Curr Neurol Neurosci Rep (2014) 14:447
DOI 10.1007/s11910-014-0447-7

PEDIATRIC NEUROLOGY (DR NORDLI, JR., SECTION EDITOR)

Epilepsy: Old Syndromes, New Genes

Sarah Weckhuysen · Christian M. Korff

Published online: 17 April 2014

Abstract Next-generation sequencing technologies have tremendously increased the speed of gene discovery in monogenic epilepsies, enabling us to identify a genetic cause in an increasing proportion of patients, and to better understand the underlying pathophysiology of their disease. The rapid speed with which new genes are being described lately, confronts clinicians with the difficult task of keeping up to date with the continuous supply of new publications. This article aims to discuss some of the genes that were recently discovered in monogenic familial epilepsy syndromes or epileptic encephalopathies for which an underlying cause remained unknown for a long time.

Keywords Epilepsies · Epileptic encephalopathies · Genes · Ion channels

Introduction

Epilepsy is a one of the commonest neurological diseases, with a lifetime risk of 3 % [1]. Genetics is thought to play a role in at least 70 % of patients with epilepsy [2], both through the action of multiple genetic risk factors in common epilepsies, such as childhood absence epilepsy or juvenile myoclonic epilepsy, and through single gene mutations in rare monogenic epilepsy syndromes. The list of epilepsy genes is rapidly growing, and several of these genes can now be readily screened in clinical practice.

In the last few years, major advances have been made in the field of monogenic epilepsy syndromes. The rate of gene discovery in these syndromes has mainly been driven by the availability of genomic sequencing techniques. At the time of the description of the first epilepsy gene, *CHRNA4* in 1995 [3], genetic studies were mainly restricted to large families with inherited (mild) forms of epilepsy. With use of linkage analysis, the genetic cause of familial epilepsy syndromes, such as autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE) and genetic epilepsy with febrile seizures plus (GEFS+), was described [4, 5]. Most of these gene findings supported the still prevailing concept of epilepsies being channelopathies.

Linkage analysis did, however, not allow gene discovery in isolated patients with epilepsy. Genetic factors in patients with epileptic encephalopathies (EE), severe forms of epilepsies associated with developmental stagnation or regression, therefore remained poorly studied for a long time. Candidate gene screening has been a successful approach to tackle this problem. The best known example is the detection of mutations in *SCN1A*, a gene initially identified in GEFS+ families, in Dravet syndrome patients [6]. This candidate gene approach is still leading to major breakthroughs, as shown by the recent elucidation of the cause of some of the most devastating epilepsies, such as malignant migrating partial seizures of infancy (MMPSI) [7] and other forms of neonatal EE [8••]. Nevertheless, this approach creates a bias towards already known genes and pathways. A first step towards an unbiased gene discovery approach has been the advent of microarray techniques allowing genome-wide detection of microdeletions and duplications, and leading to the discovery of EE genes such as *STXBP1* and *GRIN2A* [9, 10••, 11••, 12••]. It was,

This article is part of the Topical Collection on *Pediatric Neurology*

S. Weckhuysen (✉)
Neurogenetics Group, Department of Molecular Genetics, VIB, Antwerp, Belgium
e-mail: sarah.weckhuysen@molgen.vib-ua.be

S. Weckhuysen
Laboratory of Neurogenetics, Institute Born-Bunge, University of Antwerp, Antwerp, Belgium

C. M. Korff
Pediatric Neurology, University Hospitals, Geneva, Switzerland

however, the introduction of massive parallel sequencing technology, used to rapidly and cost-effectively screen a whole exome or a whole genome, that has led to a real explosion of genetic discoveries in epilepsy. This technology has finally enabled us to tackle the genetics of both monogenic familial and sporadic epilepsies, without the need to have prior assumptions. The rapid speed with which new genes are being described lately confronts clinicians with the difficult task of keeping up to date with the continuous supply of new publications. This article aims to discuss some of the genes that were recently discovered in monogenic familial epilepsy syndromes or EE for which an underlying cause remained unknown for a long time.

Neonatal Epileptic Encephalopathy and *KCNQ2*

Early in 2012, de novo missense mutations in *KCNQ2* were identified in 10 % of patients with neonatal EE with a presumed genetic cause [8••]. Since this report, several studies have confirmed this high frequency of mutations in patients with neonatal EE, and have further delineated the phenotype associated with *KCNQ2* encephalopathy [13–15].

This gene was, however, not unfamiliar to pediatric neurologists. *KCNQ2* and *KCNQ3*, encoding the voltage-gated potassium channel subunits Kv7.2 and Kv7.3, were long known to be present in 60-70 % of families with benign familial neonatal epilepsy (BFNE) [16]. Children with this benign autosomal dominant epilepsy syndrome experience seizures in the first week of life. The seizures often begin with a tonic component followed by a range of autonomic and motor changes, and are often accompanied by apnea. The seizures are brief but can occur up to 30 times a day. Prognosis is, however, favorable: the seizures remit between 1 and 12 months of age, and the children develop normally.

Children with *KCNQ2* encephalopathy have a similar early neonatal onset, and present with similar seizure symptoms. In contrast to the EEG in BFNE, however, the EEG is grossly abnormal, showing a burst suppression pattern or multifocal epileptic activity, and neonates soon show delayed development with axial hypotonia and lack of visual tracking. The seizures are difficult to treat, although some patients respond well to sodium channel blockers such as phenytoin and carbamazepine. Two thirds of patients become seizure-free some months or years after seizure onset, but all children show developmental delay, ranging from mild to profound intellectual disability. Older children often have axial hypotonia, sometimes associated with limb spasticity, and most patients are not ambulatory.

In over half of patients, early MRI of the brain shows hyperintensities in basal ganglia and thalamus that later resolve. At a later stage, cerebral atrophy and a thin corpus callosum can be seen, correlating with the severity of developmental delay.

Almost all reported patients with *KCNQ2* encephalopathy had seizure onset in the first week of life, but one patient with onset at 5 months has been reported. A similar spectrum of onset age is also seen for *KCNQ2* mutations in benign infantile epilepsies: a recent report found *KCNQ2* mutations in patients with onset of seizures at up to 6 months of age.

Whereas individuals with BFNE develop normally and pass mutations to the next generation, mutations in *KCNQ2* encephalopathy occur de novo. Mutations in BFNS range from missense mutations, over frameshift, splicing, and nonsense mutations to whole-gene deletions. Loss of function has been proven for several missense mutations, and whole-gene deletions show that even a 50 % reduction of the amount of protein leads to the benign phenotype [17]. All mutations reported in *KCNQ2* encephalopathy so far are novel missense mutations, and a dominant negative effect has been shown for most of the mutations studied [18, 19].

Retigabine, a recently marketed enhancer of Kv7 opening, has been shown to reverse some of the functional effects of these severe mutations [18]. Further clinical studies are warranted to investigate whether the early use of this drug in *KCNQ2* encephalopathy can positively influence neurodevelopmental outcome.

Neonatal and Infantile Epileptic Encephalopathy and *SCN2A*

KCNQ2 was not the only gene involved in a benign infantile epilepsy syndrome that has now been implicated in EE. Mutations in *SCN2A* were described in 2002 in a subset of families with benign neonatal and infantile epilepsy [20]. Individuals with this benign syndrome have a phenotype intermediate between BFNE and benign familial infantile epilepsy (BFIE). The mean age of seizure onset is 11 weeks, but within a single family both neonatal and infantile seizure onset is seen. Rare *SCN2A* mutations have also been identified in GEFS+ families [21], and subsequently de novo mutations were identified in a few patients with Dravet syndrome [22]. The use of unbiased next-generation sequencing (NGS) techniques has led to the identification of *SCN2A* mutations in a wide range of EE and to identification of the genetic entity *SCN2A* encephalopathy [23–26]. De novo *SCN2A* mutations are reported to be present in 13 % of patients with Ohtahara syndrome, and a minority of patients with West syndrome, Dravet syndrome, and unclassified EE with seizure onset from birth to the age of 1 year. Cognitive outcome ranges from mild to severe intellectual disability, and this does not always seems to correlate with seizure duration and severity. Patients can be microcephalic, and brain MRI shows cerebral atrophy and/or a thin corpus callosum in severely affected patients. Detailed

phenotypical descriptions of larger cohorts of patients with *SCN2A* encephalopathy are warranted to show us what the common phenotypic characteristics are.

Remarkably, whole-exome studies have also revealed de novo *SCN2A* mutations in patients with intellectual disability or autism without seizures [27–30]. These findings show that the mutation affects neurodevelopment independently from its effect on seizure susceptibility.

Phenotype–genotype correlations remain speculative so far. Both gain of function and loss of function have been described for mutant channels. In general, the mutations identified in EE tend to alter the channel properties to a greater extent than the mutations seen in benign neonatal and infantile epilepsy. Truncating *SCN2A* mutations have only been described in patients with EE, autism, or intellectual disability, and both whole-gene deletions and whole-gene duplications lead to a more severe phenotype. Also, mutations linked to more severe phenotypes tend to be located more frequently in the linker regions between the transmembrane segments of the protein, or in the voltage sensor domain. Genetically engineered animal models of specific *SCN2A* mutations will help us to understand better the underlying pathogenetic mechanisms and the role of *SCN2A* in neurodevelopment and epileptogenesis.

Infantile Convulsions and *PRRT2*

Mutations in *PRRT2*, a gene located on chromosome bands 16p11.2 and 16q11.2 and coding for proline-rich transmembrane protein 2 (PRRT2), were initially discovered by whole-exome sequencing in eight Han Chinese families with a history of paroxysmal kinesigenic dyskinesia (PKD) [31]. Around the same time, *PRRT2* mutations were reported in 14 of 17 families (82 %) with BFIE, and in five of six families (83 %) with infantile convulsions with choreoathetosis (ICCA) [32]. Linkage analysis studies had previously linked these two conditions to the same pericentromeric region of chromosome 16, also found to be involved in PKD [33, 34].

BFIE and ICCA share the presence of clusters of self-limited focal seizures with onset between 3 and 12 months, but in ICCA, PKD appears in late childhood or adolescence. Within the same family, individual family members can have infantile seizures, PKD, or a combination of both [33].

Several publications have confirmed these findings, and have identified mutations in sporadic epilepsy patients with self-limited infantile seizures. Asymptomatic carriers are frequent owing to the reduced penetrance of *PRRT2* mutations [35•]. *PRRT2* was also shown to play a role in various other paroxysmal disorders, such as hemiplegic migraine, paroxysmal torticollis, and episodic ataxia [36–38]. Mutations were identified in rare individuals with febrile seizures [37, 39], although their direct role in fever sensitivity has been debated [40]. Recessive *PRRT2* mutations have been described in a consanguineous family with intellectual disability and in two siblings of a consanguineous family with intellectual disability, absences, and episodic ataxia in addition to BFIE and PKD [41]. This suggests not only that recessive mutations may considerably worsen the phenotype, but also that PRRT2 dysfunction influences neurodevelopment. Most *PRRT2* mutations described so far are nonsense, frameshift, and splice site mutations predicted to lead to protein truncation and thus loss of function. Several missense mutations have been described too. The same recurrent frameshift mutation, c.649-650insC; p.Arg217Profs*7, has been identified in families and patients of different ethnicity [35•]. There is a surprising lack of genotype–phenotype correlation as every single mutation described can be found in individuals with any of the three main phenotypes (PKD, BFIE, ICCA). This is consistent with the phenotypic heterogeneity seen within ICCA families. Most probably, the expression of the phenotype is influenced by other, still to be determined, genetic or environmental factors.

The exact function of PRRT2 remains to be clarified, but it has been shown to interact with synaptosomal-associated protein 25 kDa (SNAP25), a protein involved in neurotransmitter release from synaptic vesicles [42]. Interestingly, the expression of *PRRT2* in the brain seems particularly important in the cerebral cortex and basal ganglia, two regions likely to be specifically involved in the main semiological features of BFIE and ICCA [32].

Malignant Migrating Partial Seizures in Infancy and *KCNT1, SCN1A, PLCB1, SCL25A22, and TBC1D24*

MMPSI is a rare but severe EE characterized by migrating polymorphic focal seizures and progressive neurological deterioration with onset in the first 6 months of life. The seizures are pharmacoresistant and arise from different areas in both hemispheres. The "migrating" pattern of seizures on ictal EEG is the main feature of this syndrome. Seizures gradually become more frequent in the first year of life, often becoming almost continuous for several days. Brain MRI is normal at the onset but signal abnormalities may appear during the course of the disease [43]. A genetic cause has long been suspected, and several groups have now identified five different genes implicated in this devastating syndrome.

KCNT1

A recent study identified de novo missense mutations in the gene *KCNT1* in half of sporadic epilepsy patients with MMPSI [44••]. At the very same time, another group identified missense mutations in the same gene in three families and one sporadic epilepsy patient with ADNFLE [45••]. Compared with ADNFLE families with mutations in nicotinic

acetylcholine receptor subunit genes such as *CHNRA4*, patients with *KCNT1* mutations have an earlier age of seizure onset and frequently have comorbidities of intellectual disability and psychiatric features. More recently, one patient with an infantile EE with leukoencephalopathy and a de novo missense mutation and one patient with Ohtahara syndrome and a homozygous missense mutation in *KCNT1* have been reported [46, 47]. The latter suggests that both dominant and recessive inheritance patterns can be seen in disorders linked to this gene.

KCNT1 encodes a sodium-activated potassium channel that contributes to the slow hyperpolarization that follows repetitive firing. Missense mutations in MMPSI have been proven to lead to a gain of function of the channel [44••]. The large differences in phenotypic expression of mutations might depend on their influence on non-ion-conductance pathways of the protein. Indeed, the C-terminus interacts with developmental proteins such as fragile X mental retardation protein (a messenger RNA binding protein), and mutations altering this developmental signaling pathway might lead to more severe neurodevelopmental disorders.

SCN1A

SCN1A mutations are associated with a wide spectrum of epilepsies, ranging from the benign febrile seizures in families with GEFS+, to intractable epilepsy and intellectual disability in Dravet syndrome [48]. De novo mutations in *SCN1A* are found in 70-80 % of patients with Dravet syndrome. Two MMPSI patients with a de novo mutation in *SCN1A* have now been described, making MMPSI the most severe end of the spectrum of epilepsies associated with sodium channel gene defects [7].

PLCB1, SLC25A22, and TBC1D24

Rare recessive mutations in three different genes were identified in isolated families with MMPSI. One affected sib pair carried a recessive mutation in the mitochondrial glutamate carrier *SLC25A22* [49], and a second sib pair had a recessive mutation in the gene *TBC1D24* [50]. A sporadic epilepsy patient with consanguineous parents carried a homozygous deletion disrupting *PLCB1*, encoding phospholipase C β_1 [51]. Follow-up screening of these genes in additional patients with MMPSI did not reveal any further patients, showing that these are rare causes of MMPSI.

Again, the phenotypic spectrum of mutations in all these genes seems broader than pure MMPSI. Recessive mutations in *SLC25A22* were also identified in patients with neonatal EE and a suppression burst pattern [52], and another homozygous deletion in *PLCB1* was identified in a patient with infantile EE with infantile spasms [53]. The gene *TBC1D24* has the most puzzling phenotypic variability. Recessive mutations were identified in a family with benign familial infantile myoclonic epilepsy [54], in a consanguineous family with focal epilepsy, intellectual disability, and cortical thickening [55], and in a family with severe myoclonic EE with dystonia and progressive neurodegeneration [56]. Finally, mutations seem to be an important cause of the rare DOORS syndrome, consisting of deafness, onychodystrophy, osteodystrophy, intellectual disability, and seizures [57]. The seizure types in individuals with *TBC1D24* mutations included generalized tonic–clonic, focal dyscognitive, or clonic seizures, and infantile spasms. Seizures and deafness were not consistent features.

TBC1D24 is a gene that binds GTPases such as ADP-ribosylation factor 6, a protein regulating dendritic branching, spine formation, and axonal elongation. The reason why some mutations cause DOORS syndrome and other mutations cause only epilepsy might depend on the way the mutations affect the interaction with different protein partners.

In summary, when dealing with patients with MMPSI, one should first screen for *KCNT1*, followed by the other reported genes. In consanguineous families, or in families with multiple affected sibs where recessive inheritance is suspected, screening for the three recessive genes should be prioritized.

Myoclonic Epilepsies (Including Myoclonic–Atonic Epilepsy and Dravet Syndrome) and *CHD2*

In the past year, *CHD2* was identified as a novel gene for EE using two different NGS techniques, whole-exome sequencing and a targeted gene panel. Ten patients with de novo *CHD2* mutations have been described to date [58•, 59••, 60••]. All patients had epilepsy onset between 6 months and 3 years of life. Seizure types were mostly generalized with a prominent myoclonic component, but also included tonic–clonic, absence, and atonic seizures. Several patients shared features with Dravet syndrome or myoclonic atonic epilepsy, and had been diagnosed as such. Cognitive outcome ranged from mild to severe intellectual disability, and some patients showed developmental delay prior to epilepsy onset. MRI was normal and EEG showed generalized (poly)spike wave complexes and/or multifocal discharges.

Both missense and truncating mutations have been described, and a loss-of-function mechanism has been proposed. A knockdown zebra fish model showed spontaneous seizures. *CHD2* encodes chromodomain-helicase-DNA-binding protein 2. Chromodomain-helicase-DNA-binding proteins are assumed to modify gene transcription by affecting chromatin structure through helicase function. It is not known how dysfunction of a gene with such a crucial function produces a purely neurological phenotype. Further studies will determine the role of chromatin remodelers in the

etiopathogenesis of EE, and will provide new avenues for epilepsy treatment.

Idiopathic Focal Epilepsy with Rolandic Spikes and *GRIN2A*

Idiopathic focal epilepsy with rolandic spikes is considered a spectrum that includes benign epilepsy with centrotemporal spikes (BECTS), Landau–Kleffner syndrome (LKS), and epilepsy with continuous spikes and waves during sleep (CSWS) [61]. BECTS, the most frequent of all epilepsies in childhood, manifests itself at school age by rare focal and mostly nocturnal motor seizures in otherwise normal children and spikes in the centrotemporal region on EEG. This frequent epilepsy syndrome remits by puberty, and treatment is most often not necessary. LKS and epilepsy with CSWS are more severe conditions, in which epileptic EEG abnormalities increase during sleep so that spike wave complexes occupy more than 85 % of non-REM sleep, and cognitive sequelae are the rule.

The genetics of these epilepsies is controversial. Family studies suggest that BECTS has a complex inheritance [62], and that centrotemporal spikes, the EEG hallmark of this disorder, are a marker of one of the BECTS genes with an autosomal dominant mode of inheritance with high but incomplete inheritance [61, 63]. For long, even less was known about the genetics of epilepsy with CSWS and LKS, until the recent simultaneous reports of three studies on this topic.

After the identification of microdeletions including the gene *GRIN2A* in patients with a peculiar phenotype associating developmental delay, dysmorphic features, and rolandic seizures [64], *GRIN2A* was sequenced in a series of patients affected by idiopathic focal epilepsies of various subtypes [10••]. Heterozygous mutations were identified in 27 of 359 individuals (7.5 %), and, more specifically, in 12 of 245 patients (4.9 %) with BECTS and in nine of 51 patients (17.6 %) with epilepsy with CSWS. Heterozygous *GRIN2A* deletions were found in 1 % of the cohort. In two parallel studies, *GRIN2A* mutations were found in 20 % of familial and sporadic cases of LKS, epilepsy with CSWS, or atypical rolandic epilepsy with verbal dysphasia or dyspraxia [12••], and in 9 % of individuals with an EE in the epilepsy–aphasia spectrum [11••]. A considerable interfamilial and intrafamilial phenotypic variability and incomplete penetrance with frequent asymptomatic carriers was seen in these studies. Although it seems that some mutations might act as risk factors rather than causal mutations, these studies clearly emphasize the important role of *GRIN2A* in the spectrum of rolandic epilepsy.

GRIN2A encodes the α_2 subunit of the NMDA glutamatergic receptor, and functional analysis of some of the missense mutations identified showed an increased activation of the channel [10••, 12••]. These findings may soon open up therapeutic possibilities.

Autosomal Dominant Focal Epilepsies and *DEPDC5*

Familial focal epilepsy with variable foci (FFEVF) is an autosomal dominant epilepsy in which various members of a same family exhibit seizures originating from different cortical regions. Seizure onset in the temporal or frontal lobe is most often seen. Affected individuals typically develop normally, although family members with intellectual disability, psychiatric disturbances, or autism spectrum disorders have been described [65]. Cerebral MRI studies are unremarkable. In a recent study, exome sequencing identified *DEPDC5* mutations in seven of eight large families with FFEVF, thereby establishing the gene as the major causal factor involved in this disorder [66••]. This was confirmed by a simultaneous study that identified *DEPDC5* mutations in three of five families with FFEVF [67••].

Both studies also identified mutations in *DEPDC5* in 12-27 % of smaller families with familial focal epilepsies, including small families with only frontal or temporal lobe epilepsy. Asymptomatic carriers are frequently present in families, and one de novo mutation was identified in a sporadic epilepsy patient with temporal lobe epilepsy. Future studies will determine the frequency of *DEPDC5* mutations in sporadic epilepsy patients with nonlesional focal epilepsies, an important patient population of the adult epilepsy clinic.

Both truncating and missense mutations are seen, and loss of function of DEPDC5 is thus the likely cause of the genesis of seizures. The exact function of the DEPDC5 protein, however, remains to be elucidated. An interaction with the mammalian target of rapamycin pathway, which is involved in cell-growth regulation, is suspected [68].

Conclusion

NGS technologies have tremendously increased the speed of gene discovery in monogenic epilepsies, enabling us to identify a genetic cause in an increasing proportion of patients. Some of the most important recent findings have been summarized in this article. Whereas ion channel genes were long considered to be the main players in genetic epilepsy, a growing number of non-ion-channel genes are now being implicated, especially in epilepsies associated with neurodevelopmental problems. It is exactly in the group of EE that most of the genetic discoveries were made in recent years, and this has had a great impact on our understanding of these disorders. The term “epileptic encephalopathy” (EE) reflects the idea that the epileptic activity itself contributes to the cognitive and behavioral impairment. In its revised version of the terminology in epilepsies, the International League Against Epilepsy acknowledged the fact that the term should be viewed as a concept and as a description of what is observed clinically, but that the actual source of the encephalopathy is usually unknown. It may be the product of

the underlying cause, the result of an epileptic process, or a combination of both [69]. Genetic knowledge has now shown us that probably very few patients have a "true" EE according to the literal definition of the term. De novo mutations in genes that are widely accepted to be a cause of EE, such as *STXBP1*, *SCN1A*, *CHD2*, and *SCN2A*, have now also been identified in individuals with intellectual disability or autism without seizures [28, 70, 71]. This clearly shows that mutations in these genes directly influence neurodevelopment, independently of seizure activity. This is also shown by the fact that some patients with mutations in EE genes show developmental delay prior to seizure onset, or that outcome does not necessarily correlate well with seizure severity. This does not mean that seizure activity does not play a role, and early control of seizures should remain the main goal. Nevertheless, future research should focus on the development of novel treatment strategies targeting the underlying cause rather than the symptom.

Lastly, NGS techniques increasingly confront us with the extent of genetic and phenotypic heterogeneity in epilepsies. Mutations in one specific gene can give rise to a broad spectrum of phenotypes, and conversely, several different genes are implicated in one specific epilepsy syndrome. Although specific clinical features might still direct the clinician in his or her choice of genetic tests, it can be difficult to directly identify the gene responsible in a specific individual. Genetic discoveries, therefore, support the evolution in clinical practice towards diagnostic screening using large targeted gene panels and eventually exome sequencing.

Compliance with Ethics Guidelines

Conflict of Interest Sarah Weckhuysen and Christian M. Korff declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Hesdorffer DC, Logroscino G, Benn EKT, Katri N, Cascino G, Hauser WA. Estimating risk for developing epilepsy: a population-based study in Rochester, Minnesota. Neurology. 2011;76:23–7.
2. Hildebrand MS, Dahl H-HM, Damiano JA, Smith RJH, Scheffer IE, Berkovic SF. Recent advances in the molecular genetics of epilepsy. J Med Genet. 2013;50:271–9.
3. Steinlein OK, Mulley JC, Propping P, Wallace RH, Phillips HA, Sutherland GR, et al. A missense mutation in the neuronal nicotinic acetylcholine receptor α4 subunit is associated with autosomal dominant nocturnal frontal lobe epilepsy. Nat Genet. 1995;11:201–3.
4. Wallace RH, Wang DW, Singh R, Scheffer IE, George AL, Phillips HA, et al. Febrile seizures and generalized epilepsy associated with a mutation in the Na^+-channel β1 subunit gene SCN1B. Nat Genet. 1998;19:366–70.
5. Escayg A, MacDonald BT, Meisler MH, Baulac S, Huberfeld G, An-Gourfinkel I, et al. Mutations of SCN1A, encoding a neuronal sodium channel, in two families with GEFS+ 2. Nat Genet. 2000;24:343–5.
6. Claes L, Del-Favero J, Ceulemans B, Lagae L, Van Broeckhoven C, De Jonghe P. De novo mutations in the sodium-channel gene SCN1A cause severe myoclonic epilepsy of infancy. Am J Hum Genet. 2001;68:1327–32.
7. Carranza Rojo D, Hamiwka L, McMahon JM, Dibbens LM, Arsov T, Suls A, et al. De novo SCN1A mutations in migrating partial seizures of infancy. Neurology. 2011;77:380–3.
8. •• Weckhuysen S, Mandelstam S, Suls A, Audenaert D, Deconinck T, Claes LRF, et al. KCNQ2 encephalopathy: emerging phenotype of a neonatal epileptic encephalopathy. Ann Neurol. 2012;71:15–25. *This is the first of several publications on the role of KCNQ2 in 10 % of patients with neonatal EE.*
9. Saitsu H, Kato M, Mizuguchi T, Hamada K, Osaka H, Tohyama J, et al. De novo mutations in the gene encoding STXBP1 (MUNC18-1) cause early infantile epileptic encephalopathy. Nat Genet. 2008;40:782–8.
10. •• Lemke JR, Lal D, Reinthaler EM, Steiner I, Nothnagel M, Alber M, et al. Mutations in GRIN2A predispose to idiopathic focal epilepsy with rolandic spikes. Nat Genet. 2013;45:1067–72. *This article and the articles by Carvill et al. [11] and Lesca et al. [12] are three concomitantly published studies on the first major gene to be identified in childhood epilepsies of the rolandic spectrum.*
11. •• Carvill GL, Regan BM, Yendle SC, O'Roak BJ, Lozovaya N, Bruneau N, et al. GRIN2A mutations cause epilepsy-aphasia spectrum disorders. Nat Genet. 2013;45:1073–6. *This article and the articles by Lemke et al. [10] and Lesca et al. [12] are three concomitantly published studies on the first major gene to be identified in childhood epilepsies of the rolandic spectrum.*
12. •• Lesca G, Rudolf G, Bruneau N, Lozovaya N, Labalme A, Boutry-Kryza N, et al. GRIN2A mutations in acquired epileptic aphasia and related childhood focal epilepsies and encephalopathies with speech and language dysfunction. Nat Genet. 2013;45:1061–6. *This article and the articles by Lemke et al. [10] and Carvill et al. [11] are three concomitantly published studies on the first major gene to be identified in childhood epilepsies of the rolandic spectrum.*
13. Weckhuysen S, Ivanovic V, Hendrickx R, Van Coster R, Hjalgrim H, Møller RS, et al. Extending the KCNQ2 encephalopathy spectrum: clinical and neuroimaging findings in 17 patients. Neurology. 2013;81:1697–703.
14. Kato M, Yamagata T, Kubota M, Arai H, Yamashita S, Nakagawa T, et al. Clinical spectrum of early onset epileptic encephalopathies caused by KCNQ2 mutation. Epilepsia. 2013;54:1282–7.
15. Milh M, Boutry-Kryza N, Sutera-Sardo J, Mignot C, Auvin S, Lacoste C, et al. Similar early characteristics but variable neurological outcome of patients with a de novo mutation of KCNQ2. Orphanet J Rare Dis. 2013;8:80.
16. Singh NA, Charlier C, Stauffer D, DuPont BR, Leach RJ, Melis R, et al. A novel potassium channel gene, KCNQ2, is mutated in an inherited epilepsy of newborns. Nat Genet. 1998;18:25–9.
17. Soldovieri MV, Miceli F, Bellini G, Coppola G, Pascotto A, Taglialatela M. Correlating the clinical and genetic features of benign familial neonatal seizures (BFNS) with the functional consequences of underlying mutations. Channels (Austin). 2007;1:228–33.
18. Orhan G, Bock M, Schepers D, Ilina EI, Reichel SN, Löffler H, et al. Dominant-negative effects of KCNQ2 mutations are

associated with epileptic encephalopathy. Ann Neurol. 2013. doi: 10.1002/ana.24080.
19. Miceli F, Soldovieri MV, Ambrosino P, Barrese V, Migliore M, Cilio MR, et al. Genotype-phenotype correlations in neonatal epilepsies caused by mutations in the voltage sensor of Kv7.2 potassium channel subunits. Proc Natl Acad Sci U S A. 2013;110:4386–91.
20. Heron SE, Crossland KM, Andermann E, Phillips HA, Hall AJ, Bleasel A, et al. Sodium-channel defects in benign familial neonatal-infantile seizures. Lancet. 2002;360:851–2.
21. Sugawara T, Tsurubuchi Y, Agarwala KL, Ito M, Fukuma G, Mazaki-Miyazaki E, et al. A missense mutation of the Na^+ channel α_{II} subunit gene $Na_v1.2$ in a patient with febrile and afebrile seizures causes channel dysfunction. Proc Natl Acad Sci U S A. 2001;98:6384–9.
22. Shi X, Yasumoto S, Nakagawa E, Fukasawa T, Uchiya S, Hirose S. Missense mutation of the sodium channel gene SCN2A causes Dravet syndrome. Brain Dev. 2009;31:758–62.
23. Nakamura K, Kato M, Osaka H, Yamashita S, Nakagawa E, Haginoya K, et al. Clinical spectrum of SCN2A mutations expanding to Ohtahara syndrome. Neurology. 2013;81:992–8.
24. Ogiwara I, Ito K, Sawaishi Y, Osaka H, Mazaki E, Inoue I, et al. De novo mutations of voltage-gated sodium channel α_{II} gene SCN2A in intractable epilepsies. Neurology. 2009;73:1046–53.
25. Touma M, Joshi M, Connolly MC, Grant PE, Hansen AR, Khwaja O, et al. Whole genome sequencing identifies SCN2A mutation in monozygotic twins with Ohtahara syndrome and unique neuropathologic findings. Epilepsia. 2013;54:e81–5.
26. Kamiya K, Kaneda M, Sugawara T, Mazaki E, Okamura N, Montal M, et al. A nonsense mutation of the sodium channel gene SCN2A in a patient with intractable epilepsy and mental decline. J Neurosci. 2004;24:2690–8.
27. De Ligt J, Willemsen MH, van Bon BWM, Kleefstra T, Yntema HG, Kroes T, et al. Diagnostic exome sequencing in persons with severe intellectual disability. N Engl J Med. 2012;367:1921–9.
28. Rauch A, Wieczorek D, Graf E, Wieland T, Endele S, Schwarzmayr T, et al. Range of genetic mutations associated with severe non-syndromic sporadic intellectual disability: an exome sequencing study. Lancet. 2012;380:1674–82.
29. Iossifov I, Ronemus M, Levy D, Wang Z, Hakker I, Rosenbaum J, et al. De novo gene disruptions in children on the autistic spectrum. Neuron. 2012;74:285–99.
30. Sanders SJ, Murtha MT, Gupta AR, Murdoch JD, Raubeson MJ, Willsey AJ, et al. De novo mutations revealed by whole-exome sequencing are strongly associated with autism. Nature. 2012;485:237–41.
31. Chen W-J, Lin Y, Xiong Z-Q, Wei W, Ni W, Tan G-H, et al. Exome sequencing identifies truncating mutations in PRRT2 that cause paroxysmal kinesigenic dyskinesia. Nat Genet. 2011;43:1252–5.
32. Heron SE, Grinton BE, Kivity S, Afawi Z, Zuberi SM, Hughes JN, et al. PRRT2 mutations cause benign familial infantile epilepsy and infantile convulsions with choreoathetosis syndrome. Am J Hum Genet. 2012;90:152–60.
33. Szepetowski P, Rochette J, Berquin P, Piussan C, Lathrop GM, Monaco AP. Familial infantile convulsions and paroxysmal choreoathetosis: a new neurological syndrome linked to the pericentromeric region of human chromosome 16. Am J Hum Genet. 1997;61:889–98.
34. Caraballo R, Pavek S, Lemainque A, Gastaldi M, Echenne B, Motte J, et al. Linkage of benign familial infantile convulsions to chromosome 16p12-q12 suggests allelism to the infantile convulsions and choreoathetosis syndrome. Am J Hum Genet. 2001;68:788–94.
35.• Heron SE, Dibbens LM. Role of PRRT2 in common paroxysmal neurological disorders: a gene with remarkable pleiotropy. J Med Genet. 2013;50:133–9. *This is a review article on both the genetic and the clinical aspects of mutations in PRRT2.*
36. Gardiner AR, Bhatia KP, Stamelou M, Dale RC, Kurian MA, Schneider SA, et al. PRRT2 gene mutations: from paroxysmal dyskinesia to episodic ataxia and hemiplegic migraine. Neurology. 2012;79:2115–21.
37. Marini C, Conti V, Mei D, Battaglia D, Lettori D, Losito E, et al. PRRT2 mutations in familial infantile seizures, paroxysmal dyskinesia, and hemiplegic migraine. Neurology. 2012;79:2109–14.
38. Cloarec R, Bruneau N, Rudolf G, Massacrier A, Salmi M, Bataillard M, et al. PRRT2 links infantile convulsions and paroxysmal dyskinesia with migraine. Neurology. 2012;79:2097–103.
39. Scheffer IE, Grinton BE, Heron SE, Kivity S, Afawi Z, Iona X, et al. PRRT2 phenotypic spectrum includes sporadic and fever-related infantile seizures. Neurology. 2012;79:1–5.
40. Djémié T, Weckhuysen S, Holmgren P, Hardies K, Van Dyck T, Hendrickx R, et al. PRRT2 mutations: exploring the phenotypical boundaries. J Neurol Neurosurg Psychiatry. 2014;85:462–5.
41. Labate A, Mumoli L, Annesi G. Homozygous c.649dupC mutation in PRRT2 worsens the BFIS/PKD phenotype with mental retardation, episodic ataxia, and absences. Epilepsia. 2012;53:e196–9.
42. Lee H-Y, Huang Y, Bruneau N, Roll P, Roberson EDO, Hermann M, et al. Mutations in the gene PRRT2 cause paroxysmal kinesigenic dyskinesia with infantile convulsions. Cell Rep. 2012;1:2–12.
43. Coppola G. Malignant migrating partial seizures in infancy: an epilepsy syndrome of unknown etiology. Epilepsia. 2009;50 Suppl 5:49–51.
44.•• Barcia G, Fleming MR, Deligniere A, Gazula V-R, Brown MR, Langouet M, et al. De novo gain-of-function KCNT1 channel mutations cause malignant migrating partial seizures of infancy. Nat Genet. 2012;44:1255–9. *This study was published simultaneously with that of Heron et al. [45]. Both illustrate the phenotypic heterogeneity of mutations in the novel gene KCNT1.*
45.•• Heron SE, Smith KR, Bahlo M, Nobili L, Kahana E, Licchetta L, et al. Missense mutations in the sodium-gated potassium channel gene KCNT1 cause severe autosomal dominant nocturnal frontal lobe epilepsy. Nat Genet. 2012;44:1188–90. *This study was published simultaneously with that of Barcia et al. [44]. Both illustrate the phenotypic heterogeneity of mutations in the novel gene KCNT1.*
46. Martin HC, Kim GE, Pagnamenta AT, Murakami Y, Carvill GL, Meyer E, et al. Clinical whole-genome sequencing in severe early-onset epilepsy reveals new genes and improves molecular diagnosis. Hum Mol Genet. 2014. doi:10.1093/hmg/ddu030.
47. Vanderver A, Simons C, Schmidt JL, Pearl PL, Bloom M, Lavenstein B, et al. Identification of a novel de novo p.Phe932Ile KCNT1 mutation in a patient with leukoencephalopathy and severe epilepsy. Pediatr Neurol. 2014;50:112–4.
48. Hirose S, Scheffer IE, Marini C, De Jonghe P, Andermann E, Goldman AM, et al. SCN1A testing for epilepsy: application in clinical practice. Epilepsia. 2013;54:946–52.
49. Poduri A, Heinzen EL, Chitsazzadeh V, Lasorsa FM, Elhosary PC, LaCoursiere CM, et al. SLC25A22 is a novel gene for migrating partial seizures in infancy. Ann Neurol. 2013;74:873–82.
50. Milh M, Falace A, Villeneuve N, Vanni N, Cacciagli P, Assereto S, et al. Novel compound heterozygous mutations in TBC1D24 cause familial malignant migrating partial seizures of infancy. Hum Mutat. 2013;34:869–72.
51. Poduri A, Chopra SS, Neilan EG, Elhosary PC, Kurian MA, Meyer E, et al. Homozygous PLCB1 deletion associated with malignant migrating partial seizures in infancy. Epilepsia. 2012;53:e146–50.
52. Molinari F, Kaminska A, Fiermonte G, Boddaert N, Raas-Rothschild A, Plouin P, et al. Mutations in the mitochondrial glutamate carrier SLC25A22 in neonatal epileptic encephalopathy with suppression bursts. Clin Genet. 2009;76:188–94.
53. Kurian MA, Meyer E, Vassallo G, Morgan NV, Prakash N, Pasha S, et al. Phospholipase C beta 1 deficiency is associated with early-onset epileptic encephalopathy. Brain. 2010;133:2964–70.

54. Falace A, Filipello F, La Padula V, Vanni N, Madia F, De Pietri Tonelli D, et al. TBC1D24, an ARF6-interacting protein, is mutated in familial infantile myoclonic epilepsy. Am J Hum Genet. 2010;87:365–70.
55. Corbett MA, Bahlo M, Jolly L, Afawi Z, Gardner AE, Oliver KL, et al. A focal epilepsy and intellectual disability syndrome is due to a mutation in TBC1D24. Am J Hum Genet. 2010;87:371–5.
56. Guven A, Tolun A. TBC1D24 truncating mutation resulting in severe neurodegeneration. J Med Genet. 2013;50:199–202.
57. Campeau PM, Kasperaviciute D, Lu JT, Burrage LC, Kim C, Hori M, et al. The genetic basis of DOORS syndrome: an exome-sequencing study. Lancet Neurol. 2014;13:44–58.
58.• Suls A, Jaehn JA, Kecskés A, Weber Y, Weckhuysen S, Craiu DC, et al. De novo loss-of-function mutations in CHD2 cause a fever-sensitive myoclonic epileptic encephalopathy sharing features with Dravet syndrome. Am J Hum Genet. 2013;93:967–75. *In this era of big genome data science, animal models are becoming increasingly important to prove the pathogenicity of detected variants. This study generated a zebra fish model to prove the involvement of the gene CHD2 in epilepsy.*
59.•• Carvill GL, Heavin SB, Yendle SC, McMahon JM, O'Roak BJ, Cook J, et al. Targeted resequencing in epileptic encephalopathies identifies de novo mutations in CHD2 and SYNGAP1. Nat Genet. 2013;45(7):825–30. *This article shows how the use of a targeted epilepsy panel in patients with EE can rapidly identify the underlying cause in 10 % of patients*.
60.•• Epi4K Consortium. Epilepsy Phenome/Genome Project. De novo mutations in epileptic encephalopathies. Nature. 2013;501:217–21. *This consortium study reports the results of trio exome sequencing in a cohort of 264 patients with infantile spasms or Lennox–Gastaut syndrome. The study illustrates the role of de novo mutations and the large genetic heterogeneity in EE*.
61. Rudolf G, Valenti MP, Hirsch E, Szepetowski P. From rolandic epilepsy to continuous spike-and-waves during sleep and Landau-Kleffner syndromes: insights into possible genetic factors. Epilepsia. 2009;50 Suppl 7:25–8.
62. Vears DF, Tsai M-H, Sadleir LG, Grinton BE, Lillywhite LM, Carney PW, et al. Clinical genetic studies in benign childhood epilepsy with centrotemporal spikes. Epilepsia. 2012;53:319–24.
63. Bali B, Kull LL, Strug LJ, Clarke T, Murphy PL, Akman CI, et al. Autosomal dominant inheritance of centrotemporal sharp waves in rolandic epilepsy families. Epilepsia. 2007;48:2266–72.
64. Reutlinger C, Helbig I, Gawelczyk B, Subero JIM, Tönnies H, Muhle H, et al. Deletions in 16p13 including GRIN2A in patients with intellectual disability, various dysmorphic features, and seizure disorders of the rolandic region. Epilepsia. 2010;51:1870–3.
65. Scheffer IE, Phillips HA, O'Brien CE, Saling MM, Wrennall JA, Wallace RH, et al. Familial partial epilepsy with variable foci: a new partial epilepsy syndrome with suggestion of linkage to chromosome 2. Ann Neurol. 1998;44:890–9.
66.•• Dibbens LM, de Vries B, Donatello S, Heron SE, Hodgson BL, Chintawar S, et al. Mutations in DEPDC5 cause familial focal epilepsy with variable foci. Nat Genet. 2013;45:546–51. *This article and the article by Ishida et al. [69] are two simultaneously published articles on the role of DEPDC5 focal epilepsies. This gene might become one of the more important genes to consider in the adult neurology practice where one is frequently confronted with patients with focal epilepsies of unknown origin*.
67.•• Ishida S, Picard F, Rudolf G, Noé E, Achaz G, Thomas P, et al. Mutations of DEPDC5 cause autosomal dominant focal epilepsies. Nat Genet. 2013;45:552–5. *This article and the article by Dibbens et al. [68] are two simultaneously published articles on the role of DEPDC5 focal epilepsies. This gene might become one of the more important genes to consider in the adult neurology practice where one is frequently confronted with patients with focal epilepsies of unknown origin*.
68. Bar-Peled L, Chantranupong L, Cherniack AD, Chen WW, Ottina KA, Grabiner BC, et al. A Tumor suppressor complex with GAP activity for the Rag GTPases that signal amino acid sufficiency to mTORC1. Science. 2013;340:1100–6.
69. Berg AT, Berkovic SF, Brodie MJ, Buchhalter J, Cross JH, van Emde Boas W, et al. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005–2009. Epilepsia. 2010;51:676–85.
70. Hamdan FF, Gauthier J, Dobrzeniecka S, Lortie A, Mottron L, Vanasse M, et al. Intellectual disability without epilepsy associated with STXBP1 disruption. Eur J Hum Genet. 2011;19:607–9.
71. O'Roak BJ, Deriziotis P, Lee C, Vives L, Schwartz JJ, Girirajan S, et al. Exome sequencing in sporadic autism spectrum disorders identifies severe de novo mutations. Nat Genet. 2011;43:585–9.