Familial Focal Epilepsies: the Genetic Link

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Summary

While the concept of a genetic origin for focal epilepsies is relatively new, there is increasing evidence for the genetic and molecular basis of focal epilepsies in the recent years. The main identified syndromes of familial focal epilepsies include autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE), familial lateral TLE (FLTLE) or autosomal dominant partial epilepsy with auditory features (ADPEAF), familial mesial temporal lobe epilepsy (FMTLE), and familial partial (focal) epilepsy with variable foci (FPEVF/FFEVF), with specific ages at onset and clinical features. While localization is often difficult on the basis of ictal semiology and interictal EEG recordings, these familial syndromes also show a certain phenotypical overlap, and the initial diagnosis may change as more affected members of the family are identified; on an individual point of view, the electroclinical picture is not different from that of sporadic cases of focal epilepsy. Different underlying biological pathways have been identified to date. Whereas mutations within the same gene can cause a clinical spectrum of different focal epilepsies (*DEPDC5* gene in FFEVF, ADNFLE and FLTLE), different genes can cause the same epileptic syndrome (e.g. genes coding for nicotinic receptor subunits, or a potassium channel, KCNT1), and the recent discovery of gene mutations in inherited epilepsies with brain structural anomalies (*DEPDC5* in focal cortical dysplasias) further adds to the genetic link. Further progress in the neurobiology of the epilepsies will help to refine the ge-notype-phenotype relations and possibly increase our understanding of responses to antiepileptic drugs.

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Keywords: Focal epilepsy, familial, genetics, ion channel, DEPDC5

Epilepsies focales familiales : le lien génétique

Bien que le concept d'une possible origine génétique pour les épilepsies focales soit relativement nouveau, les découvertes en génétique moléculaire dans les épilepsies focales se sont multipliées au cours des dernières années. Les principaux syndromes d' épilepsie focale familiale comprennent l'épilepsie frontale nocturne autosomique dominante (EFNAD), l'épilepsie temporale latérale familiale ou épilepsie partielle autosomique dominante avec hallucinations auditives, l'épilepsie mésiotemporale familiale, et l'épilepsie focale familiale à foyer variable, avec des âges d'apparition assez spécifiques; à noter que les tableaux électrocliniques sur le plan individuel ne diffèrent pas des formes sporadiques d'épilepsie focale. Il faut noter que la localisation lobaire des épilepsies est souvent difficile sur la base de la sémiologie critique et des enregistrements EEG intercritiques. De plus ces différents syndromes familiaux montrent un certain chevauchement phénotypique, et le diagnostic syndromique initial peut changer avec l'identification de nouveaux membres affectés dans la famille. Différents gènes responsables ont été identifiés à ce jour. Comme dans d'autres pathologies neurologiques, des mutations dans des gènes différents peuvent provoquer le même syndrome épileptique (par exemple des gènes codant pour des sous-unités de récepteur nicotinique, ou pour un canal potassique, pour l'EFNAD) ; par ailleurs, des mutations dans un même gène peuvent être à l'origine de différents syndromes d'épilepsie focale (par ex. le gène DEPDC5). La découverte récente de possibles anomalies cérébrales structurelles associées à certaines de ces mutations (dysplasies corticales focales en lien avec des mutations DEPDC5) complique encore davantage la classification des épilepsies qui distingue actuellement une origine génétique d'une origine structurelle. De nouveaux progrès dans la neurobiologie des épilepsies permettra d'affiner les relations génotype-phénotype et éventuellement d'accroître notre compréhension de la réponse aux médicaments antiépileptiques dans différentes formes d'épilepsie.

Mots clés : Epilepsie focale, familiale, génétique, canal ionique, DEPDC5

Familiäre fokale Epilepsien: die genetische Komponente

Dass auch bei fokalen Epilepsien eine genetische Komponente beteiligt sein könnte, ist zwar noch eine relativ neue Auffassung, doch mehrt sich seit einigen Jahren die Evidenz für die genetischen und molekularen Grundlagen fokaler Epilepsien. Zu den wichtigsten beschriebenen Syndromen familiärer fokaler Epilepsien gehören die autosomal-dominante nächtliche Frontallappenepilepsie (ADNFLE), die familiäre laterale TLE (FLTLE) oder die autosomal-dominante partielle Epilepsie mit auditiven Auren (ADPEAF), die familiäre mesiale Temporallappenepilepsie (FMTLE) und die familiäre partielle (fokale) Epilepsie mit variablen Foci (FPEVF/FFEVF), mit jeweils spezifischen Manifestationsaltern und klinischen Merkmalen. Während sich die Lokalisation auf Grundlage der iktalen Semiologie und der interiktalen EEG-Muster oftmals schwierig gestaltet, zeigen diese familiären Syndrome ausserdem gewisse phänotypische Überlappungen, und die ursprüngliche Diagnose kann sich mit der Feststellung weiterer betroffener Angehöriger ändern. Individuell betrachtet unterscheidet sich das elektroklinische Bild nicht von sporadischen Fällen fokaler Epilepsien. Unterschiedliche zugrunde liegende biologische Signalwege wurden bereits ermittelt. Während Mutationen innerhalb desselben Gens bisweilen für ein klinisches Spektrum unterschiedlicher fokaler Epilepsien verantwortlich sind (DEPDC5-Gen bei FFEVF, ADNFLE und FLTLE), kann andererseits ein und dasselbe epileptische Syndrom durch unterschiedliche Gene hervorgerufen werden (z. B. die für die Nikotinrezeptor-Untereinheiten kodierenden Gene oder das Kaliumkanal-Gen KCNT1). Die kürzlich entdeckten Genmutationen bei erblichen Epilepsien mit strukturellen Gehirnanomalien (DEPDC5 bei fokalen kortikalen Dysplasien) sprechen ebenfalls für die genetische Komponente. Der weitere Fortschritt in der Neurobiologie der Epilepsien wird zur genaueren Aufklärung des Genotyp-Phänotyp-Zusammenhangs beitragen und möglicherweise unsere Kenntnisse bezüglich des Ansprechens auf Antiepileptika erweitern.

Schlüsselwörter: Fokale Epilepsie, familiär, Genetik, Ionenkanal, DEPDC5

Introduction

A genetic background for epilepsy has been recognized for long, but recent technological advances in molecular genetics have enabled a detailed understanding of the genetic basis of many forms of epilepsies. A genetic etiology is not synonymous with generalized epilepsy; there is emerging evidence of a genetic contribution to focal epilepsies. The main familial focal epilepsies having a known genetic origin with specific age-related and electro-clinical characteristics include autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE), familial mesial temporal lobe epilepsy (FMTLE), familial lateral TLE (FLTLE) or autosomal dominant partial epilepsy with auditory features (ADPEAF), and familial partial epilepsy with variable foci (FPEVF). The new ILAE classification of the electroclinical syndromes according to the age at onset includes "autosomal-dominant nocturnal frontal lobe epilepsy" with onset in childhood, "autosomal dominant epilepsy with auditory features" with onset in adolescence or early adulthood, and "familial focal epilepsy with variable foci" (FFEVF) with a less specific age at onset relationship [1].

It has to be noted that for each affected member, the clinical picture is similar to that of focal epilepsy that may occur in a patient with a sporadic form (i.e. who does not have a family history of seizures) and even of symptomatic origin (or "structural" in the new classification by etiology). Therefore, these focal epilepsy syndromes correspond to "familial epilepsy syndromes" and not to epileptic syndromes of individuals. The rate of pharmacoresistance in the different syndromes is between 10 and 30%. The neurological status and intelligence are typically normal and interictal EEG abnormalities are usually rare. The familial occurrence of the different familial focal epilepsy syndromes is related to an inherited, autosomal dominant, molecular defect. The clinical penetrance is usually around 60 - 70%, and obligate gene carriers without a history of seizures can often be identified within a family. These familial syndromes also show phenotypic overlap, and small families may be initially labeled as ADNFLE or FLTLE/ADPEAF and later recognized as FFEVF when new affected members are identified. In addition, it may sometimes be difficult to localize the focal epilepsy for some patients on the basis of ictal semiology and scalp EEG recordings [2].

These inherited focal epilepsies are mediated by different biological pathways: ion channel subunit genes (*CHRNA4, CHRNA2, CHRNB2, and KCNT1*) linked to ADNFLE, encoding the α4, α2, and β2 subunits of the neuronal nicotinic acetylcholine receptor (nAChR) and a potassium channel subunit, respectively; a gene coding for a neuronal secreted protein (*LGI1* or *epitempin*) linked to autosomal dominant epilepsy with auditory features; and the mTORC1-repressor *DEPDC5* (DEP domain-containing protein 5) gene, reported essentially in FFEVF, but also in ADNFLE and FLTLE [3]. The discovery of *DEPDC5* mutations in individuals with familial focal epilepsy with focal cortical dysplasia [4 - 6] further adds evidence for the genetic link to inherited focal epilepsies, with the possibility of detectable structural consequences in some affected members.

The most common familial focal epilepsies and their clinical and genetic features are described here.

1. Autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE)

Autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE) was first recognized as familial focal epilepsy in 1994 in families from Australia, Canada and the United Kingdom [7]. It follows autosomal dominant inheritance with 70% penetrance and shows considerable intra-familial variation in epilepsy severity [8, 9]. The mean age at onset of ADNFLE is between 8 and 11.5 years [9 - 11, 2]. Clusters of motor seizures arising from sleep characterize the syndrome, while diurnal seizures may be observed in the most severe cases, during periods of poor seizure control. Seizures may begin with a non-specific aura prior to a motor seizure, which includes hyperkinetic (such as frantic movements of bipedal activity, pelvic thrashing), tonic or dystonic features. A sensation of choking has frequently been reported at the beginning of the seizures [12]. Awareness may be retained through the seizure, which has often led to misdiagnoses of parasomnias, night terrors or hysteria [8]. Seizures are of short duration, usually lasting less than one minute [8]. They often occur in clusters, with a mean of about ten seizures per night, clustering over one or two hours. The main provocative factors for seizures are sleep deprivation (30% of the patients) and stress (30%). Secondarily generalized seizures are observed in nearly half of the patients, at the onset of epilepsy or during the course of the disease, but they occur rarely. Neurological examination is normal. Psychiatric and neuropsychological disturbances are often subtle, with features of frontal, and sometimes also temporal, lobe dysfunction [13]. Character and behavioral disorders include irritability, aggressive and impulsive behavior, with fugue states during adolescence [9], and depression and personality disorders during adulthood. More severe psychiatric symptoms have been described in a few families: psychotic illness and other psychiatric symptoms in some patients in a Norwegian family with a mutation in a nicotinic receptor subunit [14]; a severe ADNFLE phenotype has been reported in two families with refractory epilepsy, with status epilepticus in 24%, psychiatric and behavioral disorders in half of the patients and intellectual disability in a quarter [15]. A KCNT1 mutation was later identified in one of these families as well as in two additional families and a sporadic case with severe ADNFLE and psychiatric features [16]. Mild intellectual disability was present in nearly half of the subjects from four families with ADNFLE associated with nicotinic receptor mutations, showing that cognitive dysfunction is an integral part of the broad phenotype of ADNFLE [13]. Steinlein et al. analysed the clinical features of 19 ADNFLE families from 12 countries with a total of 150 patients and grouped them with respect to their nAChR mutations. Their data suggest that certain nAChR mutations might be associated with an increased risk for major neurological symptoms such as mental retardation, schizophrenia-like symptoms or marked cognitive deficits [17]. The ictal symptoms might differ from one individual to another within the same family, and different regions of onset within the frontal lobe in different family members was confirmed by Hayman and colleagues by using ictal video-EEG recordings and functional neuroimaging [18].

Interictal EEG is normal or may show non-specific anterior focal epileptiform abnormalities, sometimes only visible during sleep recording [8, 11, 9]. Movement artifacts often obscure scalp ictal recordings, which also often appear non contributive (in about half of the patients) [2]. Video-EEG-polysomnographic recordings show that the seizures occur during non-rapid eye movement (non-REM) sleep, mainly in stage 2, starting after a transition from sleep to an arousal [19]. Magnetic resonance imaging (MRI) studies were considered normal in all patients, although recent reports have described focal cortical dysplasias in the context of DEPDC5 mutations, as mentioned above [5, 4], or even of *KCNT1* mutation (one case, personal communication). In an FDG-PET study of five ADNFLE patients with different nicotinic receptor mutations, decreased fixation was observed in a few regions including the right anterior orbitofrontal cortex [20].

The stereotyped character of seizure semiology, unchanged throughout life in a given subject, is a striking feature of ADNFLE, the exception being that when seizures begin in early childhood, they may evolve from tonic attacks to classical NFLE seizures including dystonic or hyperkinetic components [2]. In many patients, seizures persist for years, but they tend to disappear with age, particularly around the fourth or fifth decade, without relapse after cessation of drug therapy. Carbamazepine is the most effective antiepileptic medication in ADNFLE, and completely suppresses seizures in about 70% of patients. Low dosages of carbamazepine (around 600 mg/day in adults) are sufficient, which may give evidence of pathophysiological mechanisms that are different from those of other epilepsies [21]. Pharmacoresistance to carbamazepine and other antiepileptic drugs is observed in 30% of patients.

Ten to fifteen percent of the ADNFLE families bear mutations on genes coding for subunits of the neuronal nicotinic receptors (nAChRs), *CHRNA4, CHRNB2,* and *CHRNA2* [22 - 25]. The nAChRs are pentameric ligand-gated ion channel receptors, which consist of different functional subunit combinations. Most of the nAChRs are presynaptic and have a neuromodulatory role: they enhance the release of the neurotransmitter present in the neurons on which they are located (GABA, glutamate, dopamine, norepinephrine, serotonin or ACh). Other nAChRs are postsynaptic and mediate fast excitatory synaptic transmission. Among the main roles of the nAChRs, we can mention the regulation of the sleep/wake cycle, and cognitive roles.

A PET study using F-A-85380, a tracer labeling the a4b2 nAChRs, showed a nAChR density increase in mes-

encephalon in a group of patients with ADNFLE and an identified nAChR mutation, suggesting the involvement of the arousal brainstem ascending cholinergic system in the pathophysiology of ADNFLE [20].

Recently, ADNFLE mutations have been detected in *KCNT1*, which codes for a Na+-gated K+ channel [16], and in *DEPDC5* gene encoding DEP (Disheveled, Egl-10 and Pleckstrin) domain-containing protein 5 [26, 27]. Mutations in *KCNT1* were identified in four families with severe ADNFLE [16]. This severe form of ADNFLE had an earlier mean age at onset of 6 years compared to 10 years in the classical form of ADNFLE. The KCNT1, or Slack channel, is a potassium channel which is expressed in the central nervous system, yet with a location which is limited in the cortex to the frontal lobe, according to a study performed in rodents [28]. Functional studies suggest that the identified mutations result in a current increase of the KCNT1 channels [29]. It is noteworthy that a role of this channel in intellectual disability was recently reported [30]. Lastly, there is also available evidence about the implication of the corticotropin-releasing hormone gene (CRH) [31, 32].

Most recently, an autosomal recessive phenotype has been described in a single family with nocturnal frontal lobe epilepsy (NFLE) with the causative gene mutation (PRIMA1) on chromosome 14 [33].

2. Familial temporal lobe epilepsy

Several familial forms of TLE have been described, including familial lateral TLE (FLTLE), familial mesial TLE (FMTLE) without hippocampal sclerosis, and FMTLE with hippocampal sclerosis. While the inheritance is often complex in families with several affected members, it is clearly autosomal dominant in some families [34].

2.1 Familial mesial temporal lobe epilepsy (FMTLE)

Descriptions of familial mesial temporal lobe epilepsy include a spectrum, from a benign epilepsy syndrome with prominent déjà vu symptoms and without antecedent febrile seizures (FS) or MRI abnormalities, to heterogeneous epilepsies, with a frequent history of febrile seizures, and hippocampal atrophy and high T2 signal on MRI, generally more refractory [34].

In the classical form of FMTLE, there is no history of febrile seizures and no abnormalities on MRI. In more than 20 families without a history of familial FS [35 - 37], seizure onset was around adolescence or early adulthood. In the series of Crompton et al. including 20 other families, with antecedent FS in about 10 % of the patients, the mean seizure onset age was concordant, of 18 years (range: 3-46 years) [34]. FMTLE is characterized by mesial temporal lobe auras that may have psychic, or more rarely autonomic or special sensory components [35]. The most common ictal psychic symptom is déjà vu. Other possible symptoms are fear, nausea, tachycardia, complex visual or auditory distortions, or somatosensory auras such as diffuse numbness or tingling. Simple focal seizures occur in about 90% of patients and complex focal seizures, usually preceded by simple focal seizures, in two thirds. Rare generalized tonic-clonic seizures occur in about 70% of patients. Ictal symptoms may vary between the different affected members of a same family. Sometimes the diagnosis can be missed in some individuals, for the reason that symptoms can be regarded as normal phenomena when they are mild. Interictal EEG abnormalities are rare. There is usually a good outcome with frequent seizure freedom at long-term with or without antiepileptic medication.

A clinically heterogenous form of FMTLE has been described, where affected family members have variable ages of onset, commonly in the first decade of life, with a family history of FS and epilepsy [36, 38]. Interictal EEGs show frequent temporal epileptiform abnormalities. Hippocampal atrophy with high T2 signal is common (30 and 57% in these series, respectively) as was medication refractoriness.

Several loci have been mapped in families with FMTLE, but responsible genes have not been found. Chahine et al. identified a novel locus for familial TLE with FS on chromosome 3q25-q26 [39], while another locus was identified on chromosome 18p11.31 in a family with mesial temporal lobe epilepsy associated with hippocampal abnormalities [40]. Faniculli et al. also identified a locus for FMTLE in a family including 6 family members with MTLE including one with a history of FS and another member with only FS, on a region on chromosome 3q26 overlapping with the region reported by Chahine et al., however they failed to identify pathogenic mutations in genes of this region [41].

2.2. Autosomal dominant lateral temporal lobe epilepsy (ADLTLE) (or ADPEAF)

Autosomal dominant lateral TLE (ADLTLE) or autosomal dominant partial epilepsy with auditory features is a rare familial epilepsy, which onset is also usually in late adolescence or early adulthood [42]. The most frequent ictal symptoms are auditory auras often consisting of ringing or humming (about one half of the patients). Some patients may have other symptoms, alone or in association, such as aphasic seizures, or visual or olfactory hallucinations [43, 44]. Interestingly, seizures can be triggered by external noises [42]. Interictal EEGs are either normal or show mild abnormalities. Previous reports described normal MRIs in all patients, except for the description of developmental abnormalities in the lateral cortex of the temporal lobe in half of the affected members in one family [45]. Some studies, using evoked potentials, functional MRI and magneto-en-

cephalography, could demonstrate a functional impairment in auditory processing in the patients [46, 47]. Response to antiepileptic treatment is usually good [42].

In about half of the ADLTLE families, mutations have been identified in the LGI1 gene (leucine-rich glioma inactivated gene 1), also called *epitempin*, located on chromosome 10q, and coding for the *LGI1* secreted protein [48, 44, 49 - 51]. The estimated clinical penetrance of LGI1 mutations is about 70%. In addition, *de novo* LGI1 mutations were found in about 2% of sporadic cases with ADLTLE, who are clinically similar to the majority of patients with ADLTLE/ADPEAF but have no family history. About forty LGI1 mutations have been described in familial and sporadic LTLE patients [52, 53]. The mutations are distributed throughout the gene and are mostly missense mutations. The mechanisms leading from mutations of the LGI1 protein to epilepsy are still incompletely known. The two main current hypotheses are i) in the context of its participation in a complex that includes a presynaptic potassium channel and a postsynaptic AMPA receptor, through its interaction with members of the ADAM protein family (ADAM 22 and ADAM 23 receptors), the LGI1 protein may act on the AMPA-receptor-mediated synaptic excitatory transmission [54, 55], and ii) an alteration of the postnatal developmental maturation of glutamatergic transmission [56]. Recently, Boillot et al. showed in conditional knockout mice that LGI1 depletion restricted to pyramidal cells was sufficient to generate seizures [53].

It is noteworthy that LGI1 protein is also involved in another neurological disorder, an acquired auto-immune limbic encephalitis related to antibodies against LGI1, which manifests by focal seizures (mostly faciobrachial dystonic seizures) and psychiatric disturbances [57, 58].

3. Familial partial (focal) epilepsy with variable foci (FFEVF)

Familial focal epilepsy with variable foci is an autosomal dominant epilepsy with focal seizures which emanate from different regions of cortex in different family members [59], but the region is stable (and seizure semiology constant) in each given patient. Thus a single family may include individuals with frontal lobe epilepsy, others with temporal lobe epilepsy, and possibly still others with parietal lobe epilepsy or occipital lobe epilepsy [59, 60, 9, 61, 62]. Penetrance is incomplete (estimated at around 60%), as suggested by the absence of a history of seizures in some obligate gene carriers.

In the "princeps" paper, the mean age at onset was 13 years (median age, 10 years), with a large range extending from 1 month to 52 years [62]. Not all brain regions appeared equally susceptible: most of the patients have their epileptic focus in the frontal or temporal lobe, as indicated by the ictal symptoms. Patients may suffer from simple focal seizures as well as complex focal seizures. Simple focal seizures suggestive of temporal lobe epilepsy may present e.g. with psychic phenomena or olfactory hallucinations. Secondarily generalized tonic-clonic seizures may occur in about two-thirds of the patients. There is a great intra-familial variability of the severity of the epilepsy.

FFEVF was subdivided into two forms according to the seizure patterns and EEG findings. In "FPEVF2", the more common form, seizures predominantly occur during sleep [60, 9, 62]; some individuals have a typical nocturnal frontal lobe epilepsy, which could have led to a misdiagnosis of some families as ADNFLE. The form called "FPEVF1" is rarer but was the one observed in the original family with FFEVF, with seizures predominating while awake and a good response to antiepileptic medication [59].

In FPEVF1, active interictal focal epileptiform abnormalities were observed during sleep. The location of the abnormalities remained constant in affected individuals over many years, even without ongoing seizures [59]. In FPEVF2, EEG is either non contributive, or shows sparse interictal focal epileptiform anomalies. It is interesting to note that some at-risk individuals who have never had seizures may also present EEG epileptiform anomalies [59, 9], which seems to represent a marker of carrier status of the FFEVF gene. Neurological examination and cerebral MRI were reported as normal in both forms until the recent reports indicating focal cortical dysplasias in some affected subjects (associated with *DEPDC5* mutations).

Linkage studies of the first Australian family with FPEVF1 suggested linkage to chromosome 2 [59], but no other families have been linked to this chromosome and no gene has been identified. On the other side, after a linkage of several families with FPEVF2 to chromosome 22q11-q12 (60 - 63), a gene located on this locus, *DEPDC5*, was identified as the causal gene, and mutations were identified not only in large families but also in other small families with non lesional focal epilepsy [64, 65].

DEPDC5 mutations in genetic focal epilepsies

Recent studies have reported *DEPDC5* (DEP domain containing protein 5) mutations in different focal epilepsy syndromes. Mutations of the DEPDC5 gene account for 12 to 37% of inherited focal epilepsies including mostly familial focal epilepsy with variable foci (FFEVF), but also autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE) and familial temporal lobe epilepsy (FTLE) [64, 27, 28, 4]. The drug-resistance rate of around 30% in patients with familial focal epilepsies seems to be higher when DEPDC5 is causal. Recent studies have shown that DEPDC5 is an upstream negative regulator of mammalian target of rapamycin mTOR complex 1 (mTORC1) [66, 65]. Other proteins in

the same mTOR system were already described to be involved in tuberous sclerosis [67, 68]. Interestingly, MRI abnormalities have been described in some patients with familial focal epilepsy and DEPDC5 mutation: first in three patients (in two families) with bottom-of-the-sulcus dysplasia and one with focal band heterotopia [65], and in some drug-resistant patients in another reported group of seven families with familial focal epilepsy, presenting as focal cortical dysplasia (FCD) type II in the frontal or insular lobe. This finding reinforces the link between mTORC1 pathway and FCDs [4]. It remains unclear to date why a dysplasia appears in some patients and not in others and why some regions (particularly within the frontal lobe) are more prone to develop the mutation-associated dysplasias. Some of these drug-resistant patients benefited from a surgical treatment, and surprisingly had a good long-term outcome, mostly when a FCD type II was present. Recently, DEPDC5 mutations were also identified in rare cases of rolandic epilepsy and unclassified focal childhood epilepsies [69].

Other rare familial focal epilepsies include familial rolandic epilepsy with speech dyspraxia (described in 3 families to date, with autosomal dominant inheritance) [10]; Autosomal recessive rolandic epilepsy with paroxysmal exercise-induced dystonia and writer's cramp (described in one single family) [70]; and partial (focal) epilepsy with pericentral spikes (PEPS) described in one single family to date, linked to chromosome 4p15 [71].

Conclusion

Molecular genetic advances in inherited focal epilepsies have pinpointed their genetic heterogeneity and the fact that different biological pathways mediate them. There is evidence that the different subtypes of focal epilepsies are not strictly genetically separate entities but that mutations within the same gene might cause a clinical spectrum of different types of focal epilepsies. Moreover, a same syndrome of familial focal epilepsy may be caused by alterations in different genes (e.g. genes coding for nicotinic receptor subunits, for KCNT1, DEPDC5, in ADNFLE). These genetic epilepsies will probably help to understand the pathogenesis of the more frequent sporadic (non symptomatic/structural) forms of focal epilepsy. However the limits between the genetic and structural etiology are vanishing as focal cortical dysplasias seem to be associated with some of the identified mutations [65, 4]. A greater awareness of the genetic basis in this group of disorders by the treating physicians is essential for identification of new families and a more complete disentangling of the responsible genes.

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