. Among patients with GATOR1 mutations, three of the nine (33.3%) patients received neuromodulation. Two patients (*DEPDC5* mutations) had VNS placed at ages 8 and 44 years, respectively. One patient (*NPRL3* mutation) had a research ANT DBS placed at age 22 years after SEEG evaluation outside of our institution.

Among patients with non-GATOR1 mutations, 9 of the 22 (40.9%) patients received neuromodulation. Eight patients had VNS, five patients had thalamic DBS, and four patients had both VNS and DBS. Average age at VNS placement was 23 years (range: 12–37 years). Average age at DBS placement was 39.4 years (range: 23–50 years). Thalamic DBS leads were implanted to ANT bilaterally in three patients (*HCN1* and both patients with *SCN1A* mutations) and to bilateral CM nucleus in two patients (*GABRA1* and *TSC1* mutations). Four of the six DBS patients had both VNS and thalamic DBS (*GABRA1*, *HCN1*, *SCN1A*, and *TSC1* mutations), with all such patients receiving VNS prior to DBS and on average 15.8 years (range: 4–22 years) before DBS.

Surgeries recommended but not completed. In patients with GATOR1 mutations, six of the nine patients had recommended but not completed surgeries. One patient with *DEPDC5* mutation was approved for SEEG evaluation. Among the other five patients who completed one or more epilepsy surgery and additional surgery(s) are pending, two patients (*DEPDC5* and *NPRL3* mutations) were discussed for extension of the previous resection, and thalamic neuromodulation was recommended for three patients. One of these three patients had *DEPDC5* mutation and violent hypermotor seizures, which precluded his invasive EEG evaluation for seizure onset localization due to patient safety considerations. Two of the three patients (*DEPDC5* and *NPRL3* mutations) had multifocal ictal onsets localized with SEEG. Thalamic neuromodulation was recommended if LITT and resection, respectively, did not provide sufficient seizure control.

In patients with non-GATOR1 mutations, 13 of the 22 patients had recommended but not completed surgeries. Patients with *TSC1* and *TSC2* mutations (mTOR pathway) were approved for SEEG evaluation, the patient with *PIGN* mutation was discussed for VNS or DBS, and the patient with *NEXMIF* mutation was discussed for VNS. Among the other nine patients who completed one or more epilepsy surgery and additional surgery(s) are pending, one patient (*HNRNPU* mutation) was discussed for corpus callosotomy, and neuromodulation was recommended for eight patients. More than one neuromodulatory treatment option could be recommended to the same patient. The recommended devices were thalamic DBS

in five patients, VNS in four patients, RNS targeting seizure foci in two patients, and thalamic RNS in one patient.

Outcomes of resective surgery and LITT

In patients with GATOR1 mutations, three of the nine underwent resection and one underwent LITT (a total of four of the nine patients, 44.4%). Of the two patients with *DEPDC5* mutations who underwent resective epilepsy surgery or LITT, one patient was 2 months seizure-free after resection, then had seizure relapse at 3-month follow-up. The second patient did not benefit from a right insula LITT (3-month follow-up) but then was 2.5 months seizure-free after a subsequent left hippocampus LITT and is now Engel II class at 5-month postoperative follow-up (after relapse of a focal impaired awareness seizure (FIAS)).

Of the two patients with *NPRL3* mutations who underwent resective epilepsy surgery, one patient had Engel II outcome after left frontal resection (33-month follow-up) and was approved for extension of the left frontal resection. The second patient is 6-month seizure-free after right frontal resection.

Among patients with non-GATOR1 mutations, 4 of the 22 (18.2%) patients underwent resective surgery. In patients with channelopathies, a patient with *SCN8A* mutation was 18-month seizure-free after right ATL but currently has Engel III class outcome at 6-year postoperative follow-up. A patient with *CACNA1A* mutation was 2-year seizure-free after left ATL but now has Engel III class outcome at 28-year follow-up. A patient with *HCN1* mutation did not have improvement from a palliative left frontal resection at 4-year postsurgical follow-up. In patients from the "other mutations" subgroup, a patient with *TCF4* mutation is 6-month seizure-free after left ATL.

Outcomes of disconnection surgeries

In the GATOR1 mutation group, a patient with *DEPDC5* mutation had 50% seizure reduction after peri-rolandic MST at 16-year postoperative follow-up.

In the non-GATOR1 mutation group, a patient with *MECP2* mutation did not have generalized tonic-clonic seizures and drop attacks after corpus callosotomy and had 70% reduction in absence seizure frequency at 1-year postsurgical follow-up.

Neuromodulation outcomes

Among patients with GATOR1 mutations, two of the nine patients underwent VNS, which was reported as ineffective in both patients (*DEPDC5* mutations) at 18- and 19-year follow-ups.

One of the nine (11%) patients had DBS, which resulted in worsening of baseline seizures. This was a patient with *NPRL3* mutation who had a research ANT DBS placed outside of our institution, and the device was subsequently explanted due to reported worsening of focal to bilateral tonic-clonic (FBTC) seizures and side effects.

Among the patients with non-GATOR1 mutations, 8 of the 22 patients received VNS. VNS was reported as ineffective in seven of the eight patients with average 15-year (range: 6–36) follow-up, while one patient (*PAFAH1B1* mutation) had a 50% seizure reduction at 4-year follow-up.

Overall, 5 of the 22 (22.7%) patients had DBS, four of the five patients had channelopathies, and one patient had tuberous sclerosis. Among the patients with channelopathies, two patients with *SCN1A* mutations are receiving treatment with ANT DBS. One patient (high-functioning) is 1-year seizure-free. The second patient (Dravet syndrome phenotype) did not have status epilepticus after DBS placement during 4-year follow-up, did not have a generalized tonic-clonic seizures for 2 years,

and had more than 50% seizure frequency reduction overall.

The patient with *GABRA1* mutation had 90% FBTC seizure frequency reduction after CM DBS placement at 22-month follow-up.

In the patient with *HCN1* mutation, ANT DBS therapy has been ineffective at 3-year follow-up.

In the tuberous sclerosis patient subgroup, a patient with *TSC1* mutation and bilateral multiple tubers did not have FBTC seizures and had 50% FIAS reduction after CM DBS placement at 18-month follow-up.

Interestingly, four of the six patients who were treated with DBS had prior VNS treatment, which was deemed ineffective; three of these four patients had seizure reduction after DBS placement. However, the patient with *HCN1* mutation did not respond to medications or neuromodulatory or surgical treatment (VNS, then frontal resection and ANT DBS).

Discussion

We present a single-center cohort of adult epilepsy surgery patients who underwent genetic testing. A total of 236 patients were tested during a 10-year period, 233 via epilepsy MGP, one CBMP, one WES, and one WGS. Most of the previous reports on surgical treatment in genetic epilepsy were pediatric or combined pediatric and adult patient cohorts.[4,6–10] Unlike previously reported studies on genetic testing in adult epilepsy patients, our cohort was not focused on the patients with intellectual disability, who represented only 38.7% (12/31) of our study subjects.[24–25]

Thirty-one patients in our cohort were identified as having pathogenic or likely pathogenic germline mutations; 28 were diagnosed via epilepsy MGP. The diagnostic yield was 13% total (WGS, WES, and MGPs) and 12% for epilepsy MGP, similar to data reported elsewhere.[26–29] We herein added to the literature the epilepsy phenotype description and surgical decision-making in patients with *DEPDC5* (five patients), *NPRL3* (four patients), *MECP2* (two patients), *SCN1A* (two patients), *TSC1* (two patients) germline mutations, and one patient each with *CACNA1A*, *DHDDS*, *FLNA*, *GABRA1*, *HCN1*, *HNRNPU*, *NEXMIF*, *NSD1*, *PAFAH1B1*, *PCDH19*, *PIGN*, *PRRT2*, *SCN8A*, *TCF4*, *TSC2*, and *UBE3A* germline mutations. We believe this is the largest reported single-center cohort of patients with germline mutations who underwent invasive EEG evaluations (14 SEEG and one SDE), which included the intracranial onset findings in patients with *DEPDC5* (three patients), *FLNA*, *GABRA1*, *HCN1*, *NPRL3* (three patients), *PCDH19*, *SCN1A*, *SCN8A*, *TCF4*, *TSC1*, and *UBE3A* pathogenic or likely pathogenic genes. Our cohort included a few individuals from historically underrepresented racial and ethnic groups, specifically five White Hispanic (*DEPDC5*, *HNRNPU*, *MECP2*, *TCF4*, *TSC1* mutations), 2 African American (*DEPDC5* and *NPRL3* mutations), and 2 Asian (*MECP2* and *TSC2* mutations) patients.

We demonstrated that the patients with GATOR1 pathway mutations more often have focal ictal onset as localized with invasive EEG evaluations (three of the six patients; 50%) compared to patients with non-GATOR1 mutations (two of nine; 22%) despite nonlocalizing scalp EEG ictal onset in eight of the nine (88.9%) patients with GATOR1 mutations. Vice versa, in non-GATOR1 group, the scalp EEG ictal onset was localized in a sole regional focus in seven patients, but invasive EEG showed a single focus only in two of the nine evaluated patients. Patients with GATOR1 pathway mutations more frequently underwent focal resection or LITT (44.4%) compared to patients with non-GATOR1 pathway mutations (18.2%).

In contrast, patients with non-GATOR1 pathway mutations more often received neuromodulation (75% of patients with placed neuromodulatory devices) than did patients with GATOR1 mutations due to broader-onset or multifocal seizures. Impressively, patients with non-GATOR1 mutations had good response to thalamic DBS with reduction of the most devastating seizures such as generalized convulsive seizures and status epilepticus (four of the five, i.e. 80% of those receiving DBS therapy), including the three of the four patients who previously did not improve with initial VNS.

Of note, two patients with GATOR1 pathway mutations who have so far been treated with neuromodulation only could still potentially qualify and benefit from future resective surgery. One patient with *DEPDC5* mutation did not have resective surgery due to the violent nature of his hypermotor seizures, which precluded his invasive EEG evaluation for seizure onset localization due to patient safety considerations. One of the patients with *NPRL3* mutation had SEEG evaluation outside of our institution with reportedly broad bifrontal ictal onset not followed by resective surgery, and we do not have access to the original SEEG recording data. In one additional patient with *DEPDC5* mutation who has not had epilepsy surgery yet, SEEG and subsequent surgical recommendation is pending.

In our study, we analyzed the patients with GATOR1 mutations (*DEPDC5* and *NPRL3* in our cohort) separately from the patients with other mTOR pathway mutations such as *TSC1* and *TSC2*. The surgical decision-making algorithm (an attempt to identify the most active tuber with subsequent resection) in patients with tuberous sclerosis was described previously.[30–32] Patients with tuberous sclerosis often have visible MRI lesion(s), and their diagnostic journey may thus be more straightforward than in GATOR1 patients who typically have nonlesional brain MRI.[16,33,34]

We had only three TSC positive patients in this cohort (two *TSC1* and one *TSC2*), and only one has already undergone surgery; this patient had multiple bilateral hemispheric tubers, and the SEEG showed bilateral multifocal ictal onsets. The patient was treated with CM DBS with good response (no FBTC seizures and 50% FIAS reduction at 18-month follow-up). Two TSC positive patients were recently approved for SEEG, and their evaluation is still pending.

Our study demonstrates that patients with monogenic epilepsy disorders often have a sophisticated surgical journey, which may include more than one therapeutic or palliative surgery and is not uncommonly preceded by an invasive EEG evaluation. Is it possible to simplify this process based on genetic tests results? Our study suggests that the patients with non-GATOR1 pathway mutations may be more likely to have multifocal seizure onset and therefore may be more likely to benefit from thalamic neuromodulation. Conversely, our data is in concordance with other reports that patients with mTOR and mTOR/GATOR1 pathway mutations might be more likely to have unifocal seizure-onset zone and therefore might be more likely to benefit from targeted destructive surgery (often preceded by invasive EEG evaluation), but this conclusion still needs confirmation by larger studies.[6,14,15,35,36]

Although genetic testing is recommended by the International League Against Epilepsy "for patients with nonacquired focal epilepsies in specific familial syndromes and can be considered in patients with nonacquired focal, pharmaco-resistant epilepsies in the setting of presurgical evaluation or in the setting of malformations of cortical development," its adoption into routine clinical practice is still evolving.[5]

Every decision-making participant needs to be convinced that genetic testing is necessary, including the treating epileptologist, the patient and family, and the health insurance company.[4,37,38] Our own Level 4 center's changing clinical practice reflects this reality, and even we do not yet have a standardized decision tree for which patients will mandatorily receive genetic testing as part of their presurgical evaluation.

However, over the past decade, an increasing number of our patients now have genetic testing collected because the assays have become more readily accessible and when there was a clinical suspicion for a genetic etiology based on FH, developmental history, age of seizure onset, semiology, EEG, or imaging findings.

We hope this publication will raise epilepsy providers' awareness regarding monogenic epilepsy disorders in the adult drug-resistant epilepsy population. Our cohort of patients with germline mutations related to epilepsy was diverse. At times, patients identified with pathogenic genetic mutations were somewhat surprising (or at least challenged some earlier preconceived notions), despite some pre-test suspicion that warranted genetic testing initially. For example, 8 of the 31 patients (26%) did not have a positive FH of epilepsy or NDD, 23 of the 31 patients (74%) had normal brain MRI, and only 5 of the 31 patients (16%) had exclusively generalized epilepsy phenotype. A high-functioning patient (FSIQ score 95) tested positive for *SCN1A* mutation. The oldest patient with positive findings was tested at age 53 years (*DEPDC5* mutation).

We described patient's FSIQ scores in detail to re-demonstrate that adult patients with focal epilepsy and average or low-average FSIQ scores (61.3% in our cohort) could have monogenic epilepsy disorders, although reportedly the diagnostic yield in adult epilepsy patient population with associated developmental delay is higher (23% and 22% in studies by Johannesen et al. and Borlot et al., respectively).[24–25] Interestingly, the age of epilepsy onset (average and range) was not dramatically different in patients with GATOR1 (10 (range: 0.5–19) years), and non-GATOR1 (8 (range: 0–20) years) mutation groups. The available average FSIQ score and FSIQ score range was also similar (83.4, range: 62–105 in GATOR1 and 81.7, range: 70–98 in non-GATOR1 group), but the non-GATOR1 group was more likely to have intellectual disability (11 patients). Absence of FH of epilepsy or NDD was observed in one of the nine (11%) patients with GATOR1 germline mutations and 7 of the 22 (31.8%) patients with non-GATOR1 mutations. Brain MRI was lesional in 7 of the 22 (32%) non-GATOR1 patients, and one patient had postoperative MRI changes, but none of the patients with GATOR1 mutations had definitive MRI lesions.

All nine GATOR1 patients had focal epilepsy, yet their scalp EEG was localizing in only one of the nine, while invasive EEG was localizing in three (of the six patients who underwent invasive EEG). In the non-GATOR1 group, 14 patients had focal epilepsy, yet scalp EEG revealed a solitary regional focus in seven, while invasive EEG revealed a unifocal onset in only two of the nine non-GATOR1 patients who underwent invasive EEG.

Based on our above findings, genetic testing would be especially beneficial in patients with non-lesional MRI. If germline GATOR1 mutations are identified, there appears to be a higher probability of a single seizure focus localization with invasive EEG, which might then benefit from targeted destruction.

Per recent review, overall diagnostic yield across all genetic test modalities was 17%, with the highest yield for WGS (48%), followed by WES (24%), MGP (19%), and comparative genomic

hybridization/chromosomal microarray (9%).[39] Another study reported that a (likely) pathogenic variant was found in 40 of the 325 tested patients (12%) via different diagnostic technologies.[6] Our patients typically are restricted to epilepsy MGP only by their insurance payor. The total diagnostic yield was 13% (three patients tested via CBMP, WES, and WGS, respectively, were evaluated outside of our institution), and 12% for epilepsy MGP only.

The following questions arise from our study, requiring further investigation:

1. Should patients with mTOR pathway mutations (GATOR1, *TSC1* and *TSC2*) undergo presurgical evaluations, including invasive EEG if necessary, with the goal to proceed with the focal destruction of the epileptogenic focus as the first therapeutic surgery, while patients with non-mTOR pathway mutations be more cautiously considered for such evaluations due to a lower probability to proceed to the focal destructive surgery and low chance to be seizure-free after such intervention? For example, genetic testing revealing a non-mTOR pathway mutation might steer a surgical committee away from recommending an invasive EEG evaluation in a patient with a phenotype of a generalized epilepsy with focal features hoping to unmask a focal-onset epilepsy with secondary bilateral synchrony.
2. Our study demonstrated the good response to thalamic neuromodulation (in this case series, both ANT and CM DBS) in patients with intractable epilepsy with associated monogenic epilepsy gene mutation, even in patients who were treated previously with VNS without effect. Based on these findings, should thalamic neuromodulation be recommended as the first neuromodulatory treatment option for patients with monogenic epilepsy disorders, or to the patients with specific mutations identified in our cohort who had good response to thalamic DBS (*GABRA1*, *SCN1A*—both the patient with Dravet phenotype and the high-functioning patient, and *TSC1* with bilateral multiple tubers)?
3. Two patients with channelopathies (*CACNA1A* and *SCN8A* mutations) from our cohort were seizure-free after resective surgery for 24 and 18 months, respectively, and the patient with *CACNA1A* mutation does not have status epilepticus episodes after ATL, which this patient had once per month preoperatively. If similar surgical outcomes could be replicated across more cohorts, counseling patients with certain mutations regarding epilepsy surgery outcome could be more precise.

Our study has limitations, particularly its retrospective nature, single-center study design, low sample size with no statistically significant values, and short postoperative follow-up duration of several patients. However, publications on germline genetic findings in adult epilepsy surgery patients are limited, and our manuscript adds to the body of existing literature. Larger studies are needed to clarify how germline mutations affect selection of epilepsy surgery candidates for initial and subsequent surgeries and how specific mutations influence surgical interventions and outcomes, including destructive surgeries and neuromodulation.

Conclusions

In conclusion, genetic testing may be helpful for selection of epilepsy surgery candidates for destructive surgery vs. neuromodulation and for counseling regarding expected epilepsy surgery outcome. Genetic testing may ultimately streamline the surgical journey of affected patients. Reproductive counseling

based on genetic test findings may also be meaningful for the families, while the health-care system may benefit from optimization of distribution of the available resources.

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Author contributions

IP: Conceptualization, Data curation, Methodology, Project administration, Resources, Supervision, Investigation, Validation, Visualization, Formal analysis, Writing—original draft, Writing—review and editing. SAL: Data curation, Formal analysis, Resources, Writing—review and editing. KD: Data curation, Formal analysis, Resources, Writing—review and editing. GP: Data curation, Resources, Writing—review and editing. RH: Conceptualization, Data curation, Methodology, Project administration, Resources, Supervision, Investigation, Validation, Visualization, Formal analysis, Writing—review and editing.

Availability of data and materials

Data are contained within the article and supplementary materials. Further inquiries can be directed to the corresponding author.

Consent for publication

Not applicable.

Declaration of conflicting interest

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Ethics approval and consent to participate

This study was approved by the Institutional Review Board of the University of Texas Southwestern Medical Center. Patient consent was waived because this study was a retrospective chart review.

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Supplementary material

Supplemental material for this article is available online.

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