Epileptic Disord 2022; 24 (2): 221-228

Epileptic Disorders

ILAE Genetic Literacy Series: familial focal epilepsy syndromes

Samuel Gooley[1,2], Douglas E. Crompton[1,2], Samuel F. Berkovic[1], on behalf of the ILAE Genetics Literacy Taskforce*

[1] Epilepsy Research Centre, Department of Medicine, University of Melbourne, Austin Health, Heidelberg, Victoria 3084, Australia
[2] Department of Neurology, Northern Health, Epping, Victoria 3076, Australia

Received May 23, 2021; Accepted October 2, 2021

*Full list of Genetics Literacy Taskforce members: Helen Cross, UCL-Institute of Child Health, Great Ormond Street Hospital for Children, London & Young Epilepsy, Lingfield, UK
Peter De Jonghe, Neurogenetics Group, Department of Molecular Genetics, VIB, Laboratory of Neurogenetics, Institute Born-Bunge, University of Antwerp, and Division of Neurology, Antwerp University Hospital, Antwerp, Belgium
Ingo Helbig, Division of Neurology, The Children's Hospital of Philadelphia, Philadelphia, PA, USA and Department of Neuropediatrics, University Medical Centre Schleswig-Holstein, Christian-Albrechts-University, Kiel, Germany
Yuwu Jiang, Department of Pediatrics, Peking University First Hospital, Beijing, China
Daniel H Lowenstein, Department of Neurology, University of California, San Francisco, USA
Nigel CK Tan, Department of Neurology, National Neuroscience Institute, Singapore, Singapore

ABSTRACT

There are a number of familial focal epilepsy syndromes, each with distinct clinical characteristics. Here, we review the epilepsy phenotypes and the genetic architecture of these syndromes. Using an illustrative clinical case, we describe the important steps in making a diagnosis and ordering appropriate genetic tests. Our discussion on the genetics of the familial focal epilepsies will provide a framework for interpreting the results of genetic testing, and allow us to apply this information to patient management.

Key words: familial focal epilepsy, focal epilepsy genetics, *DEPDC5*, mTOR, *GRIN2A*, *LGI1*

Clinical scenario

A 22-year-old woman was referred to the neurology outpatient clinic for management of focal impaired awareness seizures. She described stereotyped events that begin with a rising epigastric sensation and a feeling of anxiety, followed by a period of impaired awareness. These events started three months earlier and were occurring approximately once a week. Her father has witnessed many of the events and reported that during each of them she would rub her fingers together repetitively and make chewing actions with her mouth. She does not respond to anyone during the episodes. They each last for approximately one minute, and afterwards she feels tired. Her EEG showed left temporal interictal spikes and her MRI brain was normal. Her father has a history of seizures from sleep, and her paternal uncle has epilepsy but no further details are known.

The clinical and electrophysiological evidence is convincing for temporal lobe epilepsy, and there appears to be a strong family history, so you wonder whether there may be an identifiable genetic cause for her focal epilepsy.

Questions

1. Which group of patients with focal epilepsy should have genetic testing?
2. Could this family have an autosomal dominant focal epilepsy syndrome?
3. Will finding a causative gene influence the management of your patient with focal epilepsy?

• **Correspondence:**
Samuel F. Berkovic
Epilepsy Research Centre, Level 2, Melbourne Brain Centre,
245 Burgundy St. Heidelberg, Victoria 3084, Australia
<s.berkovic@unimelb.edu.au>
<l.johnson@unimelb.edu.au>

doi:10.1684/epd.2021.1393

Genetic architecture of focal epilepsy

Focal epilepsies account for more than half of all cases of epilepsy. A genetic cause for non-acquired focal epilepsy was initially suggested by population studies and twin studies. Twin studies showed a higher concordance of mesial temporal lobe epilepsy in monozygotic twins when compared to dizygotic twins [1], and population studies have shown a 2.5-fold increased risk of focal epilepsy in first-degree relatives of probands with focal epilepsy when compared to the general population [2].

Recently, a number of familial focal epilepsy syndromes have been identified, leading to the discovery of many genes that are now known to cause focal epilepsy in familial cases. These discoveries have revealed a complex genetic architecture in the familial focal epilepsies that involves a wide range of clinical phenotypes, inheritance patterns and both locus and genetic heterogeneity.

We will discuss the clinical characteristics of each of the familial focal epilepsy syndromes, highlighting the importance of careful phenotyping to optimally ascertain the focal epilepsy characteristics in the patient and their relatives. We will discuss the genetics of these syndromes and the significance of making a genetic diagnosis. This will provide a framework to help us answer the questions raised by our case vignette. The learning objective for this paper maps to Learning Objective 1.2 (Genetic Testing) of the ILAE competency-based educational curriculum in epileptology [3].

Autosomal dominant sleep-related hypermotor epilepsy (ADSHE)

The first familial focal epilepsy to be recognized was ADSHE, previously known as autosomal dominant nocturnal frontal lobe epilepsy. ADSHE is characterized by seizures from sleep that usually begin in childhood and persist throughout adulthood. The seizures are typically brief tonic or hyperkinetic seizures that tend to occur in clusters shortly after falling asleep or before waking. Daytime attacks are rare. Auras are common and awareness is often preserved during the seizure [4, 5]. Most patients have a relatively benign course and respond well to carbamazepine. However, some people have a more severe phenotype, with drug resistance or co-morbid conditions, including psychiatric disorders and intellectual disability [6].

Variants in a number of genes have been shown to cause ADSHE including *CHRNA4*, *CHRNB2* and *CHRNA2*, which encode subunits of the nicotinic acetylcholine receptor. Mutations in these genes account for a minority of cases [7]. More recently, pathogenic variants in *DEPDC5* and *KCNT1* have also been shown to cause ADSHE [8-10].

Knowing the underlying genetic cause may help determine the likely course of ADSHE, and therefore guide patient counselling. For example, some missense variants in the *KCNT1* gene, which are known to cause both familial and sporadic cases of ADSHE, result in a more severe phenotype compared to ADSHE caused by variants in *CHRNA4* and *CHRNB2*. Variants in *KCNT1* result in an earlier age of onset, higher penetrance, co-morbid psychiatric symptoms and intellectual disability [10].

Autosomal dominant epilepsy with auditory features (ADEAF)

ADEAF is a familial focal epilepsy characterized by seizures that originate in the lateral temporal lobe, causing prominent auditory auras and, in some cases, receptive aphasia. The most commonly reported auditory symptoms are poorly formed sounds such as ringing or buzzing noises, but can include voices and even a sudden loss of surrounding noise [11-13]. Seizures typically begin in adolescence or early adulthood, and individuals can have focal aware seizures, focal impaired awareness seizures, and focal to bilateral tonic-clonic seizures. In some individuals, seizures may be triggered by sudden external sounds [14]. The interictal EEG is often normal but in some cases shows epileptiform discharges over the temporal region [14, 15]. Seizures tend to be well controlled on medication [11-13].

Like the other familial focal epilepsies, ADEAF is genetically heterogeneous. The most common gene associated with this condition is *LGI1* (*table 1*). Genetic testing can reveal a causative mutation in *LGI1* in 30-50% of families [12, 13]. Variants in the gene encoding for the protein, Reelin, (*RELN*) have been reported in a further 17% of families with ADEAF [16], but data curation by ClinGen in 2019 classified the claim for pathogenicity as "disputed" (https://search.clinicalgenome.org/kb/gene-validity/c654081c-5abd-4f86-a3f7-90d7f117b93d–2019-05-01T16:00:00).

Familial focal epilepsy with variable foci (FFEVF) and the GATOR1-related familial focal epilepsies

FFEVF is a familial syndrome characterized by multiple family members with focal epilepsy, where the focus of seizures can differ between family members, but remains constant in each individual.

▼ **Table 1.** Genes definitely implicated in familial focal epilepsy syndromes.

Familial focal epilepsy syndrome	Genes
Familial focal epilepsy with variable foci	*DEPDC5, NPRL2, NPRL3*
Autosomal dominant sleep-related hypermotor epilepsy	*DEPDC5, CHRNA4, CHRNA2, CHRNB2, NPRL2, NPRL3, KCNT1*
Autosomal dominant epilepsy with auditory features	*LGI1*
Familial mesial temporal lobe epilepsy	*DEPDC5* (but most unknown)
Familial neonatal epilepsy	*KCNQ2, KCNQ3*
Familial neonatal-infantile epilepsy	*SCN2A*
Familial infantile epilepsy	*PRRT2, SCN2A, SCN8A*

For example, a single family may have individuals who have temporal lobe epilepsy and other members of the same family who have frontal lobe or even parietal or occipital lobe epilepsy. The time of seizure onset varies from infancy to adult life and the severity can vary significantly between family members, some of whom may have co-morbid neuro-psychiatric conditions [17-20].

FFEVF has been recognized in a number of large family pedigrees displaying autosomal dominant inheritance with a penetrance of ~60% [19]. These large families with FFEVF are rare, but they are important, as they led to the discovery of variants in *DEPDC5* as the usual cause. Causative variants in *DEPDC5* account for ~80% of families with FFEVF [19], and since the discovery of *DEPDC5* in these large families, this gene has been shown to be a cause of many cases of familial focal epilepsy where there may be only two or a few family members affected. These smaller families can present as either familial temporal lobe epilepsy, familial frontal lobe epilepsy or as a mixture of different focal epilepsies in the same family [9, 19-22].

Variants in *DEPDC5* have also been found to account for ~13% of families with ADSHE [9], and a similar percentage of families with ADEAF [21]. In addition to the non-lesional focal epilepsies, variants in *DEPDC5* have been shown to cause malformation-associated focal epilepsies, including focal cortical dysplasia and subcortical grey matter heterotopia; within a family certain affected individuals may have a demonstrated malformation and others may have a normal MRI [20, 23]. Finally, the importance of variants in *DEPDC5* in focal epilepsies is underscored as it emerged as the leading candidate gene in genome-wide assessments of variants in the Epi4K consortium study where family pairs of focal epilepsy were assessed [25], and the Epi25 collaborative where family history was not an entry criterion [26].

The protein encoded by *DEPDC5* is a member of the GATOR1 complex, which inhibits the mammalian target of rapamycin (mTOR) pathway, which is important for cell growth and proliferation. Dysregulation of this pathway is known to be important in other conditions such as tuberous sclerosis and certain types of cancer [27]. Pathogenic variants in the *NPRL2* and *NPRL3* genes, which encode a different part of the GATOR1 complex, have also been shown to cause familial focal epilepsies, including familial cases of focal cortical dysplasia [28, 29]. Whilst patients with mutations in GATOR1 genes have a wide range of focal epilepsy phenotypes, they share a common biological mechanism for their focal epilepsy, which raises the possibility of a common treatment targeted at this molecular pathway.

Familial mesial temporal lobe epilepsy (FMTLE)

FMTLE was first recognized in twins, where its strong genetic basis was demonstrated by high concordance in monozygotic twins [1]. FMTLE has since been described in a large number of families. It typically begins in adolescence or early adulthood and is characterized by focal aware seizures with prominent psychic or autonomic features, sometimes with focal impaired awareness seizures, which infrequently progress to bilateral tonic-clonic seizures. Bilateral tonic-clonic seizures are typically in sleep. These focal seizures most commonly manifest as either intense *déjà vu*, dream-like states, stereotyped flashbacks, fear, epigastric discomfort, flushing or olfactory sensations [30, 31]. In contrast to ADEAF, the molecular basis of this form of inherited temporal lobe epilepsy remains largely undiscovered, with the exception of some small pedigrees with *DEPDC5* variants (see above). Nonetheless, the familial form of mesial temporal lobe

epilepsy (MTLE) represents a large proportion of inherited focal epilepsies, and has been shown to account for ~20% of new diagnoses of non-lesional MTLE when detailed interviewing of family members is undertaken [32]. Without direct questioning of relatives, this syndrome typically goes unrecognized as many affected individuals only experience focal aware seizures with *déjà vu* which are perceived as 'physiological' experiences. Clinical genetic analysis suggests complex inheritance rather than an autosomal dominant pattern, which is rare in FMLTE [30].
This form of FMTLE highlights the usefulness of collecting a detailed history from family members, as making this diagnosis is important for patient counselling, including reassurance that, in most cases, it is a relatively benign syndrome that responds well to medication. There are, however, families with a more severe form of FMTLE who tend to have an earlier age at onset, antecedent febrile seizures, hippocampal sclerosis, and drug resistance [33].

Other familial focal epilepsies

Familial neonatal epilepsy (FNE), familial neonatal-infantile epilepsy (FNIE) and familial infantile epilepsy (FIE) are autosomal dominant focal epilepsy syndromes. In FNE, seizures begin in the first week of life and remit by 4-6 months of age [34]. In contrast, for FIE, seizures usually begin around six months of age and remit within one year of onset and remarkably, some develop paroxysmal dyskinesias in mid-childhood [35, 36]. In FNIE seizures begin at any time within the first six months in different family members [37]. All three syndromes are characterized by brief focal seizures, including focal motor seizures, which can alternate sides from seizure to seizure. Other focal seizure types occur, including focal impaired awareness seizures and focal to bilateral tonic-clonic seizures. Children are developmentally normal, and only a minority have epilepsy in later life.
Pathogenic variants in *KCNQ2* are the most common cause of FNE [38] whereas variants in *PRRT2* are the most common cause of FIE [39], and variants in *SCN2A* usually cause FNIE [37]. Causative variants in *KCNQ3* and *SCN8A* have also been described [40, 41].
Other familial focal epilepsies have been described such as partial epilepsy with pericentral spikes [42], but they are rare and the genetic etiology is not well understood. The genetics of childhood epilepsy with centro-temporal spikes (previously benign rolandic epilepsy) remains unclear, but rare dominant forms with speech dyspraxia associated with *GRIN2A* pathogeneic variants [43] and recessive families with exercise-induced dystonia and variants in *TBC1D24* have been described [44].

Returning to our case

Returning to our case vignette, it is quite possible that our patient has a familial focal epilepsy syndrome, and the differential diagnoses include a familial temporal lobe epilepsy or FFEVF. At the next clinic appointment you were able to clarify that the patient's father has infrequent seizures from sleep and occasional seizures from wakefulness. His EEG demonstrated interictal frontal lobe epileptiform activity. You were able to speak to the patient's paternal uncle with epilepsy and he described having infrequent focal impaired awareness seizures, which were often preceded by a prominent feeling of intense *déjà vu*. With this more detailed family history, it was confirmed that there are two family members with temporal lobe epilepsy and one with likely frontal lobe epilepsy. Your patient was keen to know the cause of her epilepsy, and you explained that there are genes that are known to cause mixed focal epilepsies in families, and that testing for these genes can be done efficiently with an epilepsy gene panel.

Genetic testing

A number of studies have evaluated the diagnostic yield of genetic testing in familial focal epilepsies. When genetic testing is done on patients with focal epilepsy and a family history of epilepsy, the chance of finding a causative variant is currently somewhere in the order of 15% [25, 45-48]. This is significantly higher than the yield in sporadic cases of focal epilepsy, where genetic testing reveals a causative variant in less than 1% of cases [25, 28, 49].
If we look at a specific type of focal epilepsy, for example, focal epilepsy with auditory features, we see that genetic testing in familial cases reveals a causative variant in 30-50% of cases [12, 13], compared to around 2% of sporadic cases [50-52].
The genetic architecture of the focal epilepsies is not yet fully understood, but many genetic causes are now known, and in familial cases, can be efficiently tested for. Careful phenotyping is important as we know that if a patient has sleep-related hypermotor epilepsy, and a family history of the same, then genetic testing may reveal causative variants in *CHRNA4, CHRNB2, CHRNA2, KCNT1* or *DEPDC5*. In contrast, as we see in our case, if there is a family history of a mixture of different types of focal epilepsy then the chance of finding a causative variant in *DEPDC5, NPRL2* or *NPRL3* is quite high (*table 1*).

Practical management considerations

Identifying a familial focal epilepsy syndrome has implications for patient counselling and can also

potentially alter management strategies. If an autosomal dominant syndrome such as ADSHE, ADEAF or FFEVF is identified then we can say with some confidence that the likelihood of the trait being passed on to the children of an affected individual is in the realm of ~30-40%, based on the incomplete penetrance of these conditions. In an alternative scenario where a patient has a focal epilepsy but no autosomal dominant familial syndrome is identified, we could, based on population studies, quote a ~3% risk of epilepsy in their first degree relatives [2]. Moreover, these autosomal dominant syndromes are often relatively benign epilepsies which are well controlled on monotherapy. However, as outlined above, some of the familial focal epilepsies such as ADSHE caused by pathogenic variants in *KNCT1* have a worse prognosis, and therefore knowing the specific genetic etiology may allow for more accurate counselling.

In the relatively common group of patients with a familial focal epilepsy due to mutations in genes related to GATOR1 and the mTOR pathway, there are a number of potential management implications for genetic counselling and for therapeutics. In genetic counselling, it is important to appreciate the heterogeneity of *DEPDC5* epilepsies and neuropsychiatric phenotypes: even parents with less severe epilepsies carry some risk of having severely affected children.

Therapies that target GATOR1 are already in use in the treatment of other mTORopathies such as tuberous sclerosis and some cancers. It is possible that these therapies, or future precision medicines targeted at other parts of the mTOR pathway could be used to treat the wide variety of epilepsy phenotypes caused by a disruption in this common molecular pathway. Moreover, the discovery that mutations in GATOR1 genes can cause focal epilepsy due to focal cortical dysplasia raises the possibility of curative surgical resection in these patients, as with careful neuroimaging, subtle lesions may be found in these patients who were previously thought to have lesion-negative focal epilepsy.

Thus, the identification of a familial focal epilepsy syndrome is important for patient counselling, and can lead to the identification of a specific gene mutation which offers the prospect of more accurate prognostication and the possibility of a mutation-specific management strategy.

Case resolution

In our case, the epilepsy gene panel revealed a pathogenic missense variant in *DEPDC5*. Our patient was keen to know the risk of epilepsy in her children, and was counselled that they have a ~30-40% chance of having a focal epilepsy, though the exact type and severity is not possible to predict. We explained that this estimate is based on studies of other families who have multiple members with focal epilepsy and a *DEPDC5* variant that displayed an autosomal dominant pattern of inheritance with ~60% penetrance [9, 19-22], which means each family member has a 50% chance of inheriting the variant and a ~60% chance that the variant would result in a focal epilepsy (60% x 50% = 30-40%.) We explained that these figures were approximations only, as the genetic architecture of familial epilepsies is not yet fully understood. She was referred to a clinical genetics service for further counselling. She was kept on carbamazepine and remained seizure-free.

As more genes are discovered in focal epilepsy, the diagnostic yield of genetic testing will increase, and more molecular targets for precision medicine will be discovered. Thus, knowing that our patient harbors a mutation in *DEPDC5* means that she and her family may benefit from future therapeutic options tailored to their genotype. ■

Key points

- Each of the familial focal epilepsy syndromes has distinct clinical characteristics.
- Careful phenotyping can allow identification of a familial syndrome, which can inform us about the likely inheritance patterns, and significantly increase the diagnostic yield of genetic tests.
- A number of different genes are known to cause familial focal epilepsies (summarized in table 1.)
- Mutations in *DEPDC5, NPRL2* and *NPRL3* result in dysregulation of the mTOR pathway and are the most common cause of familial focal epilepsy. These genes can be efficiently tested for with epilepsy gene panels.
- Knowing the genetic cause of your patient's epilepsy can provide valuable prognostic information.

Disclosures.
None of the authors have any conflicts of interest to disclose.

References

1. Berkovic SF, McIntosh A, Howell RA, Mitchell A, Sheffield LJ, Hopper JL. Familial temporal lobe epilepsy: a common disorder identified in twins. *Ann Neurol* 1996; 40: 227-35.

2. Peljto AL, Barker-Cummings C, Vasoli VM, Leibson CL, Hauser WA, Buchhalter JR, *et al*. Familial risk of epilepsy: a population-based study. *Brain* 2014; 137: 795-805.

3. Blumcke I, Arzimanoglou A, Beniczky S, Wiebe S. Roadmap for a competency-based educational curriculum in epileptology: report of the Epilepsy Education Task Force of the International League Against Epilepsy. *Epileptic Disord* 2019; 21: 129-40.

4. Scheffer IE, Bhatia KP, Lopes-Cendes I, Fish DR, Marsden CD, Andermann E, *et al*. Autosomal dominant nocturnal frontal lobe epilepsy. A distinctive clinical disorder. *Brain* 1995; 118: 61-73.

5. Tinuper P, Bisulli F, Cross JH, Hesdorffer D, Kahane P, Nobili L, *et al*. Definition and diagnostic criteria of sleep-related hypermotor epilepsy. *Neurology* 2016; 86: 1834-42.

6. Derry CP, Heron SE, Phillips F, Howell S, MacMahon J, Phillips HA, *et al*. Severe autosomal dominant nocturnal frontal lobe epilepsy associated with psychiatric disorders and intellectual disability. *Epilepsia* 2008; 49: 2125-9.

7. Combi R, Dalpra L, Tenchini ML, Ferini-Strambi L. Autosomal dominant nocturnal frontal lobe epilepsy – a critical overview. *J Neurol* 2004; 251: 923-34.

8. Steinlein OK. Genetic heterogeneity in familial nocturnal frontal lobe epilepsy. *Prog Brain Res* 2014; 213: 1-15.

9. Picard F, Makrythanasis P, Navarro V, Ishida S, de Bellescize J, Ville D, *et al*. DEPDC5 mutations in families presenting as autosomal dominant nocturnal frontal lobe epilepsy. *Neurology* 2014; 82: 2101-6.

10. 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.

11. Ottman R, Risch N, Hauser WA, Pedley TA, Lee JH, Barker-Cummings C, *et al*. Localization of a gene for partial epilepsy to chromosome 10q. *Nat Genet* 1995; 10: 56-60.

12. Ottman R, Winawer MR, Kalachikov S, Barker-Cummings C, Gilliam TC, Pedley T, *et al*. LGI1 mutations in autosomal dominant partial epilepsy with auditory features. *Neurology* 2004; 62: 1120-6.

13. Michelucci R, Poza JJ, Sofia V, de Feo MR, Binelli S, Bisulli F, *et al*. Autosomal dominant lateral temporal epilepsy: clinical spectrum, new epitempin mutations, and genetic heterogeneity in seven European families. *Epilepsia* 2003; 44: 1289-97.

14. Winawer M, Ottman R, Hauser A, Pedley T. Autosomal dominant partial epilepsy with auditory features: defining the phenotype. *Neurology* 2000; 54: 2173-6.

15. Brodtkorb E, Steinlein OK, Gu W, Nakken KO, Fischer C. Familial temporal lobe epilepsy with aphasic seizures and linkage to chromosome 10q22-q24. *Epilepsia* 2002; 43: 228-35.

16. Dazzo E, Fanciulli M, Serioli E, Minervini G, Pulitano P, Binelli S, *et al*. Heterozygous reelin mutations cause autosomal-dominant lateral temporal epilepsy. *Am J Hum Genet* 2015; 96: 992-1000.

17. 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.

18. Berkovic SF, Serratosa JM, Phillips HA, Xiong L, Andermann E, Díaz-Otero F, *et al*. Familial partial epilepsy with variable foci: clinical features and linkage to chromosome 22q12. *Epilepsia* 2004; 45: 1054-60.

19. 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(5): 546-51.

20. 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.

21. Pippucci T, Licchetta L, Baldassari S, Palombo F, Menghi V, D'Aurizio R, *et al*. Epilepsy with auditory features: a heterogeneous clinico-molecular disease. *Neurol Genetics* 2015; 1: e5.

22. Martin C, Meloche C, Rioux MF, Nguyen DK, Carmant L, Andermann E, *et al*. A recurrent mutation in DEPDC5 predisposes to focal epilepsies in the French-Canadian population. *Clin Genet* 2014; 86: 570-4.

23. Baulac S, Ishida S, Marsan E, Miquel C, Biraben A, Nguyen DK, *et al*. Familial focal epilepsy with focal cortical dysplasia due to DEPDC5 mutations. *Ann Neurol* 2015; 77: 675-83.

24. Scheffer IE, Heron SE, Regan BM, Mandelstam S, Crompton DE, Hodgson BL, *et al*. Mutations in mammalian target of rapamycin regulator DEPDC5 cause focal epilepsy with brain malformations. *Ann Neurol* 2014; 75: 782-7.

25. Epi4K consortium; Epilepsy Phenome/Genome Project. Ultra-rare genetic variation in common epilepsies: a case-control sequencing study. *Lancet Neurol* 2017; 16: 135-43.

26. Epi25 Collaborative. Ultra-rare genetic variation in the epilepsies: a whole-exome sequencing study of 17606 individuals. *Am J Hum Genet* 2019; 105: 267-82.

27. 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.

28. Ricos MG, Hodgson BL, Pippucci T, Saidin A, Ong YS, Heron SE, *et al*. Mutations in the mammalian target of rapamycin pathway regulators NPRL2 and NPRL3 cause focal epilepsy. *Ann Neurol* 2016; 79: 120-31.

29. Weckhuysen S, Marsan E, Lambrecq V, Marchal C, Morin-Brureau M, An-Gourfinkel I, *et al*. Involvement of GATOR complex genes in familial focal epilepsies and focal cortical dysplasia. *Epilepsia* 2016; 57: 994-1003.

30. Crompton DE, Scheffer IE, Taylor I, Cook MJ, McKelvie PA, Vears DF, *et al*. Familial mesial temporal lobe epilepsy: a benign epilepsy syndrome showing complex inheritance. *Brain* 2010; 133: 3221-31.

31. Striano P, Gambardella A, Coppola A, Di Bonaventura C, Bovo G, Diani E, *et al*. Familial mesial temporal lobe epilepsy (FMTLE): a clinical and genetic study of 15 Italian families. *J Neurol* 2008; 255: 16-23.

32. Perucca P, Crompton DE, Bellows ST, McIntosh AM, Kalincik T, Newton MR, *et al*. Familial mesial temporal lobe epilepsy and the borderland of *déjà vu*. *Ann Neurol* 2017; 82: 166-76.

33. Cendes F, Lopes-Cendes I, Andermann E, Andermann F. Familial temporal lobe epilepsy: a clinically heterogeneous syndrome. *Neurology* 1998; 50: 554-7.

34. Ronen GM, Rosales TO, Connolly M, Anderson VE, Leppert M. Seizure characteristics in chromosome 20 benign familial neonatal convulsions. *Neurology* 1993; 43: 1355-60.

35. Vigevano F, Fusco L, Di Capua M, Ricci S, Sebastianelli R, Lucchini P. Benign infantile familial convulsions. *Eur J Pediatr* 1992; 151: 608-12.

36. Caraballo RH, Cersósimo RO, Amartino H, Szepetowski P, Fejerman N. Benign familial infantile seizures: further delineation of the syndrome. *J Child Neurol* 2002; 17: 696-9.

37. Berkovic SF, Heron SE, Giordano L, Marini C, Guerrini R, Kaplan RE, *et al*. Benign familial neonatal-infantile seizures: characterization of a new sodium channelopathy. *Ann Neurol* 2004; 55: 550-7.

38. 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.

39. 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.

40. Charlier C, Singh NA, Ryan SG, Lewis TB, Reus BE, Leach RJ, Leppert M. A pore mutation in a novel KQT-like potassium channel gene in an idiopathic epilepsy family. *Nat Genet* 1998; 18: 53-5.

41. Gardella E, Becker F, Møller RS, Schubert J, Lemke JR, Larsen LH, *et al*. Benign infantile seizures and paroxysmal dyskinesia caused by an SCN8A mutation. *Ann Neurol* 2016; 79: 428-36.

42. Kinton L, Johnson MR, Smith SJ, Farrell F, Stevens J, Rance JB, *et al*. Partial epilepsy with pericentral spikes: a new familial epilepsy syndrome with evidence for linkage to chromosome 4p15. *Ann Neurol* 2002; 51: 740-9.

43. 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.

44. Lüthy K, Mei D, Fischer B, De Fusco M, Swerts J, Paesmans J, *et al*. TBC1D24-TLDc-related epilepsy exercise-induced dystonia: rescue by antioxidants in a disease model. *Brain* 2019; 142: 2319-35.

45. Perucca P, Scheffer IE, Harvey AS, James PA, Lunke S, Thorne N, *et al*. Real-world utility of whole exome sequencing with targeted gene analysis for focal epilepsy. *Epilepsy Res* 2017; 131: 1-8.

46. Helbig KL, Farwell Hagman KD, Shinde DN, Mroske C, Powis Z, Li S, *et al*. Diagnostic exome sequencing provides a molecular diagnosis for a significant proportion of patients with epilepsy. *Genet Med* 2016; 18: 898-905.

47. Møller RS, Larsen LH, Johannesen KM, Talvik I, Talvik T, Vaher U, *et al*. Gene panel testing in epileptic encephalopathies and familial epilepsies. *Mol Syndromol* 2016; 7: 210-9.

48. Oates S, Tang S, Rosch R, Lear R, Hughes EF, Williams RE, *et al*. Incorporating epilepsy genetics into clinical practice: a 360 degrees evaluation. *NPJ Genom Med* 2018; 3: 13.

49. Hildebrand MS, Myers CT, Carvill GL, Regan BM, Damiano JA, Mullen SA, *et al*. A targeted resequencing gene panel for focal epilepsy. *Neurology* 2016; 86: 1605-12.

50. Bisulli F, Tinuper P, Avoni P, Striano P, Striano S, d'Orsi G, *et al*. Idiopathic partial epilepsy with auditory features (IPEAF): a clinical and genetic study of 53 sporadic cases. *Brain* 2004; 127: 1343-52.

51. Bisulli F, Tinuper P, Scudellaro E, Naldi I, Bagattin A, Avoni P, *et al*. A *de novo* LGI1 mutation in sporadic partial epilepsy with auditory features. *Ann Neurol* 2004; 56: 455-6.

52. Michelucci R, Mecarelli O, Bovo G, Bisulli F, Testoni S, Striano P, *et al*. A de novo LGI1 mutation causing idiopathic partial epilepsy with telephone-induced seizures. *Neurology* 2007; 68: 2150-1.

TEST YOURSELF

(1) In familial focal epilepsy syndromes:

A. Accurate identification of the familial focal epilepsy syndrome rarely helps to provide accurate information for genetic counselling

B. The majority of affected patients develop refractory epilepsy

C. Patients with familial focal epilepsy with variable foci who have causative variants in *DEPDC5* may have cortical malformations

D. It is important to identify familial mesial TLE (FMTLE) as the syndrome as 80% of patients with FMTLE have causative variants in *CHRNB2*

(2) In families with autosomal dominant sleep-related hypermotor epilepsy (ADSHE), in which gene might causative variants be found?

A. *CHRNA4*
B. *GRIN2A*
C. *CSTB*
D. *SLC2A1*

(3) In familial focal epilepsy with variable foci (FFEVF):

A. Affected family members have generalized polyspikes on their EEGs
B. There is an autosomal dominant inheritance pattern with a penetrance of ~60%
C. The majority present by six years of age
D. Causative variants in *DEPDC5* are seen in ~15-20% of affected families

Also, try our online MCQs at http://www.geneticliteracy.info/GL-test3.

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com.