

Genetic Advances in Epilepsy

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Abstract

Approximately 40–70 % of all epilepsies are now estimated to have a genetic cause. Though most epilepsies are genetically complex, the past decade has seen an explosion of advances in genetic etiologies. Early gene discovery in epilepsy was limited to large families with milder, inherited monogenic epilepsies using linkage analysis. Newer techniques underlie the past decade's accelerated gene discovery, especially in noninherited, severe epileptic encephalopathies, and have reinforced the diverse role of cellular functions that may be affected. This review examines recently discovered epilepsy genes and discusses the importance of a genetic diagnosis in patient care.

Keywords

Genetics, epilepsy, mutations

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Significant advances in understanding the genetic mechanisms behind epilepsy have been made in the past 20 years, especially in the case of epileptic encephalopathies. Though approximately 20–30 % of epilepsies can be attributed to an obvious acquired etiology, such as stroke or traumatic brain injury,^{1,2} genetic factors are estimated to underlie 40–70 % of all epilepsies.^{3–5} The ultimate goal of human genetics research is to aid the development of disease-targeted treatment. Is this achievable in the field of epilepsy? We have known since the early 1930s that genetics play an important role in epilepsy. However, epilepsies are known to be genetically complex disorders for most patients, and not until the past decade have advances been made to unravel the genetics. This review discusses recent progress in epilepsy genetics, and *Table 1* summarizes the main syndromes and associated genes, including some additional syndromes otherwise beyond the scope of this text. We highlight the mechanistic insights gained by identification of epilepsy genes and discuss how a genetic diagnosis can influence patient treatment.

Monogenic epilepsies are interesting symptomatic epilepsies, with more than 300 genetic disorders described to date. These include ion and non-ion channel disorders in familial cases. These disorders started with the discovery of the first epilepsy gene, *CHRNA4*, in 1995.⁶ At that time, genetic discoveries were mostly restricted to large families having milder, inherited epilepsies using linkage analysis. This technique led to the discovery of the genes behind autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE)⁶ and genetic/generalized epilepsy with febrile seizures plus (GEFS+).⁷ However, linkage analysis is not sufficient to uncover *de novo* mutations responsible for severe epileptic encephalopathies. More recently, candidate gene screening, microarray techniques, and massive parallel

sequencing technology have been responsible for accelerated discovery of epilepsy genes.^{8,9}

Gene discovery has reinforced the complex nature of genetics in disease. A given genotype may be expressed as a range of phenotypes and severities. For example, a missense mutation in the *SCN1A* gene may result in the milder GEFS+ phenotype,^{7,10–12} whereas a loss of function mutation may result in severe myoclonic epilepsy of infancy (SMEI)/Dravet syndrome (DS).^{13–15} Conversely, myriad genotypes may be expressed in a similar phenotype. Culprit genes may encode proteins having as diverse roles in cellular signaling as receptors, transporters, neurotransmitter releasers, and transcription factors regulating neuronal migration/maturation, or those having more general roles in cellular metabolism.

Epileptic encephalopathies represent a spectrum of disorders in which seizures, often refractory, accompany global cognitive and developmental impairments. *KCNQ2* encephalopathy is characterized by seizures beginning in the first week of life.^{16,17} A *de novo* missense mutation in a voltage-gated potassium channel subunit, $K_v7.2$, leads to refractory seizures and a grossly abnormal EEG exhibiting multifocal epileptiform discharges or a burst suppression pattern. Although roughly two-thirds of patients can achieve seizure freedom some months to years after onset, they are developmentally delayed, with intellectual disabilities ranging from mild to profound, and have axial hypotonia, limb spasticity, and impaired visual tracking.

At the other end of the spectrum are autosomal dominant mutations in $K_v7.2$ or $K_v7.3$, linked with 60–70 % of cases of benign familial neonatal

epilepsy (BFNE).¹⁸ Like patients who have *KCNQ2* encephalopathy, BFNE patients have seizure onsets in the first week of life. Seizures are brief but can occur as many as 30 times daily and are characterized by a tonic component that evolves into autonomic and motor symptoms and, often, apnea. However, EEG and development are normal; seizures resolve a month to a year after onset. Many patients do not require antiepileptic therapy. These two very closely associated mutations are a prime example of the complexity of genetics in clinical practice.

Recently, next-generation sequencing has identified four *de novo* mutations in *KCNA2*, the gene encoding voltage-gated potassium channel $K_v1.2$, in six patients (one mutation occurred three times).¹⁹ Patients have epileptic encephalopathy consisting of both febrile and afebrile seizures, as well as mild to moderate intellectual disability and speech delay, with or without ataxia. Mutations resulted in either loss or gain of function, implicating both hyperexcitability and electrical silencing of the voltage-gated potassium channel as playing a role in neurodevelopmental disorders.

SCN2A mutations may be seen in patients who have benign neonatal and infantile epilepsy, which has onset ranging from birth up to 1 year old.²⁰ Additionally, *SCN2A* may be seen in patients who have benign neonatal and infantile epilepsy, which has a phenotype intermediate between BFNE and benign familial infantile epilepsy (BFIE). *SCN2A* mutations underlie 13 % of Ohtahara cases, a smaller percent of West syndrome cases, and, rarely, cases of GEFS+ or DS.^{11,21–25}

Recent studies by the Epi4K Consortium and Epilepsy Phenome/Genome Project of patients having two classic epileptic encephalopathy syndromes, infantile spasms or West syndrome and Lennox-Gastaut syndrome (LGS) found *de novo* mutations in 15 % of patients.^{8,9} In addition to genes having previously established associations with epileptic encephalopathy (*SCN1A*, *SCN2A*, *SCN8A*, *CDKL5*, *STXBP1*, *KCNQ2*, and *KCNT1*), the studies identified a significant excess of *de novo* mutations in *ALG13*,⁸ *GABRB3*,⁸ and *DNM1*.⁹ *ALG13* is an X-linked gene encoding a subunit of uridine diphosphate-*N*-acetylglucosamine transferase and had previously been reported in a female patient who had seizures and severe intellectual disability.⁸ *GABRB3* encodes a subunit on CNS ligand-gated chloride channels and has previously been implicated in epilepsy in Angelman's syndrome.²⁶ *DNM1* encodes dynamin 1, a GTPase expressed exclusively in brain that provides mechanical force to pinch off synaptic vesicles budding from the membrane. It is expressed during postnatal brain development, peaking during neurite and synapse formation, which may also account for findings of developmental delay with severe to profound intellectual disability, hypotonia, and absence of speech in the five patients who had the mutation.⁹ Overall, patients who had epileptic encephalopathies were found to carry more *de novo* mutations than controls.⁹

A recent study showed that 1 % of patients having epileptic encephalopathy and no previous genetic diagnosis were discovered to carry a mutation for *SCN8A*, which encodes $Na_v1.6$.²⁷ These individuals developed multiple seizure types, intellectual disability, and motor manifestations, such as hypotonia, dystonia, ataxia, and hyperreflexia.

Four non-consanguineous families that carry *CACNA1A* loss-of-function mutations have been recently described as having epileptic

Table 1: Epilepsy Syndromes and their Associated Genes

Syndrome	Gene
<i>KCNQ2</i> encephalopathy ¹⁶	<i>KCNQ2</i>
LGS, infantile spasms ^{8,9}	<i>SCN1A</i> , <i>SCN2A</i> , <i>SCN8A</i> , <i>CDKL5</i> , <i>STXBP1</i> , <i>KCNQ2</i> , <i>KCNT1</i> , <i>ALG13</i> , <i>GABRB3</i> , and <i>DNM1</i>
Other epileptic encephalopathies ^{19,27,28}	<i>KCNA2</i> , <i>SCN8A</i> , <i>CACNA1A</i>
Ohtahara syndrome ^{22,24}	<i>SCN2A</i> (13 % of patients)
MMPSI ¹⁷	<i>KCNT1</i> , <i>SCN1A</i> , <i>PLCB1</i> , <i>SCL25A22</i> , and <i>TBC1D24</i>
Paroxysmal nocturnal dyskinesia, BFIE, ICCA ^{17,29–31}	<i>PRRT2</i>
SMEI/DS ^{13–15}	<i>SCN1A</i> (~85 % of cases); also <i>SCN2A</i> , <i>SCN1B</i> , <i>SCN9A</i> , <i>GABRG2</i>
GEFS+ ^{7,10–12}	<i>SCN1A</i> (~10 % of cases), <i>SCN2A</i> , <i>SCN1B</i> , <i>GABRG2</i> , <i>GABRD</i>
<i>GLUT1</i> deficiency ⁴⁰	<i>GLUT1</i>
Pyridoxine-dependent epilepsy ⁴²	<i>ALDH7A1</i>
PMEs Unverricht–Lundborg disease/Baltic myoclonus ^{33,34}	<i>EPM1/CSTB</i>
Lafora body disease ³³	<i>EPM2A</i> (80 % of cases)
MERRF ³³	tRNA mutation in mitochondrial DNA
Unidentified PME ³²	<i>KCNK1</i>
Somatic mutations in cortical malformations ³⁷	<i>DCX1</i> , <i>LIS1</i> , <i>FLNA1</i> , <i>TUBB2B</i>
Somatic mutations in hemimegalencephaly ^{38,39}	<i>IK3CA</i> , <i>AKT3</i> , <i>MTOR</i>
Idiopathic focal epilepsy with Rolandic spikes (includes benign rolandic epilepsy, Landau–Kleffner syndrome, epilepsy with continuous spikes and waves during sleep) ^{45–47}	<i>GRIN2A</i>
Familial focal epilepsy with variable foci ^{48,49}	<i>DEPDC5</i>
ADNFLE ⁶	<i>CHRNA4</i>
BFNE ¹⁸	<i>KCNQ2</i> , <i>KCNQ3</i>
Benign neonatal and infantile epilepsy ²⁰	<i>SCN2A</i>
GGE ³⁵	Deletions at 15q13.3, 15q11.2, and 16p13.11 each account for 1 %

ADNFLE = autosomal dominant nocturnal frontal lobe epilepsy; BFIE = benign familial infantile epilepsy; BFNE = benign familial neonatal epilepsy; GEFS+ = genetic/generalized epilepsy with febrile seizures plus; GGE = genetic/idiopathic generalized epilepsies; ICCA = infantile convulsions with choreoathetosis; LGS = Lennox-Gastaut syndrome; MMPSI = malignant migrating partial seizures of infancy; MERRF = myoclonic epilepsy with ragged red fibers; PMEs = progressive myoclonic epilepsies; SMEI/DS = severe myoclonic epilepsy of infancy/dravet syndrome.

encephalopathies.²⁸ *CACNA1A* loss-of-function mutations classically cause episodic ataxia type 2 (EA2), familial hemiplegic migraine type 1 (*FHM1*), and spinocerebellar ataxia type 6 (*SCA6*). Affected family members suffered multiple seizure types, including both typical and atypical febrile seizures, generalized tonic-clonic seizures, absence seizures, and focal seizures, as well as learning difficulties, attention deficit hyperactivity disorder (ADHD), autism, developmental delay, intellectual disability, ataxia, and nystagmus.

Malignant migrating partial seizures of infancy (MMPSI) is a devastating epilepsy featuring multifocal seizures and progressive neurologic decline over the first 6 months of life. Five different genes, *KCNT1*, *SCN1A*, *PLCB1*, *SCL25A22*, and *TBC1D24*, have been associated with this syndrome.

Seizures become more frequent over the first year of life and may be nearly continuous for several days.¹⁷

PRRT2, which encodes an identically named protein that interacts with *SNAP25*, a mediator of synaptic vesicle release, is also expressed as a variety of phenotypes. It was initially associated with paroxysmal nocturnal dyskinesia but may also be seen in BFIE and infantile convulsions with choreoathetosis (ICCA). Nonsense, missense, frameshift, and splice site mutations can be responsible for any of these phenotypes.^{17,29–31}

The progressive myoclonic epilepsies (PMEs) are characterized by myoclonus, tonic–clonic seizures, ataxia, and progressive neurologic decline.^{32,33} PMEs include Unverricht–Lundborg disease (*EPM1*), Lafora body disease (*EPM2A*), myoclonic epilepsy with ragged red fibers (MERRF), and neuronal ceroid lipofuscinoses. Recently, a *de novo* mutation in *KCNC1* was identified in 16 out of 84 unrelated individuals who had unidentified PME.³² *KCNC1* encodes for a subunit of the K_v3 voltage-gated potassium channels. Many of these individuals had normal development with report of myoclonus between ages 6 and 14, with infrequent generalized tonic–clonic seizures. Myoclonus worsened into adolescence, eventually interfering with ambulation. About half the subjects had mild cognitive decline.

The vast majority (90–99 %) of patients having *EPM1* have a genetic mutation in *CSTB*, which encodes cystatin B. Patients with *EPM1* can have *CSTB* alleles with dodecamer repeats; longer repeats were found to have a modulating effect on the age of disease onset and severity of myoclonus in a Finnish population.³⁴

Copy number variants (CNVs), deletions or duplications of chromosomal regions, are found in both the healthy and the diseased genome and have emerged as an increasingly recognized factor predisposing to epilepsy. Additionally, patients having CNV with epilepsy are more likely to have developmental delay, intellectual disability, or autism spectrum disorder.³⁵ In addition, CNVs are responsible for 3 % of genetic/idiopathic generalized epilepsies (GGEs): Deletions at 15q13.3, 15q11.2, and 16p13.11 each account for 1 % of GGEs.^{35,36}

Although germline mutations may account for a large percent of epilepsy mutagenesis, postzygotic mutations and mosaicism can also cause divergent epilepsy phenotypes. Using next-generation sequencing techniques, disease-associated somatic mutations have been demonstrated in peripheral blood in patients who have subcortical band heterotopia (double cortex syndrome), pachygyria, and periventricular nodular heterotopia.³⁷ Mutations in *DCX1* and *LIS1* were associated with subcortical band heterotopia, *FLNA1* with periventricular nodular heterotopia, and *TUBB2B* with pachygyria. More recently, exome sequencing in patients with hemimegalencephaly who underwent hemispherectomy has demonstrated *de novo* somatic mutations in *IK3CA*, *AKT3*, and *MTOR* genes in 30 % of cases.^{38,39}

With the emerging picture of complexity in epilepsy and genetics, the clinician may be inclined to abandon gene testing altogether. However, some conditions warrant consideration of genetic diagnosis, for it may influence treatment. Diagnosis of BNFE may influence a decision to defer treatment. Genetic testing can identify inborn errors of metabolism such as *GLUT1* deficiency and pyridoxine-dependent epilepsy when successful therapy hinges on specific nutritional approaches (ketogenic diet and pyridoxine supplementation, respectively).^{5,40–42} Sodium channel blockers may exacerbate seizures in patients who have GEFS+ and DS.⁴³ More challenging, advances in genetics may illustrate the molecular basis for pharmacoresistance to specific medications in some patients and may help predict more effective alternatives. They may also help identify individuals at higher risk for sudden unexplained death in epilepsy (SUDEP): *KCNQ1*, in addition to encoding a voltage-gated potassium channel expressed in brain, also encodes a cardiac potassium channel that is the most common cause for longed QT syndrome.⁴⁴

It is likely that the next 5 years will see major developments in gene sequencing and analytics. The availability of inexpensive whole genome analysis in epilepsy will significantly affect diagnosis and management. The time is soon arriving for *idiopathic epilepsy* to disappear from our lexicon and for precision genetic diagnosis and therapeutics to replace uncertainty and tribulations. ■

- Hauser WA, Annegers JF, Kurland LT, Incidence of epilepsy and unprovoked seizures in Rochester, Minnesota: 1935–1984, *Epilepsia*, 1993;34:453–68.
- Jallon P, Loiseau P, Loiseau J, Newly diagnosed unprovoked epileptic seizures: presentation at diagnosis in CAROLE study, Coordination Active du Réseau Observatoire Longitudinal de l'Epilepsie, *Epilepsia*, 2001;42:464–75.
- Kjeldsen MJ, Corey LA, Christensen K, Friis ML, Epileptic seizures and syndromes in twins: the importance of genetic factors, *Epilepsy Res*, 2003;55:137–46.
- Helbig I, Scheffer IE, Mulley JC, Berkovic SF, Navigating the channels and beyond: unravelling the genetics of the epilepsies, *Lancet Neurol*, 2008;7:231–45.
- Guerrini R, Noebels J, How can advances in epilepsy genetics lead to better treatment and cures? In: *Issues in clinical epileptology: a view from the bench*, 309–17.
- Steinlein OK, Mulley JC, Propping P, et al., A missense mutation in the neuronal nicotinic acetylcholine receptor $\alpha 4$ subunit is associated with autosomal dominant nocturnal frontal lobe epilepsy, *Nat Genet*, 1995;11:201–3.
- Escayg A, MacDonald BT, Meisler MH, et al., Mutations of *SCN1A*, encoding a neuronal sodium channel, in two families with GEFS+, *Nat Genet*, 2000;24:343–5.
- Epi4K Consortium; Epilepsy Phenome/Genome Project, *De novo* mutations in epileptic encephalopathies, *Nature*, 2013;501:217–23.
- EuroEPINOMICS-RES Consortium; Epilepsy Phenome/Genome Project; Epi4K Consortium, *De novo* mutations in synaptic transmission genes including *DNM1* cause epileptic encephalopathies, *Am J Hum Genet*, 2014;95:360–70.
- Escayg A, Heils A, MacDonald BT, et al., A novel *SCN1A* mutation associated with generalized epilepsy with febrile seizures plus and prevalence of variants in patients with epilepsy, *Am J Hum Genet*, 2001;68:866–73.
- Sugawara T, Tsurubuchi Y, Agarwala KL, et al., A missense mutation of the Na⁺ channel α -II subunit gene Nav1.2 in a patient with febrile and afebrile seizures causes channel dysfunction, *Proc Natl Acad Sci U S A*, 2001;98:6384–9.
- Wallace RH, Scheffer IE, Barnett S, et al., Neuronal sodium-channel $\alpha 1$ -subunit mutations in generalized epilepsy with febrile seizures plus, *Am J Hum Genet*, 2001;68:859–65.
- Mulley JC, Scheffer IE, Petrou S, et al., *SCN1A* mutations and epilepsy, *Hum Mutat*, 2005;25:335–42.
- Fujiwara T, Clinical spectrum of mutations in *SCN1A* gene: severe myoclonic epilepsy in infancy and related epilepsies, *Epilepsy Res*, 2006;70:S223–30.
- Escayg A, Goldin AL, Sodium channel *SCN1A* and epilepsy: mutations and mechanisms, *Epilepsia*, 2010;51:1650–8.
- Weckhuysen S, Mandelstam S, Suls A, et al., *KCNQ2* encephalopathy: emerging phenotype of a neonatal epileptic encephalopathy, *Ann Neurol*, 2012;71:15–25.
- Weckhuysen S, Korff CM, Epilepsy: old syndromes, new genes, *Curr Neurol Neurosci Rep*, 2014;14:447–54.
- Singh NA, Charlier C, Stauffer D, et al., A novel potassium channel gene, *KCNQ2*, is mutated in an inherited epilepsy of newborns, *Nat Genet*, 1998;18:25–9.
- Syrbe S, Hedrich UBS, Riesch E, et al., *De novo* loss- or gain-of-function mutations in *KCNA2* cause epileptic encephalopathy, *Nat Genet*, 2015;47:393–9.
- Heron SE, Crossland KM, Andermann E, et al., Sodium-channel defects in benign familial neonatal-infantile seizures, *Lancet*, 2002;360:851–2.
- Shi X, Yasumoto S, Nakagawa E, et al., Missense mutation of the sodium channel gene *SCN2A* causes Dravet syndrome, *Brain Dev*, 2009;31:758–62.
- Nakamura K, Kato M, Osaka H, et al., Clinical spectrum of *SCN2A* mutations expanding to Ohtahara syndrome, *Neurology*, 2013;81:992–8.
- Ogiwara I, Ito K, Sawashi Y, et al., *De novo* mutations of voltage-gated sodium channel α II gene *SCN2A* in intractable epilepsies, *Neurology*, 2009;73:1046–53.
- Touma M, Joshi M, Connolly MC, et al., Whole genome sequencing identifies *SCN2A* mutation in monozygotic twins with Ohtahara syndrome and unique neuropathologic findings, *Epilepsia*, 2013;54:e81–5.
- Kamiya K, Kaneda M, Sugawara T, 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.
- Tanaka M, DeLorey TM, Delgado-Escueta A, Olsen RW, *GABRB3*, epilepsy, and neurodevelopment. In: Noebels JL, Avoli M, Rogawski MA, et al. (eds.), *Jasper's Basic Mechanisms of the Epilepsies*, 4th ed., Bethesda, MD: National Center for Biotechnology Information (US), 2012.
- Larsen J, Carvill GL, Gardella E, et al., The phenotypic spectrum of *SCN8A* encephalopathy, *Neurology*, 2015;84:480–9.
- Damaj L, Lupien-Mellieur A, Lortie A, et al., *CACNA1A* haploinsufficiency causes cognitive impairment, autism, and epileptic encephalopathy with mild cerebellar symptoms, *Europ J Hum Genet*, 2015 [Epub ahead of print].
- Chen W-J, Lin Y, Xiong Z-Q, et al., Exome sequencing identifies truncating mutations in *PRRT2* that cause paroxysmal kinesigenic dyskinesia, *Nat Genet*, 2011;43:1252–5.
- Heron SE, Grinton BE, Kivity S, et al., *PRRT2* mutations cause

- benign familial infantile epilepsy and infantile convulsions with choreoathetosis syndrome, *Am J Hum Genet*, 2012;90:152–60.
31. Szepietowski P, Rochette J, Berquin P, et al., 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.
 32. Muona M, Berkovic SF, Dibbens LM, et al. A recurrent *de novo* mutation in *KCNK1* causes progressive myoclonus epilepsy, *Nat Genet*, 2015;47:39–46.
 33. Delgado-Escueta AV, Ganesh S, Yamakawa K, Advances in the genetics of progressive myoclonus epilepsy, *Am J Med Genet*, 2001;106:129–38.
 34. Hyppönen J, Aikia M, Joensuu T, et al., Refining the phenotype of Unverricht–Lundborg disease (*EPM1*): a population-wide Finnish study, *Neurology*, 2015;84:1–8.
 35. Scheffer IE, Mefford HC, Beyond the single nucleotide variant in epilepsy genetics, *Nat Rev Neurol*, 2014;10:490–1.
 36. Scheffer IE, Epilepsy genetics revolutionizes clinical practice, *Neuropediatrics*, 2014;45:70–4.
 37. Jamuar SS, Lam A-T N, Kircher M, et al., Somatic mutations in cerebral cortical malformations, *New Eng J Med*, 2014;371:733–43.
 38. Lee JH, Huynh M, Silhavy JL, et al., De novo somatic mutations in components of the *PI3K-AKT3-mTOR* pathway cause hemimegalencephaly, *Nat Genet*, 2012;44:941–6.
 39. Poduri A, Evrony GD, Cai X, et al., Somatic activation of *AKT3* causes hemispheric developmental brain malformations, *Neuron*, 2012;74:41–8.
 40. Klepper J, *GLUT1* deficiency syndrome in clinical practice, *Epilepsy Res*, 2012;100:272–7.
 41. Hoffman GF, Schmitt B, Windfuhr M, et al., Pyridoxal 50-phosphate may be curative in early-onset epileptic encephalopathy, *J Inherit Metab Dis*, 2007;30:96–9.
 42. Mills PB, Struys E, Jakobs C, et al., Mutations in antiquitin in individuals with pyridoxine-dependent seizures, *Nat Med*, 2006;12:307–9.
 43. Brunklaus A, Ellis R, Reavey E, et al., Prognostic, clinical, and demographic features in *SCN1A* mutation-positive Dravet syndrome, *Brain*, 2012;135(Pt 8):2329–36.
 44. Goldman AM, Glasscock E, Yoo J, et al., Arrhythmia in heart and brain: *KCNQ1* mutations link epilepsy and sudden unexplained death, *Sci Transl Med*, 2009;1:2ra6.
 45. Lemke JR, Lal D, Reinthaler EM, et al., Mutations in *GRIN2A* predispose to idiopathic focal epilepsy with rolandic spikes, *Nat Genet*, 2013;45:1067–72.
 46. Carvill GL, Regan BM, Yendle SC, et al., *GRIN2A* mutations cause epilepsy–aphasia spectrum disorders, *Nat Genet*, 2013;45:1073–6.
 47. Lesca G, Rudolf G, Bruneau 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.
 48. Dibbens LM, de Vries B, Donatello S, et al., Mutations in *DEPDC5* cause familial focal epilepsy with variable foci, *Nat Genet*, 2013;45:546–51.
 49. Ishida S, Picard F, Rudolf G, et al., Mutations of *DEPDC5* cause autosomal dominant focal epilepsies, *Nat Genet*, 2013;45:552–5.