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Epilepsy surgery for patients with genetic refractory epilepsy: a systematic review

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ABSTRACT – *Aims*. In recent years, many different DNA mutations underlying the development of refractory epilepsy have been discovered. However, genetic diagnostics are still not routinely performed during presurgical evaluation and reports on epilepsy surgery outcome for patients with genetic refractory epilepsy are limited. We aimed to create an overview of the literature on seizure outcome following epilepsy surgery in patients with different genetic causes of refractory epilepsy.

Methods. We systematically searched PubMed and Embase prior to January 2017 and included studies describing treatment outcome following epilepsy surgery in patients with genetic causes of epilepsy. We excluded studies in which patients were described with epilepsy due to Tuberous Sclerosis Complex or Sturge-Weber syndrome (since this extensive body of research has recently been described elsewhere) and articles in which surgery was aimed to be palliative.

Results. We identified 24 eligible articles, comprising a total of 82 patients who had undergone surgery for (mainly childhood-onset) refractory epilepsy due to 15 different underlying genetic causes. The success rate of surgery varied widely across these different genetic causes. Surgery was almost never effective in patients with epilepsy due to mutations in genes involved in channel function and synaptic transmission, whereas surgery was significantly more successful regarding seizure control in patients with epilepsy due to mutations in the mTOR pathway. Patients with a lesion on MRI tended to have higher seizure freedom rates than those who were MRI-negative.

Conclusion. Although the evidence is still scarce, this systematic review suggests that studying genetic variations in patients with refractory epilepsy could help guide the selection of surgical candidates.

Key words: seizure, mutation, hereditary, mTOR, epilepsy surgery, MRI-negative, channelopathies

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It is estimated that around 60% of epilepsy patients have focal epilepsy, of whom nearly half are medically refractory (West *et al*., 2015). Epilepsy surgery is the only treatment that may be curative in patients with medically refractory epilepsy. However, epilepsy surgery is strongly under-utilised and currently less than half of refractory epilepsy patients are referred for evaluation of epilepsy surgery candidacy (de Flon *et al*., 2010; Uijl *et al*., 2012).

The relatively low proportion of potential surgical candidates who actually undergo surgery is largely due to a lack of factual information regarding epilepsy surgery and uncertainty around treatment outcome (Dewar and Pieters, 2015). Although there are several prognostic factors for surgical success (West *et al*., 2015), it is often unclear for which patients surgery is indicated or contraindicated. Currently, on average, only 65% of patients achieve seizure freedom after surgery (West *et al*., 2015).

Over recent years, it has increasingly been acknowledged that many patients with either generalized or focal types of epilepsy have an underlying genetic cause (Helbig *et al*., 2008; Hildebrand *et al*., 2013). These include single gene mutations that are related to channelopathies and disorders of synaptic transmission (Helbig *et al*., 2008), or the mammalian target of rapamycin (mTOR) pathway, involved in various processes such as neuronal growth, migration, and proliferation (Baldassari *et al*., 2016). In addition, there are several microdeletions and other chromosomal abnormalities that are known to be associated with epilepsy. This heterogeneity in molecular genetic aetiology points to differences in the underlying pathophysiology and is reflected by phenotypic differences between patients. It is possible that these different causes are also associated with differences in response to epilepsy surgery.

It is commonly accepted that epilepsy patients with a genetically determined focal structural lesion(s), such as tuberous sclerosis, may be candidates for surgery (Zhang *et al*., 2013). However, many patients with genetic causes of epilepsy do not have detectable epileptogenic lesions on MRI, so called "MRI-negative" patients. In general, the absence of a visible brain lesion on MRI significantly decreases the chance of surgical success (Téllez-Zenteno *et al*., 2010; Bast, 2013). MRI-negative patients with focal epilepsy can still be considered surgical candidates (Bast *et al*., 2016) as there may be an undetected underlying focal epileptogenic brain lesion, such as mild malformations of cortical development (mMCD) or focal cortical dysplasia (FCD) (So and Lee, 2014). Greater MR field strength, improved MRI sequences, and new post-processing techniques have increased the detection rate of such mMCDs and FCDs (So and Lee, 2014). Even in truly MRI-negative patients with refractory focal epilepsy and a consistent electrophysiological focus, epilepsy surgery is increasingly considered due to advances in multimodal functional neuroimaging and invasive monitoring techniques, such as stereo-electroencephalography (S-EEG). Pathology often subsequently reveals an underlying mMCD or FCD (So and Lee, 2014). However, surgery has been successful in some (18-47%) patients without demonstrated pathological abnormalities (Téllez-Zenteno *et al*., 2010). A still unknown proportion of MRI-negative patients with focal refractory epilepsy who are evaluated for epilepsy surgery may have a genetic epilepsy syndrome. Identification of such genetic causes could have prognostic value for surgical outcome in these patients.

Genetic diagnostics are still not routinely performed in patients with refractory epilepsy, mostly due to the high costs and low throughput of traditional DNA sequencing techniques (Hildebrand *et al*., 2013). The possibility to comprehensively test all epilepsy patients for genetic causes has been enhanced in recent years, with the advent of next-generation sequencing techniques (Hildebrand *et al*., 2013).

To date, reports of epilepsy surgery for patients with genetic causes of epilepsy are sporadic. Some recent studies have shown that epilepsy surgery may be effective in patients with mutations in specific genes (Lee *et al*., 2012; Jansen *et al*., 2015), but this has never been shown in patients with other gene mutations (Barba *et al*., 2014; Skjei *et al*., 2015). Such findings suggest that routine genetic diagnostics for causative mutations of epilepsy prior to surgery could be of importance to determine surgical candidacy. This systematic review provides an overview of the reported outcomes of epilepsy surgery in patients with an established genetic cause of epilepsy. Future aims include the use of genetic diagnostics in the presurgical assessment of patients with refractory epilepsy in order to assist the clinician in the often complex dilemma of whether to proceed to surgery or rather stop the time-consuming, costly, and often invasive, presurgical trajectory in patients with a proven genetic epilepsy syndrome.

Methods

Search strategy and study selection

Our search strategy and study selection are summarised in *figure 1*. A literature search in PubMed and Embase was performed by one author (RS) in order to identify articles in which epilepsy, genetics, and surgery were described together, using various

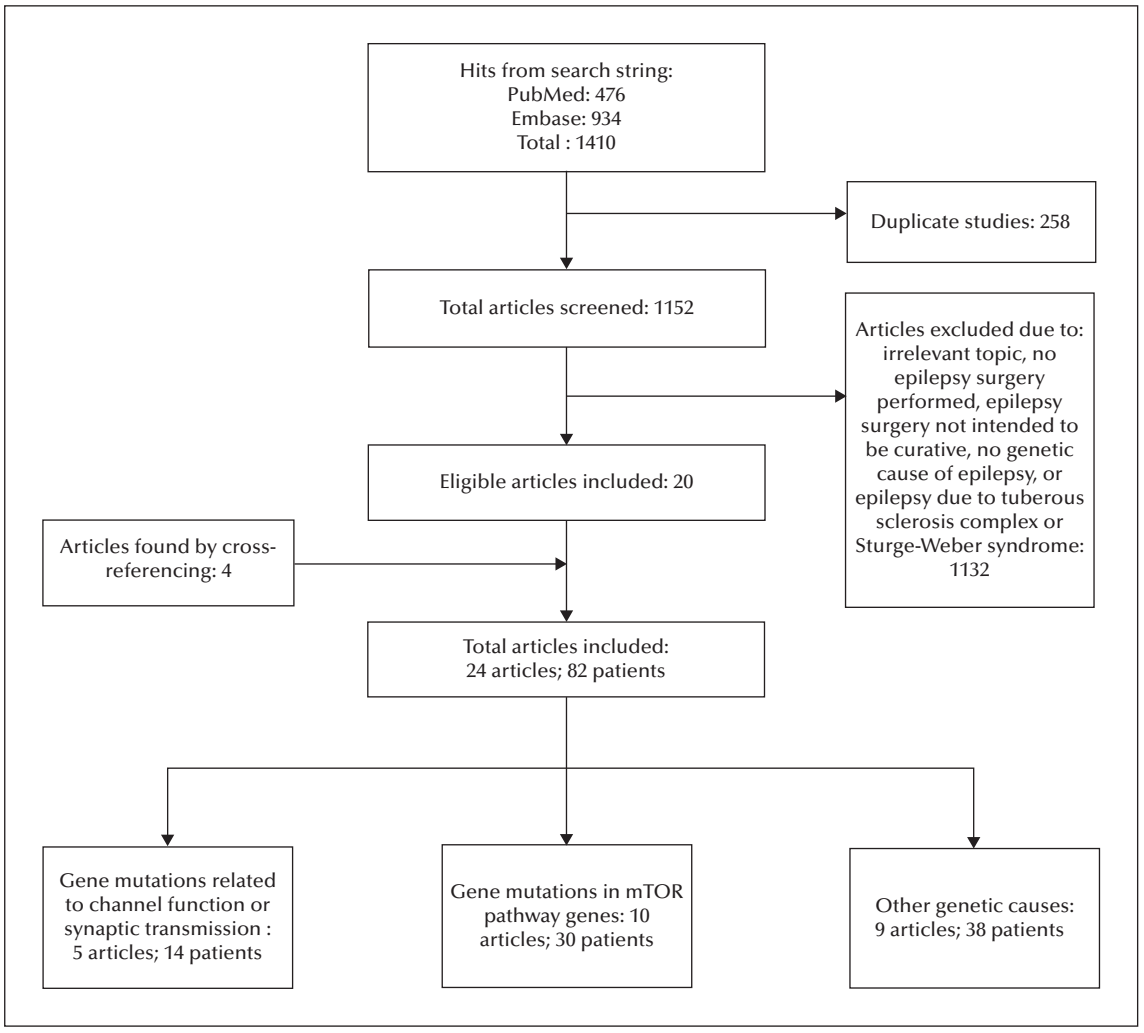

Figure 1. Flowchart of search strategy and study selection.

synonyms (*supplementary tables S1 and S2*). The search was initially performed in June 2016 and updated in November 2016. The search yielded a total of 1,345 articles.

We included all studies reporting on epilepsy surgery and seizure outcome and collected details only on patients who either had a definite clinical diagnosis of a genetic syndrome with co-morbid epilepsy, or who had a mutation or other genetic abnormality detected that was highly likely to be the cause of their epilepsy. All patients with genetic causes of epilepsy who were described in the reports were included, regardless whether the causative mutation was somatic/mosaic or germline, although we describe the results for these subgroups separately. We excluded articles on patients with epilepsy due to tuberous sclerosis complex or Sturge Weber syndrome from this systematic review, since this extensive body of research has recently been described elsewhere (Bourgeois *et al*., 2007; Zhang *et al*., 2013). Furthermore, we excluded articles in which epilepsy surgery was described for patients with genetic mutations that were associated with, but not considered monogenic causes of, their epilepsy; for example, BRAF mutations in glioneuronal tumours, reported as potential prognostic factors for surgery outcome (Prabowo *et al*., 2014). Moreover, we excluded surgical cases when the intention of surgery was stated to be palliative, rather than curative.

All search results were reviewed based on title and abstract. The full-text was reviewed in potentially eligible articles. Moreover, references of the included articles were reviewed, as well as other articles in which the eligible articles are cited, using the "cited by" functions in PubMed and Embase. The article search and selection were checked by a second author (MS).

Data processing

A standardised data extraction form was created, containing nine variables: affected gene, causative genetic variants, number of patients, histology of resected tissue, MRI findings, surgery type, mean follow-up time in years, post-surgical seizure outcome, and whether the surgery was successful. We divided the included articles into three main categories of genetic causes of epilepsy:
– pathogenic variants of genes related to ion channel function and synaptic transmission;
– pathogenic variants of mTOR pathway genes;
– other genetic causes of epilepsy.
Extraction of raw data from the included articles was performed by RS and checked by MS.
Whenever possible, we classified histological descriptions of resected or isolated tissue according to the standardised classification system of focal cortical dysplasia (FCD) defined by the ILAE.
Where possible, we categorised descriptions of MRI findings as FCD, hippocampal sclerosis (HS) or hemimegalencephaly. Patients were defined as MRI-negative based on either no abnormalities or only non-specific abnormalities, not judged to be the cause of epilepsy, on MRI. All patients without detectable causative lesions on MRI were used for subgroup analysis.
Successful surgery was defined as Engel Class I ("free of disabling seizures"), the equivalent ILAE Class 1, or a description of seizure outcome equivalent to these classifications, based on the last reported follow-up visit.

Results

Search results

The literature search yielded a total of 20 eligible articles and a further four publications were identified through a cross-reference check of the citations of the included articles, as well as all publications in which the eligible articles are cited.
The 24 included studies described a total of 82 patients, with 15 different genetic causes of (mainly childhood-onset) epilepsy, who underwent surgery. The success rate of surgery varied widely amongst these different genetic causes (*table 1*).

Genes related to channel function and synaptic transmission

The literature search yielded five articles that described a total of 14 surgery cases with epilepsy due to pathogenic variants in genes related to ion channel function and synaptic transmission (*table 2*). These epileptogenic mutations were found in the voltage-gated sodium channels *SCN1A* and *SCN1B* (Helbig *et al*., 2008), the gene *CNTNAP2* which is involved in AMPA-receptor trafficking and excitatory neuronal network activity (Anderson *et al*., 2012; Varea *et al*., 2015), and *STXBP1*, which is involved in the release of neurotransmitters (Weckhuysen *et al*., 2013).
Epilepsy surgery did not lead to complete seizure freedom in any of the eight patients with *SCN1A* mutations who underwent epilepsy surgery, even though six of them had focal seizure semiology which co-localized with MRI-visible lesions (Barba *et al*., 2014; Skjei *et al*., 2015). Outcome data concerning specific seizure types that were primarily targeted by the surgical procedure (*e.g.* temporal lobe seizures in patients with HS) were not provided in the publications included. Seven of the patients with *SCN1A* mutation had a clinical phenotype consistent with Dravet syndrome and the other had a clinical phenotype most consistent with genetic epilepsy with febrile seizures plus (GEFS+). Two patients had no MRI-visible lesion.
Two patients underwent surgery for epilepsy due to mutations in *SCN1B* and both patients became seizure-free after temporal lobectomy (Scheffer *et al*., 2007); one had underlying HS, whereas no brain abnormality, on MRI or histopathological examination of resected tissue, was detected in the other patient.
All three patients with epilepsy due to a homozygous mutation in *CNTNAP2* had a recurrence of seizures after surgery (Strauss *et al*., 2006).
One patient with epilepsy due to a *STBXP1* mutation underwent surgery since she had prominent focal findings on EEG, despite having no abnormalities on MRI. Epilepsy surgery did not lead to cessation of seizures although her seizure frequency had decreased (Weckhuysen *et al*., 2013). Pathology of the resected tissue revealed FCD.
Overall, surgery was successful regarding the control of seizures for only two of 14 patients (14%) with pathogenic variants in genes related to channelopathies and disorders of synaptic transmission.

mTOR pathway genes

The search yielded 10 articles that described a total of 30 patients who underwent surgery for epilepsy in relation to mutations in the following mTOR pathway genes: *DEPDC5*, *PTEN*, *PIK3CA*, *AKT3*, *NPRL2*, *NPRL3,* and mTOR itself (*table 3*). In 12 patients, germline mutations were found in *DEPDC5*, *PTEN*, *NPRL2* or *NPRL3* genes, whereas in 18 patients (somatic or mosaic) mutations were detected in resected tissue, involving the genes *PIK3CA*, *AKT3,* and mTOR.
Epilepsy surgery controlled seizures completely in seven of 12 patients with mutations in *DEPDC5*, *PTEN*,

Table 1A. Success rates of epilepsy surgery for patients with different genetic causes (**germline mutations**) of epilepsy.

Genetic cause		MRI-positive seizure-free/total	MRI-negative seizure-free/total	Total group seizure-free/total
Pathogenic variants of genes related to ion channel function and synaptic transmission	*SCN1A*	FCD: 0/2 HS: 0/2 Encephalomalacia: 0/1 Subcortical area of abnormal signal: 0/1	0/2	0/8
	SCN1B	HS: 1/1	1/1	2/2
	CNTNAP2	HS: 0/2	0/1	0/3
	STXBP1	-	0/1	0/1
	Overall	**1/9**	**1/5**	**2/14 (14%)**
Pathogenic variants of mTOR pathway genes	*DEPDC5*	FCD: 3/6	2/3	5/9
	PTEN	HME: 1/1	-	1/1
	NPRL2	-	0/1	0/1
	NPRL3	FCD: 1/1	-	1/1
	Overall	**5/8**	**2/4**	**7/12 (58%)**
Other genetic causes of epilepsy	Microdeletions	HS: 9/10	0/2	9/12
	Neurofibromatosis type 1	FCD: 2/2 HS: 4/6 Polymicrogyria: 0/1 Tumour: 5/11	1/1	12/21
	Fragile-X syndrome	HS: 2/2	-	2/2
	Mitochondrial mutations	HS: 1/3	-	1/3
	Overall	**23/35**	**1/3**	**24/38 (63%)**
Total		**29/52 (56%)**	**4/12 (33%)**	**33/64(52%)**

FCD: focal cortical dysplasia; HS: hippocampal sclerosis. HME: hemimegalencephaly.

NPRL2 or *NPRL3*, of whom eight had a lesion on MRI (Baulac *et al*., 2015; Carvill *et al*., 2015; Jansen *et al*., 2015; Scerri *et al*., 2015; Weckhuysen *et al*., 2016). Three more patients had a significant improvement in seizure frequency, whereas two patients had no improvement. Fifteen of 18 patients with somatic or mosaic mutations in *PIK3CA*, *AKT3* or mTOR, who were all reported to have lesions on MRI, became seizure-free after epilepsy surgery (Lee *et al*., 2012; Poduri *et al*., 2012; Conti *et al*., 2015; Jansen *et al*., 2015; Leventer *et al*., 2015; Nakashima and Saitsu, 2015). One patient reported some improvement, in another monthly seizures persisted, and the last patient did not become seizure-free, however, outcome was not further specified.

After examination of histology in relation to MRI findings, 19 of the 30 patients (somatic/mosaic or germline combined) had focal cortical dysplasia (FCD) due to mTOR pathway pathogenic variants as a structural substrate of epilepsy, whereas 10 other patients had hemimegalencephaly as the structural cause of their epilepsy. One patient had normal MRI and

Table 1B. Success rates of epilepsy surgery for patients with different genetic causes (**somatic mutations**) of epilepsy.

Genetic cause		MRI-positive seizure-free/total	MRI-negative seizure-free/total	Total group seizure-free/total
Pathogenic variants of mTOR pathway genes	*PIK3CA*	HME: 5/5 FCD: 1/1	-	6/6
	AKT3	HME: 1/3 FCD: 1/1	-	2/4
	mTOR	HME: 1/1 FCD: 6/7	-	7/8
Total		**15/18 (83%)**	**-**	**15/18 (83%)**

FCD: focal cortical dysplasia; HME: hemimegalencephaly.

histology. Epilepsy surgery successfully controlled seizures in eight of the 10 patients with hemimegalencephaly (80%) and in 14 of the 19 patients with FCD (74%). Epilepsy surgery was not successful for the patient with normal MRI and histology.

Overall, epilepsy surgery completely controlled seizures in seven of 12 patients (58%) with epilepsy due to germline mutations in the mTOR pathway. The success rate was 71% (22 of 30 patients) for germline and somatic mutations combined.

Epilepsy due to other genetic causes

Eleven articles described a total of 38 patients (all but three were positive for MRI lesions) who had epilepsy in relation to the following other genetic causes: microdeletions, neurofibromatosis type 1, fragile-X syndrome, and mitochondrial mutations (*table 4*).

Twelve patients who underwent epilepsy surgery have been reported with microdeletions, four of which were identified in 16p13.11 (Catarino *et al*., 2011; Liu *et al*., 2012). Nine of 12 patients (75%) became seizure-free after surgery, one patient became seizure-free for seven years after surgery, and the other two patients experienced no improvement.

Twenty-one patients with neurofibromatosis type 1, caused by mutations in *NF1* or microdeletions in 17q11.2 encompassing this gene, underwent epilepsy surgery (Barba *et al*., 2013; Jang *et al*., 2013; Ostendorf *et al*., 2013). These patients had a variety of neurofibromatosis-related epileptogenic lesions, such as HS or low-grade tumours. Epilepsy surgery successfully controlled seizures in 12 of 21 patients (57%) with neurofibromatosis type 1.

Two patients with epilepsy due to Fragile-X syndrome, both with HS, became seizure-free after epilepsy surgery (Wouters *et al*., 2006; Kenmuir *et al*., 2015).

Three patients with epilepsy and mitochondrial mutations, who all had HS (detected on MRI), underwent epilepsy surgery; only one became seizure-free (Niehusmann *et al*., 2011; Azakli *et al*., 2013).

MRI-negative patients with genetic epilepsy

A subgroup analysis of all MRI-negative patients with genetic causes of epilepsy yielded a total of 12 patients with mutations (all detected in blood, and not in tissue) in *SCN1A*, *SCN1B*, *CNTNAP2*, *STXBP1*, *DEPDC5*, and *NPRL2*, and microdeletions in 16p13.11, or neurofibromatosis type 1 (*table 1 and table 5*).

Five MRI-negative patients had epilepsy due to mutations in genes related to channelopathies and disorders of synaptic transmission (Strauss *et al*., 2006; Scheffer *et al*., 2007; Weckhuysen *et al*., 2013; Skjei *et al*., 2015). According to the reports, surgery was considered in these patients based on focal seizure semiology in combination with consistent EEG source localization and results from functional imaging (Scheffer *et al*., 2007; Skjei *et al*., 2015), EEG (Weckhuysen *et al*., 2013) or S-EEG results (Strauss *et al*., 2006). Surgery did not successfully control seizures in any of these patients, except in one with a mutation in *SCN1B*.

Surgery was performed in four MRI-negative patients who had epilepsy due to mutations in the mTOR pathway genes, DEPDC5 or *NPRL2*, and showed focal abnormalities on EEG, S-EEG or PET (Baulac *et al*., 2015; Carvill *et al*., 2015; Weckhuysen *et al*., 2016). Two MRI-negative patients with *DEPDC5* mutations showed FCD on pathological examination and became seizure-free after surgery, whereas surgery did not successfully control seizures in one patient with a pathology-negative *DEPDC5* mutation and another with a mutation in *NPRL2* and FCD on pathological examination.

Epilepsy surgery did not successfully control seizures in either of the two MRI-negative patients with epilepsy due to a microdeletion in 16p13.11. These patients underwent surgery for clinically presumed HS, although neither had HS on pathological examination (Catarino *et al*., 2011; Liu *et al*., 2012). One MRI-negative patient with epilepsy due to neurofibromatosis type 1, with focal abnormalities in the temporal region on EEG and pathology revealing HS in resected tissue, underwent epilepsy surgery and subsequently became seizure-free (Barba *et al*., 2013).

After histological examination, five of the 12 MRI-negative patients were shown to have features of FCD (type Ia, IIa, or not further specified), one patient had HS, and another had a small epileptogenic hamartoma. Five of the 12 MRI-negative patients (42%) had no abnormalities on histological examination.

Overall, a seizure freedom rate of 33% (4 of 12 patients) was reported in the MRI-negative group; two with a mutation in a mTOR pathway gene, one with a *SCN1B* mutation, and one with an *NF1* mutation. Histological examination showed a lesion in three of these patients but no abnormality in the patient with the *SCN1B* mutation. One of the five MRI-negative patients without pathological abnormalities became seizure-free after epilepsy surgery, whereas three of seven MRI-negative patients with pathological abnormalities became seizure-free.

Statistical analyses

Surgery was more successful for patients with mTOR pathway mutations, compared to patients with mutations in genes involved in channelopathies and disorders of synaptic transmission (only patients with germline mutations: 58% versus 14%; Chi-square=5.54; df=1; p=0.019; germline and somatic mutations combined: 73% versus 14%; Chi-square=13.42; df=1; p<0.001; only patients with MRI-visible lesions: 77% versus 11%; Chi-square= 12.07; df=1; p<0.001). The difference in surgery success rate between patients with MRI-visible lesions and MRI-negative patients was at trend level (63% versus 33%, Chi-square=3.679; df=1; p=0.055).

Discussion

In this systematic review, we provide an overview of the reported seizure outcomes of patients with different genetic causes of refractory epilepsy who have undergone epilepsy surgery. Not unexpectedly, there was a large difference in success rate of epilepsy surgery between patients with mutations in genes related to channelopathies and disorders of synaptic transmission and those with mutations in the mTOR pathway, even when somatic mutations were excluded for analysis. This difference remains significant when only MRI-positive cases are compared. mTOR pathway genetic variants are thought to increase seizure susceptibility due to abnormal neuronal migration and growth, which leads to (micro)structural epileptogenic malformations of cortical development, such as hemimegalencephaly and FCD (Jansen *et al*., 2015). Such malformations are thought to arise from a combination of a germline mTOR pathway mutation and a somatic second-hit mutation in the same gene or in a different gene of the mTOR pathway (Poduri *et al*., 2013; Baulac *et al*., 2015). This typically results in focal malformations, since the second hit usually only affects part of the brain. It is reasonable to assume that resection of such localised epileptogenic malformations could be a curative treatment for seizures, as reflected by the relatively high surgical success rate of patients with mTOR pathway mutations. It has been estimated that 11% of all focal epilepsies are due to germline mutations in the mTOR genes *DEPDC5*, *NPRL2* and *NPRL3* (Weckhuysen *et al*., 2016). Considering the associated high success rate of epilepsy surgery, it could be of benefit to routinely screen for such mutations in presurgical evaluation; particularly in MRI-negative, but presumed lesional cases. Finding mTOR pathway mutations would increase the chance of identifying an underlying cryptic malformation of cortical development, and thereby suggest surgical candidacy. The high success rate (83%) of surgery in patients with somatic/mosaic mTOR pathway gene mutations is inherent to the fact that these patients already had established epileptogenic lesions (FCD and hemimegalencephaly); two factors associated with good surgical outcome. Screening for somatic/mosaic mutations in presurgical evaluation is more difficult than for germline mutations. However, investigation of mosaic mutations may be considered in samples of blood, a buccal swab, or sputum using ultra-deep sequencing (Qin *et al*., 2010).

Epilepsy surgery was almost never successful in patients with epilepsy due to mutations in genes involved in channelopathies and disorders of synaptic transmission. Germline mutations in these genes involved in ion channel function and synaptic transmission are likely to cause widespread aberrant neuronal activity (Helbig *et al*., 2008), which is rarely confined to a specific part of the brain. It is unlikely that a local resection would be curative to prevent all seizure types. Surgery did not lead to seizure freedom for any reported patient with mutations in *SCN1A*, *CNTNAP2* or *STXBP1* in this series, despite focal semiology for (at least some of their) seizures, and the fact that most of the patients had coincident structural (possibly) epileptogenic lesions. It is likely that these lesions were either not directly related to the genetic cause of

Table 2. Seizure outcome for patients with epilepsy due to pathogenic variants of genes related to **ion channel function** and **synaptic transmission**.

Study	Gene	Pathogenic variants	Number of patients	Histology of epileptic focus	MRI findings	Surgery type	Post-surgery seizure outcome	Successful epilepsy surgery	Mean follow-up time in years (range)
Barba *et al.*, 2014	*SCN1A*	c.317C>T; c.2584C>G	2	FCD type Ia (1/2); FCD type IIa (1/2)	FCD (2/2)	Right temporal lobectomy and parieto-occipital corticectomy	Engel Class IV (1/2), post-operative death (1/2)	0/2	Not reported
Skjei *et al.*, 2015	*SCN1A*	c.2927del; c.5434T>G; c.4587del; c.5018T>G; c.1661A>G; deletion at exons 17-20	6	Mild MCD (4/6); non-specific findings, possibly due to sampling errors (2/6)	HS (2/6); haemorrhage and encephalomalacia after injury (1/6); small area of abnormal signal (1/6); MRI-negative or non-specific (2/6)	Frontal lobectomy (2/6); temporal lobectomy and frontal gyrus resection (1/6); focal lesionectomy (3/6)	ILAE Class 5 (5/6) ILAE Class 4 (1/6)	0/6	3.15 (1.5 - 5.9)
Scheffer *et al.*, 2007	*SCN1B*	c.363C>G	2	HS (1/2); non-specific findings (1/2)	HS (1/2); non-specific (1/2)	Temporal lobectomy	Seizure-free (2/2)	2/2	2.5 (2 - 3)
Strauss *et al.*, 2006	*CNTNAP2*	3709delG	3	Diffuse dysplasia (3/3)	Temporal lobe abnormalities suggestive of MTS (2/3), MRI-negative (1/3)	Temporal lobectomy (1/3), amygdalohip-pocampectomy (1/3) and limited cortical resection (1/3)	All patients had a recurrence of seizures from 6 to 15 months after surgery	0/3	Not reported
Weckhuysen *et al.*, 2013	*STXBP1*	c.1631G>T	1	FCD type IA	Normal	Complete occipital disconnection and multiple subpial transections	95% reduction in seizure frequency (equivalent to Engel Class III)	0/1	Not reported

FCD: focal cortical dysplasia; MCD: malformations of cortical development; MRI; magnetic resonance imaging; HS: hippocampal sclerosis; N/A: not applicable; ILAE Class: International League Against Epilepsy classification for seizure outcome following epilepsy surgery.

Table 3. Seizure outcome after epilepsy surgery in patients with pathogenic variants of **mTOR pathway genes**.

Study	Gene	Pathogenic variants	Number of patients	Histology of epileptic focus	MRI findings	Surgery type	Post-surgery seizure outcome	Successful epilepsy surgery	Mean follow-up time in years (range)
Baulac *et al.*, 2015	*DEPDC5*	c.715C>T; c.4841G>A; c.1264C>T; c.1759C>T	5	FCD type I (1/5); type IIa (2/5); not conclusive due to fragmented specimen (2/5)	FCD (3/5); MRI-negative (2/5)	Local resection at different sites	Seizure-free (3/5), worthwhile improvement (1/5) no improvement (1/5)	3/5	8 (4 - 13)
Carvill *et al.*, 2015	*DEPDC5*	c.3092C>A; c.842A>T	2	Normal (1/2); FCD type IIa (1/2)	Normal (1/2); FCD (1/2)	Temporal corticectomy (1/2); lobectomy followed by functional hemispherectomy (1/2)	No improvement (1/2) and seizure-free for 2.5 years, after which monthly staring spells (1/2)	0/2	Not reported
Scerri *et al.*, 2015	*DEPDC5*	c.1663C>T	2	FCD type IIa (2/2)	FCD (2/2)	Hemispherectomy (1/2); local resection (1/2)	Seizure-free (2/2)	2/2	13 (10 - 16)
Jansen *et al.*, 2015	*PTEN*	p.Tyr68His (germline)	1	HME and FCD	HME	Hemispherectomy	Seizure-free	1/1	Not reported
	PIK3CA	p.His1047Arg (1/2), p.Glu545Lys as well as p.Thr544Asn (1/2); all mosaic mutations	2	HME (1/2), FCD type IIa (1/2)	HME (1/2); FCD (1/2)	Hemispherectomy (1/2) and occipital resection (1/2)	Seizure-free	2/2	Not reported
Conti *et al.*, 2015	*AKT3*	Mosaic trisomy of the 1q21.1-q44	1	FCD type Ib	FCD	Lesionectomy	Seizure-free, except when withdrawing medication	1/1	3
Lee *et al.*, 2012	*PIK3CA*	Somatic p.Glu54Lys mutation	4	HME and FCD (4/4)	HME (4/4)	Hemispherectomy	Seizure-free (4/4)	4/4	Not reported

Table 3. Seizure outcome after epilepsy surgery in patients with pathogenic variants of **mTOR pathway genes** (*continued*).

Study	Gene	Pathogenic variants	Number of patients	Histology of epileptic focus	MRI findings	Surgery type	Post-surgery seizure outcome	Successful epilepsy surgery	Mean follow-up time in years (range)
	AKT3	Somatic p.Glu17Lys mutation	1	HME and FCD	HME	Hemispherectomy	Not seizure-free	0/1	Not reported
	mTOR	Somatic p.Cys1483Tyr mutation	1	HME and FCD	HME	Hemispherectomy	Seizure-free	1/1	Not reported
Nakashima and Saitsu, 2015	*mTOR*	Somatic p.Ser2215Tyr (2/6); p.Ala1459Asp; p.Leu1460Pro; p.Ser2215Phe; p.Leu1460Pro mutations	6	FCD (6/6)	FCD (6/6)	Lesionectomy (5/6); amygdalohip-pocampectomy and temporal lobectomy (1/6)	Seizure-free (5/6); monthly seizures (1/6)	5/6	Not reported
Poduri *et al.*, 2012	*AKT3*	Somatic p.E17K activating mutation in AKT3 (1/2) and mosaic trisomy of chromosome 1q involving AKT3 (1/2)	2	HME and FCD (2/2)	HME (2/2)	Hemispherectomy	Seizure-free (1/2); reduction to 1-4 per month (1/2)	1/2	5.5 (5 - 6)
Leventer *et al.*, 2015	*mTOR*	Mosaic c.4487T>G mutation	1	FCD type IIa	FCD	Hemispherectomy followed by removal of right frontobasal connection	Seizure-free	1/1	Not reported
Weckhuysen *et al.*, 2016	*NPRL2*	C68_69delCT	1	FCD type Ia	Normal	Fronto-orbital resection	50% seizure reduction	0/1	Not reported
	NPRL3	c.1270C>T	1	FCD type IIa	FCD and hippocam-pal atrophy	Lesionectomy for FCD, twice due to incomplete resection	Rare seizures when medication errors	1/1	Not reported

FCD: focal cortical dysplasia; MRI: magnetic resonance imaging; HME: hemimegalencephaly.

Table 4. Seizure outcome after epilepsy surgery in patients with epilepsy due to other **genetic causes**.

Study	Genetic cause/syndrome	Number of patients	Histology of epileptic focus	MRI findings	Surgery type	Post-surgery seizure outcome	Successful epilepsy surgery	Mean follow-up time in years (range)
Catarino *et al.*, 2011	Microdeletions in: 16p13.11 (3/10); 17p12 (2/10); 15q11.2 (2/10); 4q32.3 (1/10: 4q35.2 (1/10); 7q31.32-31-33	10	HS (8/10); hamartoma (1/10); non-specific findings (1/10)	HS (7/10), hippocampal atrophy (1/10), hippocampal asymmetry (1/10) and MRI-negative (1/10)	Anterior temporal lobectomy (7/10); amygdalo-hippocampectomy (2/10); neocor-ticectomy and amygdalec-tomy (1/10)	ILAE Class 1 (8/10); ILAE Class 5 (1/10); ILAE Class 1 for 7 years then ILAE Class 3 (1/10)	8/10	4.9 (1 - 13)
Liu *et al.*, 2012	Microdeletions in 16p13.11	2	HS (1/2) and hamartia in white matter of middle temporal gyrus (1/2)	Hippocampal atrophy (1/2) and MRI-negative (1/2)	Hippocampal and temporal cortical resection (2/2)	Seizure-free (1/2) and still experiencing frequent seizures (1/2)	1/2	Not reported
Barba *et al.*, 2013	Neurofibromatosis type 1	12	DNET tumour (5/s12); HS (4/12); polymicrogyria (1/12); mixed pathology (1/12); no pathology (1/12)	HS (3/12); cystic lesion (3/12); cortical dysplasia (2/12); hyperin-tensities (2/12); polymicrogyria (1/12); MRI-negative (1/12)	Lobectomy (7/12), lesionectomy (1/12), corticectomy (1/12), cor-tico+lesionectomy (2/12), focal resec-tion+disconnection (1/12)	Engel Class Ia (8/12), Engel Class IV (4/12)	8/12	2.6 (1 - 10)

Table 4. Seizure outcome after epilepsy surgery in patients with epilepsy due to other **genetic causes** (*continued*).

Study	Genetic cause/syndrome	Number of patients	Histology of epileptic focus	MRI findings	Surgery type	Post-surgery seizure outcome	Successful epilepsy surgery	Mean follow-up time in years (range)
Ostendorf *et al.*, 2013	Neurofibromatosis type 1	8	HS (2/8); astrocytoma (3/8); glioma (1/8); DNET tumour (1/8); epidermoid (1/8)	MRI and histology not separated in paper	Resection (5/8); lobectomy (3/8)	Engel Class Ia (3/8), Engel Class IIb (1/8), Engel Class IV (4/8)	3/8	7.4 (1 - 33)
Jang *et al.*, 2013	Neurofibromatosis type 1	1	HS	HS	Anteromesial temporal resection	Seizure-free	1/1	Not reported
Wouters *et al.*, 2006	Fragile-X syndrome: expansion of CGG repeats in FMR1 gene	1	HS	HS	Temporal lobectomy	Seizure-free	1/1	"to date"
Kenmuir *et al.*, 2015	Fragile-X syndrome: expansion of CGG repeats in FMR1 gene	1	HS	HS	Left anterior temporal lobectomy	Seizure-free	1/1	1
Niehusmann *et al.*, 2011	Mitochondrial mutations in ND2 (1/2) and ND4 (1/2)	2	HS (1/2); non-specific (1/2)	HS (2/2)	Amygdalohipp-ocampectomy (1/2) and lesionectomy, sparing hippocampus and amygdala (1/2)	Engel Class III (1/2); Engel Class IIIa (1/2)	0/2	Not reported
Azakli *et al.*, 2013	Mitochondrial mutation in ND1	1	HS	HS	Amygdala hip-pocampectomy	Seizure-free 3 years after surgery	1/1	3

FCD: focal cortical dysplasia; DNET: dysembryoplastic neuroepithelial tumour; HS: hippocampal sclerosis; N/A: not applicable; ILAE Class: International League Against Epilepsy classification for seizure outcome following epilepsy surgery.

Table 5. Seizure outcome after epilepsy surgery in the subgroup of **MRI-negative patients with genetic epilepsy**.

Study	Gene	Pathogenic variants	Number of patients	Histology of epileptic focus	MRI findings	Surgery type	Post-surgery seizure outcome	Successful epilepsy surgery	Mean follow-up time in years (range)
Skjei *et al.*, 2015	*SCN1A*	c.2927del, c.1661A>G	2	No gross abnormalities (2/2); increased cell numbers in 1 patient	Non-specific (2/2)	Frontal lobectomy (1/2) and focal lesionectomy (1/2)	ILAE Class 5 (1/2); ILAE Class 4 (1/2)	0/2	3.4 (3 - 4)
Scheffer *et al.*, 2007	*SCN1B*	C121W	1	Non-specific findings	Non-specific scattered and diffuse white matter hyper-intensities	Anterior temporal lobectomy	Seizure-free	1/1	2
Strauss *et al.*, 2006	*CNTNAP2*	3709delG	1	FCD	No dysplasia	Temporal lobectomy, amygdalohip-pocampec-tomy and limited cortical resection	Recurrence of seizures started somewhere between 6 to 15 months after surgery (not further specified)	0/1	Not reported
Weckhuysen *et al.*, 2013	*STXBP1*	c.1631G>T	1	FCD type Ia	Normal	Complete occipital disconnection and multiple subpial transections	95% reduction in seizure frequency	0/1	Not reported

Table 5. Seizure outcome after epilepsy surgery in the subgroup of **MRI-negative patients with genetic epilepsy** (*continued*).

Study	Gene	Pathogenic variants	Number of patients	Histology of epileptic focus	MRI findings	Surgery type	Post-surgery seizure outcome	Successful epilepsy surgery	Mean follow-up time in years (range)
Baulac *et al.*, 2015	*DEPDC5*	c.484-1G>A (1/2); c.715C>T and c.1264C>T (1/2)	2	FCD type I (1/2); FCD type IIa (1/2)	Normal	Local resection	Seizure-free (2/2)	2/2	13
Carvill *et al.*, 2015	*DEPDC5*	c.3092C>A	1	Normal	Normal	Temporal corticectomy	No improvement	0/1	Not reported
Weckhuysen *et al.*, 2016	*NPRL2*	C68_69delCT	1	FCD type Ia	Normal	Fronto-orbital resection	50% seizure reduction	0/1	Not reported
Catarino *et al.*, 2011	*16p13.11*	chr16:15387380-16198600 microdeletion	1	Non-specific findings	Normal	Neocorticectomy and amygdalectomy	ILAE 1 for 7 years then ILAE 3	0/1	13
Liu *et al.*, 2012	*16p13.11*	*NDE1*-containing microdeletion in resected tissue	1	Hamartia in subcortical white matter	Normal	Hippocampal and temporal cortical resection	Still experiencing frequent seizures	0/1	Not reported
Barba *et al.*, 2013	*NF-1*	17q11.2 microdeletion (Neurofibromatosis type 1)	1	HS	Normal	Temporal lobectomy	Engel Class Ia	1/1	2

FCD: focal cortical dysplasia; HS: hippocampal sclerosis; ILAE Class: International League Against Epilepsy classification for seizure outcome following epilepsy surgery.

epilepsy or that the lesions accounted for only some of the seizures. Possibly, surgery in these patients was not aimed at curing all seizure types, but only targeted seizures originating from a specific structural lesion. However, such a goal was not specified in any of the included articles, nor was the selective outcome for these specific "targeted" seizures. The disappointing overall seizure outcomes of surgery in patients with mutations in this group of genes suggest a relative contraindication for epilepsy surgery, particularly in MRI-negative patients.

Surgery successfully controlled seizures in both patients with mutations in *SCN1B*, one of whom was MRI-negative. In mice, one of the two splice variants of *Scn1b* is known to encode a secreted cell adhesion molecule involved in neuronal pathfinding during embryonic development, and epileptogenic mutations in *Scn1b* result in a functional knockout of this splice variant (Patino *et al*., 2011). Moreover, *Scn1b* knockout mice exhibit defective neuronal proliferation and migration in the hippocampus, which precedes hyperexcitability (Brackenbury *et al*., 2013). These findings suggest that *SCN1B* mutations may be associated with structural epileptogenic abnormalities, and focal resection may thus lead to favourable surgery outcome, rather than directly influencing neuronal excitability, as is the case for *SCN1A* mutations (Helbig *et al*., 2008).

We found large differences in success rate of surgery for epilepsy due to other genetic causes. Epilepsy surgery effectively controlled seizures in most described patients with epilepsy-associated microdeletions. Most of these patients, however, had HS as an underlying structural epileptogenic substrate, which is generally associated with a favourable surgical outcome. Epilepsy surgery was effective in more than half of the neurofibromatosis type 1 patients. Similar to the situation in patients with pathogenic variants in mTOR pathway genes, *NF1* is thought to affect only those parts of the brain with a second-hit mutation (Poduri *et al*., 2013), which could explain why resection of these affected parts can be curative. Epilepsy surgery for patients with Fragile-X syndrome or mitochondrial mutations could effectively control seizures, although only a few patients have been described.

Based on a subgroup analysis, we examined whether epilepsy surgery could be effective for MRI-negative patients with genetic epilepsy. Interestingly, MRI-negative patients had a wide range of different genetic causes (*table 1*), but surgical success rate tended to be higher in cases with MRI showing visible lesions (66%) than in MRI-negative cases (33%), which is in line with previous studies (Téllez-Zenteno *et al*., 2010). Interestingly, two patients were reported after successful epilepsy surgery for genetic refractory epilepsy, but histological examination of the resected tissue did not reveal any abnormalities. However, we cannot exclude the possibility that subtle abnormalities may have gone undetected due to sampling errors, or that the resection may have removed crucial parts of the epileptogenic non-lesional network. The outcome of these patients suggests that the absence of a detectable lesion on MRI in patients with genetic abnormalities should not in itself be an absolute contraindication for epilepsy surgery.

It remains unclear whether structural lesions are truly absent in MRI-negative patients, or whether their apparent absence is simply based on limitations such as the detection sensitivity threshold of MRI performed or the experience of the radiologist (So and Lee, 2014). In accordance with previous studies (Téllez-Zenteno *et al*., 2010; So and Lee, 2014), we found that most MRI-negative patients who underwent surgery in this review had histological abnormalities suggestive of MCD in the resected tissue. New MRI methods, higher-field scanning, and post-processing techniques have already shown that it is possible to detect epileptogenic lesions which were not previously visible on conventional MRI scans, improving the identification of surgical target areas and subsequently yielding higher success rates in patients with genetic refractory epilepsy.

There are a number of limitations to this systematic review. The low number of surgical cases for most genetic causes hampers firm conclusions. Furthermore, there is significant heterogeneity between reported patient characteristics and surgical procedures. The follow-up duration largely varies between studies and is sometimes not reported. Another source of heterogeneity stems from different mutations within the same gene among patients, which could potentially affect surgical outcome. Moreover, differences of expertise in genetic analysis or surgery, accessibility to genetic testing, and indications for epilepsy surgery could relate to lower reporting and different success rates of surgery. Although not explicitly stated in most studies, we assumed that reported mutations were detected in blood, unless specified otherwise. The extent of mosaicism and the effect on the occurrence of a lesion and surgical outcome remains unclear. In addition, publication bias, recall bias, and selection bias due to the scarce number of patients described in the literature cannot be excluded; it is possible that unsuccessful surgery is less likely to be reported.

Surgical candidacy, particularly for MRI-negative patients, is still not easily determined. Some patients are declined surgery because of a presumed non-structural, genetic aetiology. Finding a germline or mosaic mTOR gene mutation could justify continuation of the presurgical diagnostic process. Others, however, are offered resective surgery or invasive

monitoring (sEEG) (because of presumed focal structural MRI-negative aetiology), although their epilepsy may have been primarily caused by a genetic and more diffuse aetiology, such as mutations in genes involved in ion channel or neurotransmitter function. Genetic testing is not yet routinely included in most surgical evaluation programmes. Nevertheless, finding specific gene mutations could prove valuable for the process of selecting surgical candidates and counselling patients on expected outcome. Larger and prospective studies are needed to further elucidate the importance of detecting genetic mutations in patients who are considered possible candidates for epilepsy surgery. □

Supplementary data.
Summary didactic slides and supplementary tables are available on the www.epilepticdisorders.com website.

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TEST YOURSELF

(1) Can all genetic variants underlying epilepsy be detected by DNA sequencing?

(2) How many patients with epilepsy due to mutations in mTOR pathway genes achieve seizure freedom after epilepsy surgery?

(3) How many patients with epilepsy due to mutations in genes related to ion channel function and synaptic transmission achieve seizure freedom after epilepsy surgery?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".