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Genetics of nonlesional focal epilepsy in adults and surgical implications

R. Karge[1] · C. Knopp[2] · Y. Weber[1,3] · S. Wolking[1]

[1] Department of Epileptology and Neurology, RWTH University Hospital Aachen, Aachen, Germany

[2] Institute of Human Genetics and Genomic Medicine, RWTH University Hospital Aachen, Aachen, Germany

[3] Department of Neurology and Epileptology, Hertie Institute for Clinical Brain Research, University of Tübingen, Tübingen, Germany

Abstract

Nonlesional focal epilepsies (nlFE) represent a heterogenous group of syndromes. They encompass self-limited focal epilepsies of childhood and youth, rare focal, familial epilepsies, epilepsies associated with brain somatic variants, and to a large extent nonfamilial epilepsies that have a complex genetic or unknown background. Genetic testing should be performed in cases of a family history suggestive of monogenic inheritance and in cases that show additional symptoms, such as intellectual impairment, autism, or dysmorphic features. Whole-exome or whole-genome sequencing is the method of choice. Growing evidence suggests including genetic testing also in the presurgical workup of individuals with drug-resistant epilepsy. While individuals that harbor variants in genes of the mammalian target of rapamycin (mTOR) pathway tend to achieve better seizure control following epilepsy surgery, the postsurgical outcome of genetic epilepsies associated with channel function or synaptic transmission appears to be poor. The aim of this article is to review the genetic background of focal epilepsies that occur or persist in adults, provide guidance for genetic testing, and discuss potential implications for presurgical evaluation.

Keywords
Genetic epilepsies · Brain somatic variants · Monogenic disorders · Complex genetic disorders · Genetic testing · Epilepsy surgery

Introduction

Nonlesional focal epilepsies (nlFE) are characterized by focal seizures, focal interictal epileptic discharges (IEDs), and the absence of epileptogenic lesions on magnetic resonance imaging (MRI). Sometimes nlFE are also described as nonacquired focal epilepsies (NAFE) as opposed to acquired, structural epilepsies, e.g., after cerebral ischemia, hemorrhage, or trauma. Nonlesional focal epilepsies account for 20–40% of all epilepsies [22] and they encompass a wide range of epilepsy syndromes, ranging from self-limited epilepsies in neonates and infants associated with distinct epilepsy genes (e.g., self-limited neonatal epilepsy, SeLNE), self-limited focal epilepsies with presumed complex inheritance in older children (e.g., self-limited epilepsy with centrotemporal spikes, SeLECTS or formerly Rolandic epilepsy), to defined genetic syndromes that begin at a variable age (e.g., epilepsy with auditory features, EAF); see **Fig. 1**. Yet, the majority of nlFE are isolated and account for a large share of patients seen in daily practice. More than 50% of focal epilepsies do not show structural abnormalities on routine magnetic resonance imaging (MRI; [8]). They can be at best classified by their seizure onset zone while their etiology often remains opaque. In this review, we focus on nlFE that occur or persist in adulthood. For self-limited focal epilep-

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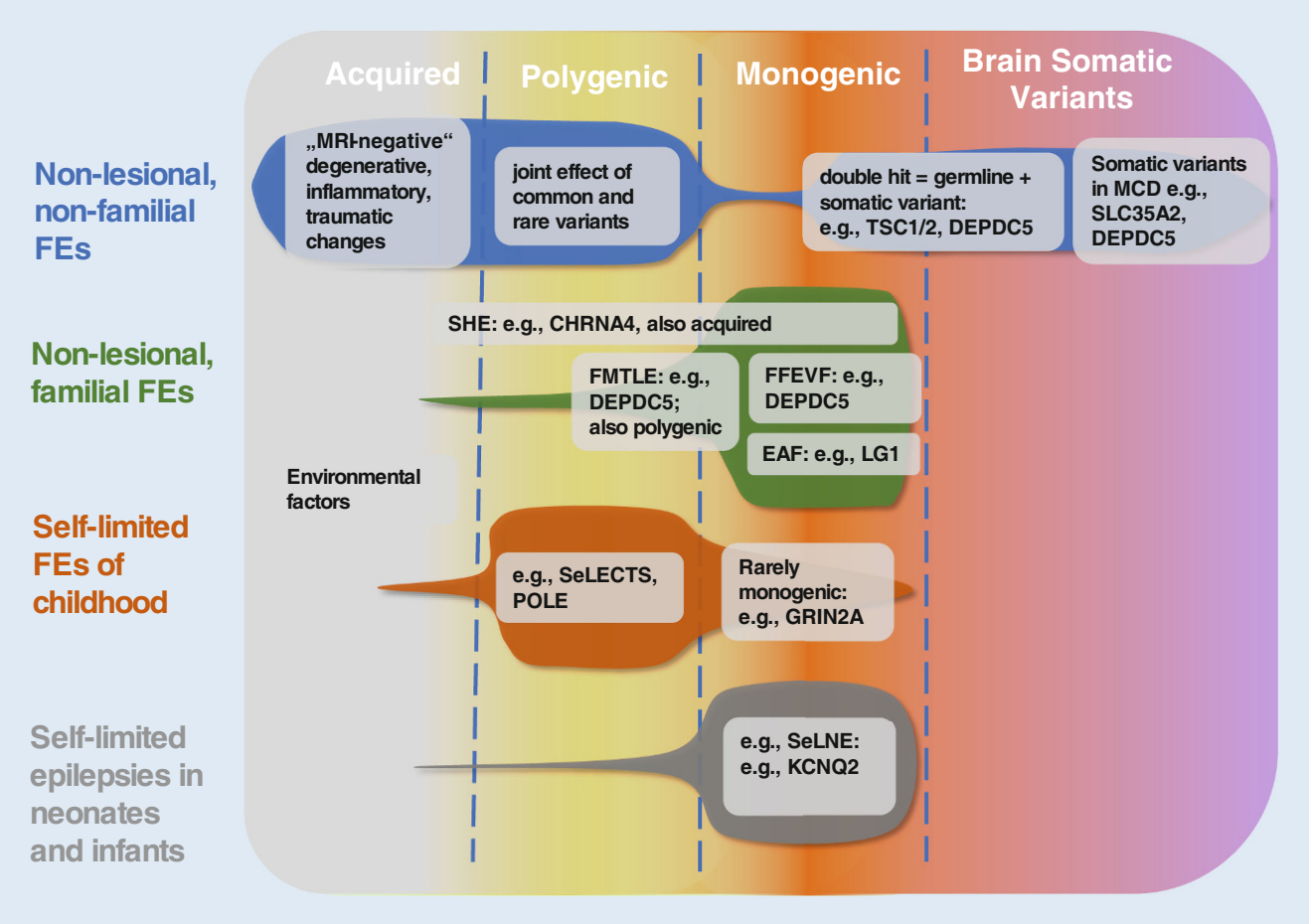

Fig. 1 ▲ Depiction of syndromic and genetic spectrum of nonlesional focal epilepsies. *EAF* epilepsy with auditory features, *FEs* focal epilepsies, *MCD* malformation of cortical development, *FFEVF* familial focal epilepsy with variable foci, *FMTLE* familial mesial temporal lobe epilepsy, *POLE* photosensitive occipital lobe epilepsy, *SeLECTS* self-limited epilepsy with centrotemporal spikes, *SeLNE* self-limited neonatal epilepsy, *SHE* sleep-related hypermotor epilepsy

sies of infancy and childhood, overview articles can be found elsewhere [36, 49].

With the advent of next-generation sequencing and advances in bioinformatics and statistical genetics, the genetic basis of nlFE was progressively unearthed. Monogenic forms that can be explained by a single, causative gene and feature classic Mendelian pedigrees are the exception. Brain somatic gene variants, i.e., variants present only in local brain tissue, have been found in MRI-negative cases in resective specimens from epilepsy surgery and are associated with microscopic changes of cortical development. The larger share of nlFE, however, seems to rely on the interplay of multiple genetic variants in analogy to idiopathic generalized epilepsies (IGE) and other complex genetic diseases (e.g., schizophrenia or type 2 diabetes; [7, 10]). Yet unlike IGE, which display a more homogeneous phenotype and are firmly established as a polygenic disorder, etiologies in nlFE are presumably more heterogeneous and stretch beyond genetics. Unrecognized autoimmune inflammation, microscopic structural anomalies, and neurodegenerative changes in older individuals offer potential explanations. A positive family history or the presence of certain comorbidities should prompt genetic testing. The indication and consequences of genetic testing in the setting of presurgical evaluation are currently debated but viewed overall favorably.

Nonlesional focal familial epilepsies

Interestingly, while the advancements in DNA sequencing technologies heralded an era of gene discoveries for developmental and epileptic encephalopathies (DEEs), the first epilepsy gene to be identified was *CHRNA4*. It was detected in a large family with sleep-related frontal lobe seizures [37]. Nonetheless, familial focal epilepsy syndromes are rare. They usually show autosomal-dominant inheritance. But family history may be sparse or not available, and reduced penetrance can further complicate the recognition of a positive family history. Furthermore, seizures in other family members might have been overlooked (e.g., in the case of exclusively nocturnal seizures) or misinterpreted (e.g., in the case of focal aware seizures such as déjà vu auras). Therefore, seizure semiologies associated with familial epilepsies, such as nocturnal hypermotor seizures or focal aware seizures with auditory features, should give rise to a thorough review of the family history [30]. In most cases, af-

Table 1 Genetic focal epilepsy syndromes (adapted from [23, 30])

Epilepsy syndrome	Age of onset	Seizure semiology	Related genes
Sleep-related hypermotor epilepsy (SHE; formerly ADNFLE)	First or second decade	Brief hypermotor or asymmetric tonic/dystonic seizures	*CHRNA4, CHRNA2, CHRNB2, DEPDC5, KCNT1, NPRL2, NPRL3, PRIMA1*
Familial mesial temporal lobe epilepsy (FMTLE)	Adolescence or adulthood	Focal aware seizures with intense déjà vu and other perceptive symptoms	*DEPDC5*
Familial focal epilepsy with variable foci (FFEVF)	First or second decade	Focal seizures depending on cortical area involved	*TSC1, TSC2, DEPDC5, NPRL2, NPRL3*
Epilepsy with auditory features (EAF)	Adolescence or adulthood	Focal aware seizures with auditory features or receptive aphasia	*LGI1, RELN, MICAL1*

fected individuals have normal intellect, normal neurological examination results, and seizures can usually be controlled well [23].

The most current classification differentiates four genetic focal epilepsy syndromes; each can be related to genetic variation in several genes ([30]; see also **Table 1**).

Sleep-related hypermotor epilepsy

Sleep-related hypermotor epilepsy (SHE), previously also known as "autosomal dominant nocturnal frontal lobe epilepsy" (ADNFLE), usually occurs during adolescence and is characterized by brief nocturnal focal seizures with hyperkinetic, tonic, and dystonic motor features [40], which often appear in clusters after falling asleep or before awakening [33]. Remarkably, some individuals retain consciousness during seizures. Misdiagnoses as parasomnia or dissociative seizures are frequent. The severity among affected family members can show considerable differences and penetrance of the autosomal-dominant disorder is ~70% [33], which can be a challenge in smaller families.

Familial mesial temporal lobe epilepsy

Familial mesial temporal lobe epilepsy (FMTLE) usually occurs during youth or early adulthood, notably in individuals without prior febrile seizures. Patients experience nearly exclusively focal aware seizures with pronounced déjà vu, and less commonly other emblematic temporal lobe semiologic features, such as epigastric sensations and anxiety. Focal impaired awareness seizures and bilateral tonic–clonic seizures are rare [24]. Since affected individuals often deem their seizures to be not pathologic, the syndrome is probably underrecognized A systematic study of patients with nonlesional temporal lobe epilepsy identified FMTLE in ~20% [24]. Family history might require interviewing family members in person.

Epilepsy with auditory features

Epilepsy with auditory features (EAF) usually has its onset in adolescence or young adulthood [18]. Focal aware seizures with a prominent auditory component or receptive aphasia are the predominant seizure type. Auditory symptoms comprise rather elementary sensations such as humming or buzzing, whereas more complex auditory hallucinations are uncommon [23]. Focal impaired awareness seizures and bilateral tonic–clonic seizures can occur. The inheritance pattern in EAF is autosomal-dominant.

Familial focal epilepsy with variable foci

Familial focal epilepsy with variable foci (FFEVF) is an autosomal-dominant disorder that features a remarkable intrafamilial variability of seizure semiology. Seizures in different family members often arise from different lobes, while being constant within the same individuals [25].

Genetics of nonlesional focal familial epilepsies

Familial nlFE usually exhibit autosomal-dominant inheritance, although penetrance may vary. Variants in nicotinic acetylcholine receptor subunits have been found in SHE, and variants in *LGI1* in EAF have been identified thanks to thorough genetic work-up of extended families [3, 37]. Next-generation sequencing technology put the focus on the gene *DEPDC5*. Together with *NPRL2* and *NPRL3* it forms the GATOR1 complex that acts as an inhibitor of the *mTOR* pathway [1]. The latter mediates essential cellular functions such as cell growth, migration, proliferation, and protein synthesis [16]. Crossing syndromic boundaries, *DEPDC5* variants have been found in various forms of familial nlFE such as FFEVF [6], SHE [26], and FMTLE [39]. Variants in *DEPDC5* as well as *NPRL2* and *NPRL3* have also been described in familial focal epilepsies, in which some of the affected individuals displayed focal cortical dysplasia (FCD) whereas others had nlFE [44].

Focal epilepsies related to brain somatic variants

Malformations of cortical development (MCD) that range from regional disturbances of cortical architecture such as FCD to complex, pan-cerebral lesions such as hemimegalencephaly have been shown to be founded on genetic factors [12]. For FCD, however, germline variants appear to play a minor role [2, 34]. Somatic variants in various genes of the *mTOR* pathway (*DEPDC5, MTOR, NPRL2/3*) were identified in postsurgical resection tissue in structural lesions [2, 19, 44]. Also, more extended lesions harbor somatic variants in *mTOR* pathway genes, such as *MTOR* itself, *AKT*, and *PIK3CA* [13]. Of late, with *SLC35A2*, a "non-*MTOR*" gene was shown to be related to malformations of cortical development with oligodendroglial hyperplasia in epilepsy (MOGHE), a milder form of MCD [4]. Moreover, for various *mTOR* pathway genes, such as *TSC1*/*TSC2* (causing tuberous sclerosis) and *DEPDC5*, a double-hit hypothesis has

Table 2 Indications for genetic testing in nonlesional focal epilepsy (from *Empfehlungen der Kommission Epilepsie und Genetik*, DGfE; http://www.dgfe.org/home/index,id,528.html)

Indication	Recommended genetic test
Familial nlFE Especially if characteristic of specific familial syndromes (e.g., EAF, SHE)	WES/WGS
Drug-resistant nlFE During presurgical workup	WES/WGS
nlFE with additional symptoms Intellectual impairment Autism spectrum disorder Dysmorphic features	WES/WGS

EAF epilepsy with auditory features, ***nlFE*** nonlesional focal epilepsies, ***SHE*** sleep-related hypermotor epilepsy, ***WES*** whole-exome sequencing, ***WGS*** whole-genome sequencing

been postulated. Here, the combined effect of a germline variant in conjunction with brain somatic variants is thought to give rise to circumscribed MCD [28, 29]. Unlike germline variants, brain somatic variants arise during cortical development resulting in somatic mosaicism. Depending on the time of occurrence, variants can be limited to small fractions of brain cells. By definition, somatic variants are not detectable in leukocyte-derived DNA samples.

The observation that often FCD are not recognizable in presurgical MRI [27] gives rise to the question of whether a share of nlFE can also be explained by somatic variants in "hidden" FCD. In a series of nlFE patients who underwent epilepsy surgery, somatic variants in *SLC35A2* were found in 17% of cases [45]. Interestingly, in two of the three reported patients, the pathologic work-up revealed FCD1a. Ongoing research will probably uncover further genes associated with brain somatic variants and nlFE [9]. Developments in structural MRI and postprocessing techniques will help identify more locally confined lesions in the future [41] and thereby render a share of today's MRI-negative epilepsies "MRI-positive."

Nonlesional nonfamilial focal epilepsies

In analogy to IGE, nlFE have been the focus of international, large-scale sequencing and genotyping consortia. Like IGE, nlFE have been shown to rely on complex genetic architecture, albeit to a lesser degree. The role of common genetic variants, i.e., variants that occur with a minor allele frequency of > 1% in the population, was established through genome-wide association studies (GWAS; [10]). These GWAS assess the association of single-nucleotide polymorphisms (SNPs) with complex traits. Since the effect size of each SNP by itself is very low, large cohorts are needed to capture significant associations. The latest and to date largest GWAS for epilepsies, including more than 29,000 individuals with epilepsy [11], showed an SNP-based heritability for nlFE of approximately 16%. In comparison to IGE, which features an SNP-based heritability for nlFE of approximately 40%, this effect appears to be rather moderate. Moreover, while the study identified 19 genome-wide significant loci for IGE, none was identified for nlFE. These data suggest a minor role of common variants for nlFE but could also mirror the higher heterogeneity of the nlFE cohort, potentially including mislabeled cases of acquired focal epilepsy, cases with brain somatic mutations, or unrecognized cases of autoimmune epilepsy that could have diluted the effect. Polygenic risk score (PRS) analyses, which estimate the aggregated effect of all SNPs weighted by their effect size on an individual level, underlined that common variants convey an increased risk for nlFE that is, however, smaller than in IGE [17, 21]. Large-scale analyses of exome sequencing data demonstrated that also ultra-rare missense variants (URVs) and truncating variants were enriched in nlFE [7], albeit less than in IGE. Truncating variants in genes, associated with familial nlFE, such as *DEPDC5*, appear to be enriched in nonfamilial nlFE [46]. Interestingly, enrichment patterns of URVs seem to differ between nlFE and IGE: While IGE exhibited a higher burden of URVs in gene sets derived from inhibitory neurons, nlFE carried a higher burden of URVs derived from excitatory neurons [14].

Genetic testing in nonlesional focal epilepsies

Genetic testing has become an established component of the diagnostic work-up of individuals with epilepsy. Decreasing costs for genetic testing and broader financial coverage by insurance companies made testing more widely available. The ascertainment of a genetic diagnosis enables genetic counseling, may give diagnostic and therapeutic guidance, and can help avoid further, potentially detrimental diagnostic tests [43]. Genetic testing should be considered for individuals with a high pretest probability. In the case of nlFE, testing should be performed of individuals with a positive family history of epilepsy, especially if the symptoms point to a specific, familial nlFE syndrome, such as SHE or EAF. Since families are often small, family members may not be contactable, and penetrance is usually incomplete, specific attention should be directed to seizure semiologies that are suggestive of familial nlFE syndromes, such as nocturnal hypermotor seizures or auditory, focal aware seizures. In nonfamilial nlFE, genetic testing should be considered in individuals who present with additional symptoms such as intellectual impairment, autism spectrum disorders, or dysmorphic features [15]. In patients with epilepsy and intellectual impairment (IQ < 70), the diagnostic yield of genetic testing can be up to 50% [47]. In this cohort, besides missense variants, also copy number variants, i.e., deletions or duplications of large DNA segments, account for about one third of positive cases.

If genetic testing is performed, either whole-exome sequencing (WES) or whole-genome sequencing (WGS) should be favored. Epilepsy gene panels that contain a curated list of known epilepsy-associated genes are obsolete since WES and WGS deliver a higher diagnostic yield (up to 45/48% for WES/WGS vs. 25% for panel diagnostics; [31, 35]). If available, WES/WGS should be performed as a trio analysis, i.e., including both parents for the sake of interpretation of unknown variants WES is today the standard in most diagnostic laboratories, and analysis pipelines usually include CNV analyses, which render chromosomal microarrays redun-

dant. See ◘ **Table 2** for an overview of indications for genetic testing in nIFE. General recommendations for genetic testing in individuals with epilepsy in Germany are published and regularly reviewed by the Epilepsy and Genetics Commission (*Kommission Epilepsie und Genetik*) of the German ILAE branch (DGfE; *Dt. Ges. für Epileptologie*; http://www.dgfe.org/home/index,id,528.html) and have recently been published by the ILAE genetics commission [15].

Genetic testing in the presurgical evaluation of drug-resistant nIFE

Resective epilepsy surgery for individuals with genetic epilepsies may seem counterintuitive at first glance. Yet, as in tuberous sclerosis, resective surgery has been established for many years [48]. Increasing knowledge about the associations of mTOR-pathway genes beyond *TSC1* and *TSC2* and their association with focal lesional as well as nonlesional epilepsies has kindled the debate about whether patients with nIFE should systematically undergo genetic testing during presurgical work-up [20, 38]. A better understanding of the relation between genetic diagnosis and postoperative outcome could empower clinicians to make better predictions about the odds of successful epilepsy surgery. Systematic reviews and large case collections testify to the low chances of effective seizure control in patients carrying variants in genes related to channel function or synaptic transmission [5, 38]. The same studies observe far more promising results for variants in mTOR-pathway genes. This trend is corroborated by findings from a Dutch epilepsy center that also highlights the increasing use of genetic testing in nIFE [32]. Although clinicians should be wary of performing surgery in patients with channelopathies or synaptopathies, these individuals should not be categorically excluded from presurgical evaluation [42]. A recent survey by the DGfE among German epilepsy centers showed that genetic testing is viewed favorably in many case constellations and, in the case of nIFE, recommended by more than 90% of the survey respondents [5]. Founded on these results, the Epilepsy and Genetics Commission (DGfE) recommends genetic testing as part of the presurgical work-up.

Practical conclusion

- **Individuals with nonlesional focal epilepsy (nIFE) should undergo a thorough examination for positive family history and hallmarks of specific familial nIFE (e.g., nocturnal hypermotor seizures, auditory seizures).**
- **Genetic testing should be performed on individuals with a family history suggestive of monogenic inheritance, patients with defined syndromes (e.g., epilepsy with auditory features), and individuals with additive symptoms (intellectual impairment, autism, dysmorphic features).**
- **Genetic testing should be considered during presurgical evaluation of patients with drug-resistant focal epilepsy.**

Corresponding address

Dr. S. Wolking, MD, MBA
Department of Epileptology and Neurology, RWTH University Hospital Aachen
Pauwelsstr. 30, 52074 Aachen, Germany
swolking@ukaachen.de

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Declarations

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Zusammenfassung

Genetik nichtläsioneller fokaler Epilepsien im Erwachsenenalter und chirurgische Implikationen

Nichtläsionelle fokale Epilepsien (nlFE) stellen eine heterogene Gruppe von Syndromen dar. Sie umfassen selbstlimitierende Epilepsien des Kindes- und Jugendalters, seltene familiäre fokale Epilepsiesyndrome, durch auf das Gehirn beschränkte somatische Mosaike ausgelöste Epilepsien sowie zu einem großen Anteil nichtfamiliäre nlFE, welche einen komplexen genetischen oder unbekannten Hintergrund aufweisen. Eine genetische Diagnostik sollte in Fällen mit positiver, auf eine monogene Vererbung hindeutende Familienanamnese erfolgen. Überdies sollte eine genetische Testung bei Vorliegen zusätzlicher Symptome wie z. B. Intelligenzminderung, Autismus oder Dysmorphiezeichen angeboten werden. Eine Exom- oder Genomsequenzierung ist die Untersuchungsmethode der Wahl. Es besteht zudem eine wachsende Evidenz, dass eine genetische Testung in die prächirurgische Evaluation pharmakoresistenter Personen integriert werden sollte. So scheinen Individuen mit genetischen Veränderungen in Genen der mammalian target of rapamycin (mTOR)-Signalkaskade von epilepsiechirurgischen Eingriffen zu profitieren, während das postoperative Ergebnis bei genetischen Epilepsien, denen Defekte der Kanalfunktionen oder der synaptischen Transmission zugrunde liegen, oftmals nicht zufriedenstellend ist. Das Ziel dieses Artikels ist die Darstellung des genetischen Hintergrunds fokaler Epilepsiesyndrome, welche bei erwachsenen Personen auftreten bzw. fortbestehen, sowie die Darreichung von Handlungsempfehlungen zur genetischen Testung und prächirurgischen Evaluation.

Schlüsselwörter
Genetische Epilepsien · Somatische Genvarianten des Gehirns · Monogentische Erkrankungen · Komplexe genetische Erkrankungen · Genetische Diagnostik · Epilepsiechirurgie

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