Genetic Testing for Epilepsy Surgery

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Summary

Dozens of novel epilepsy genes have been discovered at a very fast pace in the past decade. This progress improved understanding and management of epilepsy; however, this has not systematically been evaluated for the focal epilepsies that can be cured by epilepsy surgery. In this report we discus the impact and possible application of genetic diagnostics in epilepsy surgery evaluation. A review of the available data suggests that epilepsy gene mutations can be useful biomarkers for surgery. These may be negative predictors, such as mutations in genes encoding ion-channels or involved in synaptic function. The association of mutations in mTOR pathway genes with lesional focal epilepsy suggest that such mutations may be positive predictors that can improve selection of surgical cases, especially in the MRI-negative cases. However, it is clear that larger studies are needed to collect more detailed imaging and to interpret the link between surgery outcome, observational data, knowledge of disease aetiology, and genetics.

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Key words: Epilepsy surgery, genetics, DNA-diagnostics, prognosis

Gentests für die Epilepsiechirurgie

In den letzten zehn Jahren wurden in äusserst rascher Folge Dutzende neuer Epilepsie-Gene entdeckt. Dieser Fortschritt hat zu einem besseren Verständnis und Management der Epilepsie geführt; allerdings wurde dies für die epilepsiechirurgisch heilbaren fokalen Epilepsien nicht systematisch beurteilt. Der vorliegende Bericht erörtert die Auswirkungen und die mögliche Anwendung der Gendiagnostik bei der epilepsiechirurgischen Beurteilung. Eine Übersicht der verfügbaren Daten legt nahe, dass Mutationen in Epilepsie-Genen hilfreiche Biomarker im Hinblick auf chirurgische Optionen sein können. Dabei kann es sich um negative Prädiktoren handeln, z. B. Mutationen in Genen, die für Ionenkanäle kodieren oder an synaptischen Funktionen beteiligt sind. Der Zusammenhang zwischen Mutationen im mTOR-Signalweg und läsionsbedingten fokalen Epilepsien lässt vermuten, dass derartige Mutationen positive Prädiktoren darstellen, die eine bessere Selektion chirurgisch therapierbarer Fälle ermöglichen, insbesondere bei MRT-negativen Patienten. Allerdings steht ausser Zweifel, dass zur Erfassung detaillierterer Bildgebungsdaten und zur Klärung des Zusammenhangs zwischen chirurgischem Behandlungsergebnis, Beobachtungsdaten, Wissen um die Krankheitsätiologie und Genetik umfassendere Studien erforderlich sind.

Schlüsselwörter: Epilepsiechirurgie, Genetik, DNA-Diagnostik, Prognose

Tests génétiques pour la chirurgie épileptique

Ces dix dernières années, des douzaines de nouveaux gènes associés à l'épilepsie ont été découverts à une cadence particulièrement rapide. Si cette avancée a permis une meilleure compréhension et prise en charge de l'épilepsie, elle n'a pas systématiquement été évaluée pour les formes focales d'épilepsie pouvant être traitées par chirurgie épileptique. Le présent rapport s'intéresse à l'impact et à l'application potentielle des diagnostics génétiques dans l'évaluation de la chirurgie épileptique. Une analyse des données disponibles suggère que les mutations observées dans les gènes associés à l'épilepsie peuvent être des biomarqueurs utiles pour la chirurgie. Il peut s'agir de facteurs prédictifs négatifs, par exemple dans le cas des mutations de gènes codant des canaux ioniques ou impliqués dans une fonction synaptique. Le lien entre les mutations dans des gènes de la voie mTOR et l'épilepsie focale lésionnelle laisse penser que les mutations de ce type

peuvent être des facteurs prédictifs positifs susceptibles d'améliorer la sélection des cas pour la chirurgie, en particulier chez les patients dont l'IRM est négative. Cependant, il est certain que de plus amples études sont nécessaires pour collecter des données d'imagerie plus détaillées et pour interpréter le lien entre les résultats des traitements chirurgicaux, les données observationnelles, les connaissances sur l'étiologie de la maladie et la génétique.

Mots clés : chirurgie épileptique, génétique, diagnostic génétique, pronostic

Introduction

It stands without a doubt that genetic discoveries have progressed our understanding and management of the epilepsies. Dozens of novel epilepsy genes have been discovered in the past decades, largely as a result of inexpensive and readily available next generation sequencing. These discoveries have set several new paradigms. First, de novo mutations in various epilepsy genes are now seen as the major cause of sporadic epileptic encephalopathy. Second, the importance of genetic causes in focal epilepsy was established by the observation that inherited or de novo mutation in multiple genes, in particular genes involved in the mTOR pathway, can cause focal epilepsy.

Finally, it remains remarkable that for many, if not all epilepsy genes, a wide spectrum of clinical phenotypes, varying in type of epilepsy and severity of disease, are associated with mutations in the same gene. On the one hand, these genetic discoveries have enabled precision medicine, in which the DNA diagnosis limits the diagnostic odyssey and guides disease treatment and management. On the other hand, the variable clinical expression raises many questions on how to predict the clinical course of disease, and causes doubt whether genetics alone should determine clinical care.

From this perspective, we discuss the case of epilepsy surgery, for which the impact and importance of genetic diagnostics have not been explored substantially yet. Several studies have now reported on people with epilepsy that carry a presumed causal mutation in a known epilepsy gene and who are potentially eligible for, or have undergone, surgery. These reports suggest that genetics should play a role in the diagnostic strategy and therapeutic approach in people with epilepsy that are considered candidates for epilepsy surgery.

Monogenic causes of epilepsy

Next generation sequencing technology (NGS), in particular whole exome sequencing (WES), through which the coding sequence of all genes in the human genome can be scanned for putative disease-causing sequence variation, accelerated discovery of novel epilepsy genes in the past decade [1]. Major discoveries have been made in epileptic encephalopathy (EE) where many de novo mutations have recently been identified as causative. These include de novo mutations in *KCNQ2*, a gene that was already known for several decades, in which inherited mutations cause benign familial neonatal convulsions (BFNC) [2]. De novo missense mutations detected in severe childhood EE cluster in four hotspots of the gene that are important for essential channel properties, namely: the S4 voltage-sensor, the pore, the proximal C-terminal domain that binds phosphatidylinositol 4,5-bisphosphate (PIP2) and calmodulin (CaM A), and the more distal calmodulin binding (CaM B) domains [3, 4]. It is therefore assumed that these missense mutations cause EE through a dominant-negative effect on channel function, in contrast to the more variable effects of the mutations underlying BFNC that also include complete loss of function mutations, such as deletions. These observations illustrate the phenomena of variable clinical expression that is observed for many epilepsy genes. Like in *KCNQ2*, the type or location of the mutation can often explain the variable expression. However, this is not the case for all epilepsy genes, and for all mutations. The compelling example is *SCN1A*, a major epilepsy gene that is associated with a wide spectrum of different disease severities, and is currently associated with both common and rare, benign and severe disease. Mutations in SCN1A were reported as a major cause for severe myoclonic epilepsy of infancy (SMEI), also known as Dravet syndrome [5]. It is known as the most common genetic cause of severe epilepsy in infancy. In contrast, segregating mutations have been detected in families affected by generalized epilepsy and febrile seizure "plus" syndrome (GEFS+), a relative benign form of epilepsy with a favourable prognosis [6]. For a significant part, the difference in phenotype can be explained by the type of mutation, where complete loss of function mutations – such as non-sense mutations that result in a truncated protein that is vulnerable to nonsense mediated decay – are underlying the severe Dravet syndrome. On the other hand, GEFS+ is associated with missense SCN1A mutations specifically, that have a milder loss of function effect on the protein [7]. This clear association between variants and the two phenotypes demonstrates that rare coding variants of the gene with high to absolute risk for disease, are the main cause for these types of epilepsy. Finally, focal seizures may also be part of the semiology in Dravet syndrome, and as is discussed below, a few reports describe Dravet syndrome patients that also had a malformation of cortical development (MCD) [8, 9]. Furthermore, some families have been described in which a segregating *SCN1A* mutation was detected in family members that shared the same inherited mutation but showed clinical heterogeneous expression of disease, ranging from febrile seizures (FS), GEFS+, to Dravet syndrome and focal seizures [10, 11].

On the other side of the genetic spectrum of aetiologies of epilepsy are common variants that confer very low risk for disease that are typically detected through genome-wide association studies (GWAS). Such studies have now been performed using reasonably sized samples that detected variants in or around *SCN1A* that are associated with FS alone, focal epilepsy (in particular mesial temporal lobe epilepsy with hippocampal sclerosis and febrile seizures (mTLE-HS-FS)), and – remarkably – with all types of common epilepsy, including focal and genetic generalized epilepsy [12 - 16]. Recent large scale WES studies of common familial generalized and focal non-acquired epilepsy, showed a remarkable enrichment of ultra-rare coding variation in known epilepsy genes including *SCN1A*. This suggests that rare coding variants with a low risk of disease also increase susceptibility to epilepsy [17]. Finally, a few reports and unpublished observations described patients with focal epilepsy who were considered for epilepsy surgery and were found to be carriers of a likely pathogenic *SCN1A* mutation [8, 9]. Taken together, the genetic evidence for *SCN1A* shows a remarkable spectrum of disease associated *SCN1A* variants and their risk for disease, ranging from common low risk factors and rare inherited or de novo mutations with absolute risk for disease, to very rare relatively low risk factors. The clinical spectrum is equally broad, ranging from common benign to severe and very rare syndromes. This broad geno- and phenotypic spectrum associated with *SCN1A* must be taken into account when clinical decisions are made, especially in the case of surgical evaluation.

Even though the first gene for focal epilepsy, CHRNA4 causing autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE), was found in 1995, it has only recently been demonstrated that genetic mutations are not only associated with generalized or multifocal epilepsies, but also underlie a broad range of focal epilepsies. The most notable novel gene discoveries have been made in the mTOR-family of genes, with a clinical spectrum of focal epilepsy that ranges from MCD to familial non-lesional focal epilepsy [18 - 22]. Causal mutations underlying these epilepsies have been found to be inherited, occurred de novo in sporadic cases, and have been detected as somatic mutations in resected brain tissue, which calls for comprehensive genetic testing and careful clinical genetic counselling. Mutations in DEPDC5, a gene that functions in the GATOR1 complex that inhibits the mTORC1 pathway, are now considered to be among the most common genetic causes of focal epilepsies, including familial focal epilepsy with variable foci (FFEVF), and have been reported in 13% of autosomal dominant sleep-related hypermotor epilepsy (ADSHE or ADNFLE) families [23]. A full overview of these genes and their implication in focal epilepsy is presented in the accompanying article in this issue. The importance of DEPDC5 and related genes in (familial) non-lesional focal epilepsy (FE) and in lesional epilepsies with MCD, in particular focal cortical dysplasia (FCD), may imply that searching for causal germline and somatic gene mutations underlying sporadic FE has consequences for surgical decision making. How the detection of such gene mutations should influence the decision to accept or reject a patient for surgery remains to be established.

Goals of epilepsy surgery

Epilepsy surgery is currently the only available curative treatment for pharmacoresistant focal epilepsy. However, it is clear that surgery is an invasive and irreversible procedure, and several restrictions apply, making it a safe procedure that is only performed on individuals that have a high probability of becoming seizure-free following surgery without unacceptable deficits that are the direct result of surgery. To accomplish this, a careful set of diagnostic procedures precedes any successful epilepsy surgery, aimed to accurately localize and delineate the epileptogenic zone and possible overlap with eloquent regions.

Presurgical evaluation procedures are complex, and have been outlined and standardized. Until recently, genetic screening was not part of the standard epilepsy surgery evaluation, although it has been mentioned as an important factor to consider in a perspective by Guerrini et al., that included genetic screening in the algorithm for diagnostic strategies and therapeutic approaches in patients with FCD [24].

Although the general aim of epilepsy surgery is to completely remove the epileptogenic focus, surgery is sometimes considered in patients for palliative treatment, aiming to reduce seizure load or cure the patient from just one, most burdensome, seizure type when there is a multifocal epilepsy syndrome. Whereas in the past only patients with clear structural MRI-visible lesions were considered surgical candidates, an increasing number of people with refractory epilepsy and normal imaging undergo evaluation, under the assumption that their focal epilepsy is caused by a MR-invisible, structural lesion, in particular FCD. The number of MRI-negative patients will decrease with improved imaging techniques, such as higher-field MRI or MRI post-processing [25, 26]. Currently 60 - 70% of these MRI-negative (but presumed lesional) patients are rejected for surgery, often after extensive and invasive intracranial electrode monitoring. Operated MRI-negative patients have a lower chance of reaching seizure freedom [27]. Furthermore, the absence of a histopathological abnormality occurs in ~8% of all operated patients and is a major predictor of poor outcome [28].

MRI-negative patients with refractory focal seizures can either have an 'invisible' structural lesion – such as a developmental abnormality – or an underlying genetic syndrome, not associated with a lesional source, or a combination of the two (e.g. tuberous sclerosis). We can assume that the lesional MRI-negative patients

have a higher chance of reaching seizure-freedom after epilepsy surgery than the non-lesional MRI-negative patients with a presumed genetic underlying cause. Therefore, we hypothesize that the crucial differentiation between people with operable and non-operable epilepsy (i.e. between a presumed lesional and non-lesional cause of seizures) requires new and reliable biomarkers.

Mutations in novel epilepsy genes are such biomarkers that are currently not routinely implemented in presurgical evaluation. Below we will summarize the current experience with genetic evaluation in patients who were considered surgical candidates, and discuss how preoperative genetic screening may differentiate between eligible and non-eligible surgical candidates. The discussion may be centralized around three crucial questions regarding the utility of genetic testing for presurgical evaluation.

The first question is to what extent can a genetic mutation be a negative predictor for postoperative seizure outcome and may be used to reject patients for surgery even in the presence of an operable lesion. With this question, the distinction must be made between palliative surgery and surgery with the aim to completely cure the patient from all seizures. The second question is whether mutations in genes can predict seizure freedom in people that have MRI-negative, but presumed lesional FE.

The final question is whether genetic mutations that predict lesional and operable epilepsy (for example the genes associated with FCD) have any additional and useful predictive value next to the current evaluation procedures.

The precise localization of the seizure-onset zone and eloquent cortical regions is challenging in FCD, as predictions of their anatomic locations may not conform to traditional models utilized for other pathologic substrates. These limitations must be appreciated fully to achieve higher rates of postoperative seizure freedom. Completeness of resection is an important determinant of outcome. Colocalization of the seizure onset zone with eloquentcortex is a major contributor to incom plete resection and surgical failure. The precise localization of the seizure-onset zone and eloquent cortical regions is challenging in FCD, as predictions of their anatomic locations may not conform to traditional models utilized for other pathologic substrates.

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The published experience with epilepsy surgery in patients with genetic causes of epilepsy

There are relatively few reports on surgery cases that also carry a pathogenic mutation in an epilepsy gene. We recently reviewed the literature (until January 2017) on surgical outcome in different genetic causes of refractory epilepsy [29]. Only 24 eligible articles were found that described a total of 82 patients who underwent surgery for refractory epilepsy due to 15 different underlying genetic causes. The most frequent genetic abnormalities were mutations in *SCN1A* (8 cases), *DEPDC5* (9 cases), *NF1* (21 cases), and microdeletions (12 cases). We subdivided all cases in three broad categories including: “gene mutations involved with channelopathies and disorders of synaptic transmission”, “mTOR pathway gene mutations”, and “other genetic causes of epilepsy”. The most striking finding was the difference between the low rate of seizure-freedom in the germline mutations in genes associated with channelopathies and synaptic transmission disorders (2 out of 14 cases, 14%), versus the high rate of seizure freedom in the germline mTOR pathway gene mutations (6 out of 11, 55%) and the group of other genetic causes (24 out of 38, 63%, see **Table 1**).

These observations suggest that channelopathy and synaptic disorder genes are strong negative predictors for surgical candidacy, however, more observations for each gene, and type of mutation is clearly needed to come to definite conclusions.

The observations for the individual genes illustrate this point. For *SCN1A*, 8 cases have been described in two main papers. Barba et al. reported 4 patients who were found to have a MCD out of a series of 120 patients with *SCN1A* mutations, and two additional cases with MCD and SCN1A mutations that they included through U-task (the European taskforce for epilepsy surgery in children, [8]). All patients showed a phenotype consistent with Dravet syndrome, yet brain MRI showed periventricular nodular heterotopia (PNH) in 2, and FCD in 3 cases. Two of these FCD cases were oper-

Table 1: Success rates of epilepsy surgery for patients with different genetic causes – germline mutations – of epilepsy

Genetic Cause	MRI lesional Engel I	MRI non-lesional Engel I	all Engel I
Chanelopathies and disorders of synaptic transmission	1/9 (11%)	1/5 (20%)	2/14 (14%)
mTOR pathway mutation	4/7 (57%)	2/4 (50%)	6/11 (55%)
chromosomal other	23/35 (66%)	1/3 (33%)	24/38 (63%)
TOTAL	28/51 (55%)	4/12 (33%)	32/63 (51%)

ated after the partial seizure onset region was identified. This region was resected, but the authors report that same seizure types recurred after surgery without any reduction in seizure frequency. This report demonstrates that MCD and *SCN1A* mutations can co-occur, seemingly at a higher frequency than would be expected on the basis of the Dravet syndrome incidence of 1 in 20,000 - 40,000 births. It remains unclear whether the particular mutation had any effect on the occurrence of the MCD.

A second report described the clinical and histopathological outcome of 6 patients carrying a *SCN1A* mutation [9]. The phenotype was considered to be consistent with Dravet syndrome in 5 of these 6 patients, and one showed GEFS+. All developed focal seizures next to the generalized seizures. The patients underwent epilepsy surgery for their intractable focal seizures, and although some initial improvement was reported after surgery, recurrence of focal seizures occurred in 5 cases with an outcome classified as ILAE class 5, and one patient showed ILAE class 4.

Taken together, none of the reported 8 patients with *SCN1A* mutations seemed to benefit from epilepsy surgery with seizure reduction or reported improvement of quality of life, suggesting that surgery is unlikely to be beneficial in these children. However, larger series are needed to fully evaluate the predictive effect. It cannot be ruled out that palliative surgery can benefit some selected cases, by healing them from specific and targeted focal seizures, originating from an associated lesion, such as FCD or hippocampal sclerosis.

One report describes a family with segregating mutations in *SCN1B*, which encodes the beta-1-subunit that together with the alpha-subunit encoded by *SCN1A*, forms the voltage gated sodium channel [30]. It is described that the beta-1-subunit modulates the gating, inactivation kinetics, and localization of the ion-channel pore. Mutations in *SCN1B* are mainly detected in GEFS+ families, such as described in this paper. The family members showed variable phenotypes including febrile seizures alone, FS-plus, and 5 individuals presented TLE. Two of these patients underwent temporal lobectomy, that was successful in both. It can be hypothesized that these *SCN1B* mutations are causal for the febrile seizures that in turn may indirectly lead to the development of hippocampal sclerosis and TLE. Therefore, the effect of gene mutations on epilepsy surgery outcome must be evaluated for each gene separately and in the context of the presence of a clearly detectable focal brain lesion, that may be held responsible for at least part of the seizures.

In contrast to *SCN1A*, patients carrying mutations in genes associated with mTOR pathways appear to have better probability to become seizure free, which is in line with their association with focal epilepsy and FCD in particular. A detailed review of patients with *DEPDC5* mutation showed that for all these patients, the surgical approach was guided by a visible MRI lesion and/or by a circumscribed epileptogenic zone during invasive recordings (stereo-EEG). However, extensive presurgical imaging was performed and some patients were subjected to multiple interventions and had a wide resection including eloquent cortex, with post-surgical deficits. The main question to evaluate in such patients is whether subtle dysplastic lesions went undetected on imaging. Furthermore, in the patients with poor surgical outcome, a more complex epileptogenic network could not be excluded. A recent paper described a detailed analysis of a single patient with a *DEPDC5* mutation and sleep-related hypermotor epilepsy (SHE) who underwent a SEEG, but was rejected for surgery due to the lack of a clearly localised epileptogenic zone [31]. The authors also concluded that more tailored imaging procedures aimed at identifying a wider epileptogenic network may be essential to discriminate between *DEPDC5* patients who will benefit for surgery, irrespective of the presence of a MR visible circumvent lesion such as a FCD.

Our literature review identified 21 surgical cases with a mutation in NF1, the gene linked to neurofibromatosis type 1. The disease is associated with neurofibromatosis that may lead to epileptogenic lesions such as hippocampal sclerosis or low-grade tumours. Nevertheless, not all patients with epilepsy presented a single delineated epileptogenic zone, which is reflected by the reported seizure freedom rate of 57% (12/21). Only one MRI-negative case with NF1 was reported, who turned out to become seizure free after surgery.

A recent publication added *PCDH19* to the list of monogenic disorders that can be associated with focal seizures caused by a structural lesion [32]. The paper reports on five children with refractory epilepsy that was associated to *PCDH19* variants that underwent presurgical evaluation. *PCDH19* variants were confirmed to be de novo in three-, and FCD was reported in four out of the five children that were all girls. Interestingly, two patients underwent epilepsy surgery that resulted in a clear improvement of seizure control. On the other hand, one patient showed improvement at age 11 years without surgery, illustrating the previous observations that show seizure reduction over time and seizure freedom in some patients. Mutations in *PCDH19* are associated with early infantile epilepsy encephalopathy type 9 [33, 34]. In some cases, the phenotype resembles that of Dravet syndrome. Similarly, it is associated with a wide range of disease severity. *PCDH19* is located on the X-chromosome and heterozygous females are mostly affected, whereas males tend to show no symptoms unless they are mosaic for the mutation. This X-linked clinical expression pattern has been contributed to a phenomenon called "cellular interference" [35]. Seizure types observed in affected females include generalized tonic, clonic or tonic-clonic, and/or focal seizures, and most females have mental retardation, developmental problems, and psychiatric comorbidities [36, 37]. These observations, and the report of the *PCDH19* patients that underwent surgery, further underline the need to carefully investigate the benefit of epilepsy surgery for each epilepsy gene separately.

A growing body of evidence show that somatic mutations of several genes involved in the PI3K-AKT-mTOR pathway can also underlie MCD [38]. For example, low-level mosaic mutations of *mTOR* have been reported in the brain tissue of patients presenting with FCD type 2a [39]. Furthermore, another study showed mosaic *AKT3* mutations in brain tissue of patients presenting with focal brain malformations such as hemimegalencephaly and polymicrogyria, whereas germline or constitutional mutations presented in patients with diffuse bilateral cortical malformations, megalencephaly and heterotopia [40]. An important study of 118 children with bilateral perisylvian polymicrogyria (BPP) also showed a mixture of germline and mosaic mutations with some variability in phenotype [41]. The estimated degree of mosaicism varied widely between 5 - 73% of cells analysed. Furthermore, important for our question on the utility of genetic screening before epilepsy surgery, the authors showed that mosaic mutations can be easily missed when testing blood-derived DNA, but can be detected in saliva-derived DNA.

These observations have implications for genetic testing, suggesting that patients presenting with these MCD types must be tested using a deep sequencing technology that is able to detect low percentage of mosaic mutations, preferably using DNA derived from saliva. The importance for epilepsy surgery evaluation and prediction of post-surgery outcome needs further study, especially as somatic mutations are also reported in FCD.

Perspective for genetic testing in epilepsy surgery evaluation

Evidently, there is an urgent need for larger series of patients carrying mutations in the same epilepsy genes who are evaluated for, or have undergone epilepsy surgery. This data, ideally collected prospectively would allow clear quantification of the impact of a genetic diagnosis on presurgical selection and on its predictive capacity regarding outcome. As outlined above, several questions should be evaluated. First, the available data already suggest that genetic mutations are suitable biomarkers for selection or rejection of putative surgical candidates. This is illustrated by the data for the patients carrying pathogenic *SCN1A* mutations, who most likely do not benefit from surgery.

The second question is whether genetic testing can improve presurgical evaluation in MRI-negative patients. The data for the mTOR pathway genes seem to suggest that this would be possible, but clearly need more in-depth analysis of the clinical and imaging data.

Third, the broad phenotypes associated with *DEPDC5* mutations point to the question whether the presence of such mutations should indicate tailored, more detailed imaging prior to invasive recordings to evaluate the presence of a difficult to detect FCD, or, possibly, more widespread epileptogenic networks, even in the presence of a visible FCD. Such strategies should be evaluated for improved rate of post-surgery seizure freedom also in the mTOR pathway MRI-positive group, in which surgical outcome was only marginally better than in the mTOR pathway MRI-negative group.

Furthermore, the presence of mutations in genes encoding ion-channels or genes associated with synaptic function that are implicated in autosomal dominant forms of focal epilepsy – such as ADNFLE, or ADLTLE (autosomal dominant lateral temporal lobe epilepsy) – in MRI-negative patients, may exclude them from further evaluation. This would argue for early genetic testing prior to any invasive procedure. Finally, it is clear that recommendations should be based on both observational data and knowledge on disease aetiology. For example, in the case of *SCN1B* the occurrence of TLE – which may be operable – is probably not directly related to the mutation, but is likely secondary to the early occurrence of febrile seizures. Surgery in this case is directed to cure seizures originating from the abnormal tissue in the temporal lobe, and not to the febrile seizures.

The existence of international multi-centre collaborations, such as U-task, provides the ability to collect sufficient number of cases needed for meaningful analysis. The increase in genetic diagnostic screening of focal epilepsies, preferably with WES, will not only provide the opportunity for novel gene discovery, but will also clarify the promise of precision medicine for these patients.

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