FULL-LENGTH ORIGINAL RESEARCH

Epilepsia Open®
Open Access

Implications of genetic diagnostics in epilepsy surgery candidates: A single-center cohort study

Maurits W. C. B. Sanders[1] 🔘 | Cynthia M. C. Lemmens[1] | Floor E. Jansen[1] |
Eva H. Brilstra[2] | Bobby P. C. Koeleman[2] | Kees P. J. Braun[1] |
on behalf of the Dutch Collaborative Epilepsy Surgery Program (LWEC)

[1]Department of Child Neurology, Brain Center Rudolf Magnus, University Medical Center, Utrecht, The Netherlands

[2]Department of Genetics, Center for Molecular Medicine, University Medical Center, Utrecht, The Netherlands

Correspondence
Maurits W. C. B. Sanders, Neurology, University Medical Center Utrecht, Heidelberglaan 100, Utrecht, 3584 CX, Netherlands.
Email: m.w.c.b.sanders-5@umcutrecht.nl

Abstract

Objective: Genetic causes are increasingly identified in patients with focal epilepsy. These genetic causes may be related to the effectiveness of epilepsy surgery. We aimed to assess the use and yield of genetic testing in a large cohort of patients who were evaluated for epilepsy surgery.

Methods: We performed a retrospective single-center consecutive cohort study of patients who were evaluated for surgery between 1990 and 2016. Within this cohort, we assessed the use of genetic testing—either before or after presurgical decision-making. We evaluated genetic results as well as the outcome of presurgical decision-making and surgery, and compared these end points for different subgroups—especially MRI-positive *vs* MRI-negative patients. Patients with tuberous sclerosis (TSC) and *KRIT1* mutations were excluded from analysis.

Results: Of the 2385 epilepsy patients who were evaluated for surgery, 1280 (54%) received surgical treatment in our center. Of the entire cohort, 325 (14%) underwent genetic testing, comprising 156 of 450 MRI-negative patients (35%) vs 169 of 1935 MRI-positive patients (9%). A genetic cause of epilepsy was found in 40 of the 325 patients (12%, 2% of the entire cohort), mainly consisting of mutations in ion channel function and synaptic transmission genes, and mTOR pathway gene mutations. Three of the seven patients with mTOR pathway gene mutations underwent surgery; two achieved complete seizure freedom. One of the 17 patients with germline mutations in ion channel function and synaptic transmission genes received resective surgery but was not rendered seizure-free; two other patients underwent invasive intracranial EEG-monitoring before being rejected.

Significance: This study shows that genetic testing is increasingly applied in focal epilepsy patients who are considered for epilepsy surgery. The diagnostic yield of genetic testing is highest in next generation sequencing techniques, and the outcome of genetic testing assists selecting eligible patients for invasive intracranial monitoring and resective surgery.

1 | INTRODUCTION

Epilepsy is one of the most common neurological diseases globally, with a lifetime prevalence of 7.6 in 1000 people.[1] Up to one-third of patients develop pharmacoresistance, and many have significant comorbidities, such as developmental delay.[2–4]

In patients with pharmacoresistant focal epilepsy originating from a structural abnormality, resective surgery represents the only potentially curative treatment option provided that the lesion can be accurately delineated and is located outside eloquent cortex. In many patients, especially those without a structural abnormality, extensive preoperative diagnostic work-up is required, including invasive intracranial EEG-monitoring in an increasing number of patients.[4] Despite rapidly improving presurgical diagnostic modalities and increasing clinical experience, patient selection for surgical treatment is still suboptimal, with on average only 65%-69% of patients achieving postoperative seizure freedom.[6,7] Therefore, new and reliable markers to properly differentiate between patients with operable and non-operable epilepsy are warranted.

In the last decades, novel epilepsy genes have been increasingly identified in patients with generalized and focal epilepsy.[8] The possibilities to comprehensively test epilepsy patients for a genetic etiology have expanded throughout the last years, with the advent of readily available next generation sequencing techniques (NGS).[9] In particular whole exome sequencing (WES), through which the coding sequence of all genes in the human genome can be scanned for apparent disease-causing sequence variation, accelerated the discovery of novel epilepsy genes in the past decade.[10] The importance of genetic causes of structural focal epilepsies was first established by the observation that inherited or de novo mutations in genes involved in the mTOR pathway, can cause focal epilepsy.[11] It stands without a doubt that the identification of a causative mutation could affect treatment as well as prognostic and genetic counselling (Reif et al, 2016).[12] Moreover, recent literature shows that some of the epilepsy gene mutations may also be related to the effectiveness of epilepsy surgery in focal epilepsy patients (Stevelink et al, 2018).[13] We therefore hypothesize that genetic testing can add valuable information to current preoperative patient assessment.

To gain more insight in the evolution of diagnostic genetic testing in epilepsy surgery evaluation, we studied the application and yield of genetic testing within a large consecutive cohort of epilepsy patients who were evaluated for epilepsy surgery in a tertiary referral center over the past decades.

Key points

- Genetic testing is increasingly applied in—MRI-negative and MRI-positive— focal epilepsy patients who are considered for epilepsy surgery
- In almost half of patients who underwent genetic testing, genetic testing was performed only after the patient was already accepted or rejected for surgery
- Outcome of genetic testing assists selecting eligible patients for invasive intracranial monitoring and resective or palliative surgery

---

We assessed differences in outcome between important subgroups of evaluated patients, especially focussing on MRI-negative *vs* MRI-positive patients.

2 | METHODS

2.1 | Patient selection

Patients were identified within the database of the Dutch Collaborative Epilepsy Surgery Program group, coordinated in the UMC Utrecht. We included all children and adults who were consecutively evaluated for epilepsy surgery from January 1, 1990, to January 1, 2017. We reviewed medical records, discharge letters, and outpatient clinical summaries of all identified patients. Subjects who did not complete the presurgical program (ie, patient self-withdrawal), and those in whom the UMC Utrecht was not the operating theater were excluded from this analysis. Moreover, we excluded patients if adequate medical information on presurgical assessment could not be retrieved from the medical files. We separately report patients with tuberous sclerosis complex (TSC) and multiple cavernoma (due to KRIT1 or other CCM mutations) in this cohort, because these concern specific groups of patients in whom the diagnosis is made on the basis of the pathognomonic imaging (MRI) findings in combination with clinical criteria. Genetic testing in patients with TSC and multiple cavernoma is mainly performed to confirm the diagnosis and to facilitate genetic counselling. In addition, an extensive body of research to evaluate the role of epilepsy surgery in TSC has already been described elsewhere,[14,15] and genetic testing is not likely to be related to surgical success.

If patients were evaluated multiple times, solely the most recent episode of preoperative assessment was included as

time point of surgical decision-making. In patients who underwent reoperation for failed epilepsy surgery, we only assessed data on follow-up after the last surgery.

The medical ethics committee of the UMC Utrecht approved the study and concluded that no informed consent was required for this retrospective observational study on available data from routine clinical care.

2.2 | Data collection

We collected information on the results of all structural and functional imaging and genetic diagnostic modalities that were utilized within the presurgical evaluation trajectory of included patients. Results of brain MRI as reported by dedicated epilepsy neuroradiologists and the multidisciplinary team discussions at the time of presurgical evaluation were recorded for each of the patients. Scans were not rereviewed for the purpose of this study. In patients who underwent genetic diagnostics, results of each separate genetic test were collected. We evaluated the results of all clinical genetic tests

performed, regardless of whether the genetic results became available before, during or after the presurgical trajectory.

We classified the genetic tests into six categories according to the different technologies that were used: 1) karyotype analysis, 2) array techniques (eg, SNP-array or array-CGH), and sequencing techniques consisting of 3) individual gene analysis, 4) targeted gene panels (categorized into 10 panels; examples are as follows: focal epilepsy, fever-sensitive epilepsy or epileptic encephalopathy), 5) full epilepsy gene panel (including >130 epilepsy genes up to >170 in recent years), and 6) whole exome sequencing (WES). All tests were performed on blood samples and reported causal variants concern germline mutations. Reported genetic variants and clinical information were reviewed by two authors: EB—an experienced clinical geneticist—and MS. Variants were classified into five categories (according to the American College of Medical Genetics and Genomics criteria) that convey information about the probability of representing a pathogenic variant that is causative for the patients' epilepsy.[16] These categories comprised i) benign ii) likely benign iii) uncertain significance, iv) likely pathogenic, and v) pathogenic. For the
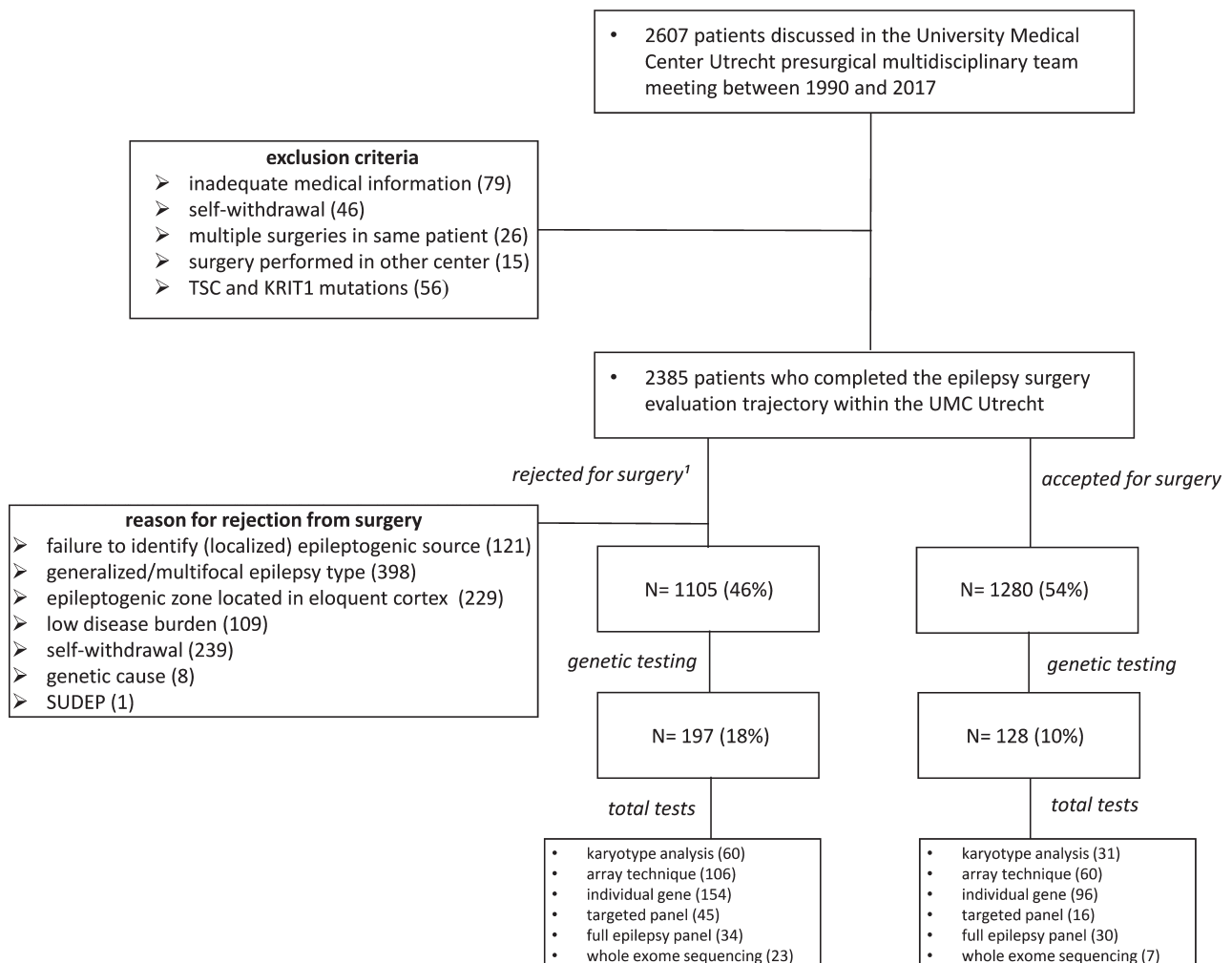
FIGURE 1 Enrolment of study patients

analysis of this study, we considered solely class iv (likely pathogenic) and v (pathogenic) variants to be causative for the epilepsy. We assessed the pathogenic nature of variants with the use of common predictors for pathogenicity such as segregation analysis, functional analysis, appearance of the mutation in variant-related control databases, and molecular features of the mutation itself.

If epilepsy surgery was performed, we extracted information on type of surgery, histopathological diagnosis, and postoperative seizure outcome from the patients' clinical files. Seizure outcomes at 1 year of follow-up after surgery were classified according to the Engel classification system; we defined seizure freedom as complete cessation of seizures—including aura's—(Engel 1A).[17]

3 | RESULTS

Medical information was retrieved of 2385 people with epilepsy (1022 children; 43%) who completed the presurgical evaluation program within the UMC Utrecht (Figure 1). Of these, 450 (19%) had no reported MRI abnormalities causative for the epilepsy ("MRI-negative"), whereas 1935 subjects (81%) were classified as "MRI-positive", with a lesion considered epileptogenic. Complete postoperative seizure freedom (Engel 1A) in all operated patients (n = 1280) occurred significantly more often in MRI-positive patients (74%) compared with the MRI-negative patients (49%, $P = <0.001$).

In total, 662 genetic tests were performed in 325 of all patients (14%). MRI-negative patients were significantly more likely to undergo genetic testing than patients who had a causative MRI-lesion (35% vs 9%, OR 3.9; 95% CI 3.2-4.7). Outcome of surgical evaluation with respect to different subgroups of patients is listed in Table 1. Overall, 181 of 325 patients (56%) underwent genetic testing with results available before completion of the presurgical evaluation trajectory, whereas in the remaining 44% genetic testing was performed only after the patient was already accepted or rejected for surgery. Fifteen of the 40 subjects (38%) in whom a genetic diagnosis could be established underwent genetic analysis only after surgical decision-making.

The annual number of patients evaluated for epilepsy surgery gradually increased from 33 (8 MRI-negative and 25 MRI-positive) in 1990 to 188 (42 MRI-negative and 146 MRI-positive) in 2016 (Figure 2A,B). The percentage of patients undergoing genetic testing increased from 3% in 1991 to an average of 30% of all evaluated patients in the past 5 years. In 1991, 13% of MRI-negative patients *vs* 0% of the MRI-positive group underwent genetic testing, and over the past 5 years, genetic testing was performed in 69% of MRI-negative patients *vs* 20% of the MRI-positive population. Genetic testing performed between 1990 and 2013

**TABLE 1** Outcome of surgical evaluation with respect to different subgroups of patients

I: Cohort Subgroup	N	II: Surgical decision Accepted for surgery - N (%)	III: Surgical outcome Seizure-free - N (%)
All patients	2385	1280 (54)	863/1209[a] (71)
MRI-negative	450	119 (26)	52/106 (49)
MRI-positive	1935	1161 (60)	811/1103 (74)
Genetic testing	325	113 (35)	49 (43)
MRI-negative	156	34 (22)	9 (26)
MRI-positive	169	79 (47)	40 (51)
Genetic diagnosis	40	13 (30)	5 (38)
MRI-negative	25	2 (8)	1 (50)
MRI-positive	15	9 (60)	3 (33)
mTOR gene mutations	7	3 (42)	2 (67)
Channel function and synaptic transmission gene mutations	17	1 (6)	0 (0)

[a]Exact data on surgery outcome could not be retrieved in 74 of 1283 cases.

resulted in 13 of the 43 (30%) genetic diagnoses, whereas the remaining 30 (70%) genetic causes were established from 2013 onwards.

Karyotyping and array techniques were among the most commonly used types of genetic testing from 1990 to 2010, whereas from 2005 onwards, NGS techniques were also used more widely (Figure 2C,D). Together with full epilepsy gene panels and WES, which were first used within this cohort in 2013 and 2014, respectively, these multiple gene sequencing techniques are currently the most widely used and efficient techniques for mutation screening in patients evaluated for epilepsy surgery.

Genetic testing yielded an abnormal finding (ie, genetic variant) in 144 of all patients (44%) tested, comprising 77 of 156 MRI-negative patients (49%) *vs* 67 of 169 MRI-positive (40%) patients. A (likely) pathogenic variant was found in 40 of the 325 tested patients and did not significantly differ between MRI-negative and MRI-positive patients (20 vs 20 patients, respectively, $P = .404$). As expected, the diagnostic yield of multiple gene sequencing (NGS) techniques was significantly higher ($P =< .001$) compared with other tests. The diagnostic yield with respect to finding disease-causing variants was lowest for array techniques (2%) and individual gene analysis (2%) and highest for full epilepsy panel sequencing (17%) and whole exome sequencing (24%). The diagnostic yield of different types of genetic testing is listed in Table 2.
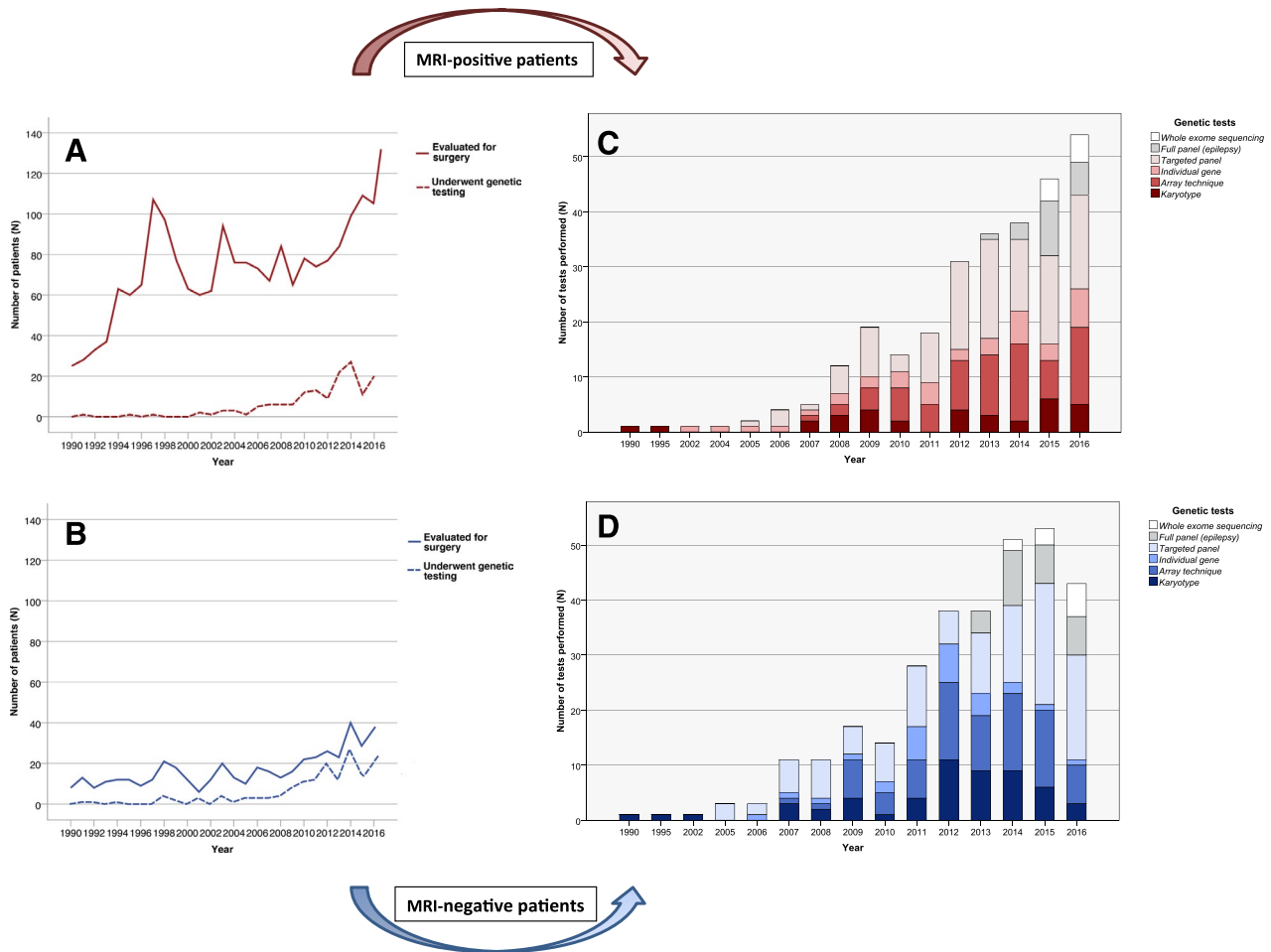
FIGURE 2 A-D, Annual (1990-2016) number of patients who underwent (i) presurgical assessment (unbroken line) and (ii) genetic testing (broken line; A, B) and quantity and type of genetic tests performed (C, D). Red color: MRI-positive patients; blue color: MRI-negative patients

3.1 | Outcome in patients with an established genetic diagnosis

Three of the seven patients with mTOR pathway gene mutations (2 *DEPDC5*; 1 *NPRL3*) underwent surgery (Tables 3 and S1). Two of these (one MRI-negative) achieved complete seizure freedom. The third (MRI-negative) operated patient was not rendered seizure-free after surgery; the surgical report noted a tailored, possibly incomplete, resection of the epileptogenic zone in an eloquent (left precentral) area. Histopathological examination of the resected tissue in this patient was not indicative for a focal cortical dysplasia (FCD, nor did it reveal any other abnormalities. Three of the four patients with mTOR pathway gene mutations who were rejected for surgery were MRI-negative, and in 2 of these 4 (1 MRI-negative and 1 MRI-positive), the genetic diagnosis was established only after rejection for surgery.

Of the 17 patients (12 being MRI-negative) with germline mutations in ion channel function and synaptic transmission genes, only one (*CNTNAP2*) was accepted for epilepsy surgery. It concerned a patient in whom the genetic diagnosis was

established preoperatively, with a subtle right temporal MRI-lesion that was consistent with the patient's semiology and ictal EEG findings. The patient underwent a focal resection and histopathological examination of resected tissue showed gliosis and was not indicative for any specific abnormalities. Five months after surgery the seizures recurred. Two other patients had undergone intracranial EEG-monitoring and were rejected for resective surgery. In both, genetic results became available only months after the presurgical evaluation was completed. Overall, in 10 of the 17 patients (59%) with germline mutations in ion channel function and synaptic transmission, the genetic etiology was established only after rejection for surgery.

Seven of the 13 patients with epilepsy due to genetic causes other than mTOR pathway gene mutations or mutations in ion channel function and synaptic transmission genes received surgery. This group comprised two patients with a *NF1* pathogenic variant; one patient with epilepsy due to a 1q44 deletion (MRI-showed unilateral polymicrogyria); one patient with a 12p13.33 deletion (MRI and histopathological examination indicative for hippocampal sclerosis);

I: Type of testing Genetic test	II: Frequency of testing Number of tests, N	III: Findings Any genetic variant, N (%)	Causative genetic variant, N (%)
Karyotype analysis	91	3 (3)	3 (3)
Array technique	165	47 (28)	4 (2)
Individual gene sequencing	56	4 (7)	1 (2)
Targeted panel sequencing[a]	257	39 (15)	14 (5)
Febrile related epilepsy	91	19 (21)	6 (7)
Focal epilepsy	42	8 (19)	3 (7)
Epileptic encephalopathy	49	7 (14)	3 (6)
Progressive myoclonic epilepsy	10	1 (10)	1 (10)
Benign neonatal convulsions	21	1 (5)	0 (0)
Epilepsy and mental retardation	37	3 (8)	2 (5)
Idiopathic generalized epilepsy	3	0 (0)	0 (0)
Paroxysmal disorders	3	0 (0)	0 (0)
Inflammation mediated epilepsy	1	0 (0)	0 (0)
Full epilepsy panel sequencing	64	34 (53)	11 (17)
Whole exome sequencing	29	17 (58)	7 (24)
Total	662	144 (22)	40 (6)

TABLE 2 Outcome (III) and diagnostic yield (disease-causing variants) of genetic testing with regard to type (I) and number (II) of genetic tests performed

[a]Panels as listed below included a number of genes that varied over time; more recent panels contained more genes. Furthermore, some genes were included in several panels.

one patient with an *ARX* mutation (MRI-showed unilateral polymicrogyria); one patient with an *ANKRD11* pathogenic variant (KBG-syndrome, MRI suggestive for FCD whereas histopathological examination was unremarkable); and one patient with a *WDR26* pathogenic variant (MRI showed hemiatrophy). Complete seizure cessation was achieved in 3 of these 10 patients. All three patients with ring chromosome 20 were rejected for surgery.

3.2 | Patients with tuberous sclerosis complex and KRIT1 mutations

There were 53 patients evaluated for surgery in whom a clinic-radiological diagnosis of TSC was established. Individual gene analysis in these patients resulted in a genetic diagnosis (*TSC1* or *TSC2* mutation) in 45 patients. In all but two patients, the genetic diagnosis was already known before the patients entered the epilepsy surgery evaluation program.

    Three patients were found with epilepsy due to cavernomas in the context of a *KRIT1* pathogenic variant. Two of

these patients were seizure-free (Engel 1A) one year after surgery.

4 | DISCUSSION

In the past decades, there is a distinct increase in the application of genetic testing among patients with pharmacoresistant epilepsy who entered the Dutch comprehensive presurgical evaluation program, particularly in those with normal MRI. Furthermore, the spectrum of genetic technologies embedded in the presurgical assessment expanded clearly over the last 10 years, with a shift toward NGS technology. These two findings are parallel and were expected due to the rapid developments in the field of genetic technologies that improved clinically available and cost-effective genetic testing in epilepsy patients. The accelerated discovery of genes in human epilepsy together with the advent of readily available multiple gene sequencing techniques resulted in a significantly increased detection of disease-causing variants in our cohort. Our findings highlight the need for genetic testing in focal epilepsy in

TABLE 3 Timing of genetic analysis (pre- vs postsurgical decision-making) and surgical outcome (seizure freedom) in patients with a pathogenic variant

Neurobiological pathway	Pathogenic variant (N) N = 40 (total)	Genetic testing							
		Before surgical decision-making (N = 22)				After surgical decision-making (N = 18)			
		Operated (N = 9) - (seizure-free: N = 3)		Rejected (N = 13)		Operated (N = 2) - (seizure-free: N = 1)		Rejected (N = 16)	
		iEEG	No iEEG	iEEG (0)	No iEEG	iEEG	No iEEG	iEEG	No iEEG
mTOR pathway (n = 7, 18%)	DEPDC5 (5)	1 (0)	-	-	2	1 (1)	-	-	1
	NPRL3 (2)	-	1 (1)	-	-	-	-	-	1
Ion channel function and synaptic transmission (n = 17, 43%)	SCN1A (6)	-	-	-	3	-	-	2	1
	KCNT1 (3)	-	-	-	-	-	-	-	3
	GRIN2A (2)	-	-	-	1	-	-	-	1
	STXBP1 (2)	-	-	-	-	-	-	-	2
	SLC35A2 (1)	-	-	-	1	-	-	-	-
	CHRNA4 (1)	-	-	-	1	-	-	-	-
	GABRA3 (1)	-	-	-	-	-	-	-	1
	CNTNAP2 (1)	-	1 (0)	-	-	-	-	-	-
Cell-cell adhesion (n = 1, 2%)	PCDH19 (1)	-	-	-	-	-	-	-	1
Protein translation and modification (n = 2, 5%)	PNKP (1)	-	-	-	1	-	-	-	-
	QARS (1)	-	-	-	1	-	-	-	-
Neuronal migration, neurogenesis (n = 1, 2%)	ARX (1)	-	1 (1)	-	-	-	-	-	-
Other causes (n = 12, 30%)	Microdeletions (4)	-	2 (0)	-	1	-	-	-	1
	Ring 20 (3)	-	-	-	2	-	-	-	1
	NF1 (2)	-	2 (1)	-	-	-	-	-	-
	ANKRD11 (1)	-	1 (1)	-	-	-	-	-	-
	NBEA (1)	-	-	-	-	-	-	-	1
	WDR26 (1)	-	-	-	-	-	1 (0)	-	-

general and its potential use in epilepsy surgery evaluation specifically.

For the purpose of this study and to maintain a "real life situation," results of brain imaging as reported by experienced clinical neuroradiologists at the time of evaluation were not rereviewed. It is commonly accepted that having a causative focal or unilateral structural abnormality on MRI (MRI-positive) is a strong predictor of good surgical outcome.[18] This finding was confirmed in our study, with 74% seizure freedom in MRI-positive compared with 49% in MRI-negative patients. This emphasises the need for improved imaging or post-processing methods, and for new, non-invasive diagnostic modalities that could improve presurgical decision-making and ultimately surgical success.

In this study, 2 of 3 operated patients with mTOR pathway gene mutations achieved seizure freedom (one of whom being MRI-negative) after surgery. These findings are in accordance with the results of our recent literature review, which showed that surgery in FE patients with mTOR pathway gene mutations—likely representing a focal, structural cause for epilepsy—had a relatively higher success rate compared with other genetic causes.[13] The characteristics of the MRI-negative third patient with no postoperative reduction of seizure frequency (small resection in an eloquent area and no pathology identified in resected tissue), point toward the possibility of an incomplete resection of the epileptogenic focus; the patient is therefore currently being reevaluated. These three epilepsy patients are representative for the population in which a genetically established diagnosis can point toward an "MRI-invisible" microstructural lesion or malformation of cortical development, probably implying a reasonable chance of postoperative seizure freedom. Genetic testing could help to differentiate between this category of patients and those with a genetic syndrome that is not accompanied with an

identifiable lesion—probably reflecting a lower chance of surgical success—, or by a combination of the two.

On the other hand, genetic testing could also improve decision-making in MRI-positive patients. The identification of an mTOR gene mutation early in the presurgical evaluation could, together with other presurgical diagnostic modalities, add strength to the congruence of a structural localized epileptogenic focus.

The finding of a pathogenic variant indicating a genetic syndrome without a structural cause of epilepsy suggests poor surgical candidacy and outcome. Of the 14 patients reported in the literature with a mutation in genes related to ion channel or synaptic function, only 2 patients (14%) became seizure-free after surgery.[13] Of our 17 patients with such mutations, 16 patients were rejected because presurgical assessment failed to localize the epileptogenic zone. One MRI-positive patient (*CNTNAP2* mutation) received surgery and was not rendered seizure-free; clinical history and surgical outcome of this patient were in accordance with the few previously reported in the literature.[19] Two patients were rejected after they underwent invasive monitoring. In these two patients, a *SCN1A* mutation was only found after the invasive monitoring had been performed. These findings suggest that identification of a pathogenic variant in this group of genes (before or during the presurgical evaluation) could prevent unnecessary extensive and expensive presurgical evaluation, and especially resective surgery or invasive source localization techniques in MRI-negative and MRI-positive patients with an epilepsy phenotype not fully in concordance with the lesion. In the latter group, however, surgery may be considered to only target lesion related seizures in patients with dual pathology (eg, patients with SCN1A mutations and hippocampal sclerosis).

In conclusion, there is a clear increase in the use of genetic testing in patients evaluated for epilepsy surgery, which can be explained by a rapid evolution of genetic techniques, the extensive discovery of novel generalized as well as focal epilepsy genes in the last decade, and the increase in number of MRI-negative patients, in whom both structural and non-structural genetic etiologies are increasingly considered in the differential diagnosis.

However, genetic diagnostics are still not routinely performed before deciding to operate patients or reject them from surgery or from invasive monitoring. In many proposed flow diagrams of presurgical evaluation, genetic testing is not listed, and in the recent ILAE evaluation of presurgical test utility, genetic tests were not included.[20,21] Moreover, in almost half of the patients who underwent genetic testing, the genetic diagnosis was established only after the patient was already accepted or rejected for surgery.

The low number of surgical cases for most genetic causes and the heterogeneity of pathogenic variants leave open questions. Therefore, a prospective study is warranted to identify causative epilepsy gene variants in patients who are evaluated

for surgery, that can either point toward structural focal and presumably surgically remedial causes of epilepsy, or toward primary genetic non-lesional causes of epilepsy. We are currently undertaking this study with the hypothesis that genetic testing in patients with pharmacoresistant epilepsy can improve differentiation between good surgical candidates, and those who are less eligible for epilepsy surgery.

CONFLICT OF INTEREST

Neither 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.

ORCID

Maurits W. C. B. Sanders https://orcid.org/0000-0003-0592-1098

REFERENCES

1. Fiest KM, Sauro KM, Wiebe S, Patten SB, Kwon C-S, Dykeman J, et al. Prevalence and incidence of epilepsy. Neurology. 2017;88: 296–303.
2. Englot DJ, Birk H, Chang EF. Seizure outcomes in nonresective epilepsy surgery: an update. Neurosurg Rev. 2017;40:181–94.
3. Kwan P, Brodie MJ. Early identification of refractory epilepsy. N Engl J Med. 2000;342:314–9.
4. Kwan P, Arzimanoglou A, Berg AT, Brodie MJ, Allen Hauser W, Mathern G, et al. Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. Epilepsia. 2010;51:1069–77.
5. Hotan GC, Struck AF, Bianchi MT, Eskandar EN, Cole AJ, Westover MB. Decision analysis of intracranial monitoring in non-lesional epilepsy. Seizure. 2016;40:59–70.
6. West S, Nolan SJ, Newton R. Surgery for epilepsy: a systematic review of current evidence. Epileptic Disord. 2016;18:113–21.
7. Jayalakshmi S, Vooturi S, Gupta S, Panigrahi M. Epilepsy surgery in children. Neurol India. 2017;65:485–92.
8. Helbig I, Tayoun ANA. Understanding genotypes and phenotypes in epileptic encephalopathies. Mol Syndromol. 2016;7:172–81.
9. Hildebrand MS, Dahl H-H, Damiano JA, Smith RJH, Scheffer IE, Berkovic SF. Recent advances in the molecular genetics of epilepsy. J Med Genet. 2013;50:271–9.
10. Orsini A, Zara F, Striano P. Recent advances in epilepsy genetics. Neurosci Lett. 2017;667:4–9.
11. Møller RS, Weckhuysen S, Chipaux M, Marsan E, Taly V, Bebin EM, et al. Germline and somatic mutations in the MTOR gene in focal cortical dysplasia and epilepsy. Neurol Genet. 2016;2:e118.
12. Reif PS, Tsai M-H, Helbig I, Rosenow F, Klein KM. Precision medicine in genetic epilepsies: break of dawn? Expert Rev Neurother. 2017;17:381–92.
13. Stevelink R, Sanders MWCB, Tuinman MP, Brilstra EH, Koeleman BPC, Jansen FE, et al. Epilepsy surgery for patients with

genetic refractory epilepsy: a systematic review. Epileptic Disord. 2018;20:99–115.

14. Bourgeois M, Crimmins DW, De Oliveira RS, Arzimanoglou A, Garnett M, Roujeau T, et al. Surgical treatment of epilepsy in Sturge-Weber syndrome in children. J Neurosurg. 2007;106:20–8.

15. Zhang K, Hu W-H, Zhang C, Meng F-G, Chen N, Zhang J-G. Predictors of seizure freedom after surgical management of tuberous sclerosis complex: a systematic review and meta-analysis. Epilepsy Res. 2013;5:377–83.

16. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17:405–24.

17. Engel J Jr, Van Ness P, Rasmussen TB, et al. Outcome with respect to epileptic seizures. In: Engel J Jr, editors. Surgical treatment of the epilepsies. New York: Raven Press; 1993: 609–21.

18. Téllez-Zenteno JF, Ronquillo LH, Moien-Afshari F, Wiebe S. Surgical outcomes in lesional and non-lesional epilepsy: a systematic review and meta-analysis. Epilepsy Res. 2010;89:310–8.

19. Strauss KA, Puffenberger EG, Huentelman MJ, Gottlieb S, Dobrin SE, Parod JM, et al. Recessive symptomatic focal epilepsy and mutant contactin-associated protein-like 2. N Engl J Med. 2010;354:1370–7.

20. Ryvlin P, Cross JH, Rheims S. Epilepsy surgery in children and adults. Lancet Neurol. 2014;13:1114–26.

21. Jayakar P, Gaillard W, Tripathi M, et al. Diagnostic test utilization in evaluation for respective epilepsy surgery in children. Epilepsia. 2014;55:507–18.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.