



Updates on the diagnostic evaluation, genotype–phenotype correlation, and treatments of genetic epilepsies

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Purpose of review

This article reviews the latest publications in genetic epilepsies, with an eye on publications that have had a translational impact. This review is both timely and relevant as translational discoveries in genetic epilepsies are becoming so frequent that it is difficult for the general pediatrician and even the general child neurologist to keep up.

Recent findings

We divide these publications from 2021 and 2022 into three categories: diagnostic testing, genotype–phenotype correlation, and therapies. We also summarize ongoing and upcoming clinical trials.

Summary

Two meta-analyses and systematic reviews suggest that exome and genome sequencing offer higher diagnostic yield than gene panels. Genotype–phenotype correlation studies continue to increase our knowledge of the clinical evolution of genetic epilepsy syndromes, particularly with regards to sudden death, auditory dysfunction, neonatal presentation, and magnetoencephalographic manifestations. Pyridoxine supplementation may be helpful in seizure management for various genetic epilepsies. There has been interest in using the neurosteroid ganaxolone for various genetic epilepsy syndromes, with clear efficacy in certain trials. Triheptanoin for epilepsy secondary to glucose transporter 1 (*GLUT1*) deficiency syndrome is not clearly effective but further studies will be needed.

Keywords

ganaxolone, genetic epilepsies, genotype–phenotype correlation, ketogenic diet, pyridoxine

INTRODUCTION

The subject of genetic epilepsies is rapidly evolving, with new insights being published monthly on the cause, semiology, and treatments of this large subclass of epilepsy. Keeping up with this literature is demanding for a general child neurologist, not to mention a general pediatrician. To help clinicians stay abreast of the latest findings, several journals have published updated summaries of the mechanistic, diagnostic, or therapeutic innovations in genetic epilepsy [1^{*,2*}]. In this review, we make a concerted effort to focus on the publications of the last 2 years in this area. After an initial PubMed search of the term ‘genetic epilepsy’, and further restricting publications to a timeframe of December 2020 to June 2022, 32 salient articles were retained for their unique contributions to the field, a sub-selection of which are discussed in this review. These contributions fall into one of three categories, which make up this review: diagnostic testing,

genotype–phenotype correlation, and therapies. New gene discovery, while a very important and thriving area of genetic epilepsy, would require a separate review on account of the large number of genes that are newly associated with epilepsy. We conclude this review with an overview of ongoing and upcoming clinical trials in genetic epilepsy.

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KEY POINTS

- Pyridoxine supplementation is helpful in seizure management for PDE-ALDH7A1 (in conjunction with lysine reduction therapy) and IGD-related epilepsy.
- There has been interest in using the neurosteroid ganaxolone for PCDH19-related epilepsy, CDKL5-related epilepsy, tuberous sclerosis complex-related epilepsy, and for refractory epilepsy generally.
- Genotype–phenotype correlation studies continue to increase our knowledge of the clinical evolution of genetic epilepsy syndromes.
- Two meta-analyses and systematic reviews suggest that exome and genome sequencing offer higher diagnostic yield than gene panels.

DIAGNOSTIC TESTING

The ideal approach to genetic sequencing for epilepsy remains an area of active research. Previous research had suggested a 20% aggregate diagnostic yield for next-generation sequencing (NGS), which includes targeted gene panels, whole-exome sequencing (WES), and whole-genome sequencing (WGS). In the past 2 years, two large meta-analyses and systematic reviews have further clarified the diagnostic yield for each type of NGS.

A meta-analysis and systematic review of 103 genetic studies for autism, intellectual disability, and epilepsy, including 32 331 individuals, revealed a 24% diagnostic yield for epilepsy [3]. The yield increased further in individuals with intellectual disability (27.9%) and early-onset seizures (36.8%). Exome sequencing (36 studies) had a higher yield than gene panel sequencing (73 studies) but this was not a statistically significant result. The diagnostic yield in the neonatal/infantile period was 29.3% compared with 14.7% in childhood [3].

A systemic evidence review (SER) evaluated 154 studies of diagnostic yield in epilepsy [4[■]]. They were included in a meta-analysis of diagnostic yield for WES, WGS, multigene panel (MGP), comparative genomic hybridization (CGH)/chromosomal microarray (CMA). The overall diagnostic yield was 17% but ranged as high as 48% for WGS and 24% for WES and as low as 9% of CGH/CMA. The only factors significantly associated with increased yield were the presence of developmental and epileptic encephalopathy (DEE) and/or the presence of neurodevelopmental comorbidities [4[■]].

From these two meta-analyses, it appears clear that genome and exome sequencing have higher diagnostic yields than gene panels, especially in patients with DEE and neurodevelopmental comorbidities.

GENOTYPE–PHENOTYPE CORRELATION

Identifying a pathogenic mutation is often very helpful to clinicians, but in some cases, the wide phenotypic spectrum associated with a gene variant leads to uncertainty about the clinical evolution of the associated genetic epilepsy syndrome. For example, pathogenic mutations in *SCN1A* are the most common cause of genetic epilepsy and lead to a wide phenotypic spectrum of epilepsy, ranging from Dravet syndrome (drug-resistant epilepsy and intellectual disability) to febrile seizure susceptibility, such as in generalized epilepsy with febrile seizures plus (GEFS+). A predictive model based on the *SCN1A* variant would help clinicians anticipate the evolution of the disease. A retrospective multicenter cohort study of 1018 patients with *SCN1A*-positive Dravet syndrome and GEFS+ evaluated the utility of age at seizure onset and developed a *SCN1A* genetic score for the purpose of predicting the clinical evolution (i.e. Dravet syndrome versus other GEFS+ phenotypes) [5[■]]. The authors relied on a training cohort to derive several prediction models, which were in turn validated with two independent blinded cohorts. A high *SCN1A* genetic score and young age at onset were independently associated with Dravet syndrome versus GEFS+ [area under the curve (AUC) 0.89] [5[■]]. This approach to prediction is innovative and one would hope that this will become a standard approach for all genes associated with a broad phenotypic spectrum.

As genetic epilepsy syndromes are rare, multicenter collaborations are needed to capture a sufficiently large number of patients. These larger cohorts lead to a much better genotype–phenotype characterization of these syndromes. In the past 2 years, several single-center and multicentric studies have generated new insights into the electrographic and phenotypic spectrum of the following genetic epilepsies: PIGS-associated early-onset developmental and epileptic encephalopathy [6], Angelman syndrome [7], *LAMA-2*-related muscular dystrophy [8], Mowat–Wilson syndrome [9], neurofibromatosis type 1 [10], *CLCN4*-related epilepsy [11], Poirier–Bienvenu syndrome [12], and familial cortical myoclonic tremor with epilepsy type 1 [13].

Although the aforementioned studies describe the electrographic and clinical features of a particular genetic epilepsy, other studies take the reverse approach of describing genetic epilepsy syndromes as a whole in terms of a single clinical feature, such as magnetoencephalography (MEG) phenotype [14[■]], auditory phoneme discrimination [15[■]], autonomic dysfunction [16[■]], and neonatal presentation [17[■]].

MEG has emerged as a complementary modality for epilepsy evaluation. Its utility in understanding genetic epilepsy is an area of ongoing investigation.

A prospective, cross-sectional study of MEG data from patients with genetic generalized epilepsy (GGE) compared with their siblings and to controls showed that patients with GGE ($n=25$) demonstrated increased functional connectivity and power compared with controls [14[■]]. The patients' siblings had levels of functional connectivity and power that fell between the level of the patients and controls. This finding suggests that metrics of brain waves are likely related to genetic factors rather than to active epilepsy or to the treatments of epilepsy [14[■]]. The use of MEG continues to grow and may become an element of the characterization of genetic epilepsy going forward.

Epilepsy comes with associated risks such as a sudden death in epilepsy (SUDEP) and, in certain cases, developmental delays. Sudden unexpected death in epilepsy (SUDEP) is defined as sudden death in a patient with epilepsy. Death can happen with or without evidence for a preceding seizure, and there should be no evidence of other disease, status epilepticus, injury, or drowning preceding the death. Rates of SUDEP appear to be more elevated in several genetic epilepsy syndromes (such as those related to *SCN1A*, *SCN1B*, *SCN8A*, *SCN2A*, *GNB5*, *KCNA1*, and *DEPDC5*) compared with nongenetic epilepsy, which may be related to genetic variants in ion channel genes that promote cardiac dysrhythmias. For a thorough review of the risk of SUDEP in genetic epilepsy and its association with autonomic dysfunction, we recommend the review by Sahly *et al.* [16[■]].

Landau–Kleffner, and to a lesser degree benign epilepsy with centrotemporal spikes (BECTS), are both associated with disorders of language and auditory processing [15[■]]. A recent publication sought to answer the question of whether epilepsy is also associated with auditory dysfunction in GEFS+ by studying how central auditory processing (CAP) – the decoding of sound waves from the outer ear to the auditory cortex – and associated phonological disorders is impacted by the presence of epilepsy [15[■]]. This case–control study found that patients with GEFS+ have significantly more frequent difficulties with articulation and auditory discrimination of phonemes, compared with healthy, nonepileptic control patients [15[■]]. The authors suggest a variety of mechanisms to account for these findings but no single genetic explanation. Screening patients with GEFS+ for speech and auditory disorders will be important for prevention of dyslexia and literacy problems.

Finding clinical and electrographic markers of genetic causes of neonatal seizure, as compared with acquired causes such as stroke or hypoxic–ischemic encephalopathy (HIE), is an important goal in neonatal epilepsy. A multicentric, international study of 20 neonates with genetic epilepsy (*KCNQ2*, *KCNQ3*,

SCN2A, *KCNT1*, *PRRT2*, *BRAT1*) compared with 40 neonates with acute provoked seizures showed that all neonates with genetic epilepsy had either tonic or myoclonic seizures [17[■]]. In comparison, the neonates with acute, provoked seizures had either electrographic-only or clonic seizures. Time to first seizure was longer for neonates with genetic epilepsies (median 60 h) compared with neonates with provoked seizures (median 15 h) [17[■]].

THERAPIES

Ketogenic diet

The ketogenic diet is a well tolerated and effective treatment for various forms of refractory epilepsy. Its use in mitochondrial disease, which manifests with epilepsy, appears beneficial as the diet leads to decreased oxidative stress through ketone production. It is indicated in pyruvate dehydrogenase deficiency but contraindicated in patients with fatty acid oxidation disorders and pyruvate carboxylase deficiency. A systematic review of ketogenic diet in mitochondrial diet-related epilepsy identified 20 cases (14 pediatric) across a single clinical trial and 15 case reports [18[■]]. Ketogenic diet led to seizure control in seven out of eight patients, which was too low a number to justify any recommendations for or against ketogenic diet in mitochondrial diet [18[■]].

Pyridoxine supplementation

Pyridoxine-dependent epilepsy from aminoadipic semi-aldehyde dehydrogenase deficiency (PDE-ALDH7A1) is associated with intellectual developmental disability (IDD), despite pyridoxine treatment. Lysine reduction therapies (LRT), with the goal of lowering putatively neurotoxic metabolites, are associated with better cognitive outcomes. The timing of treatment appears to have an impact on the neurodevelopmental outcomes of this genetic epilepsy syndrome. A retrospective, multicenter cohort study evaluated the timing of pyridoxine monotherapy compared with pyridoxine with adjunct LRT on neurodevelopmental outcomes [19]. Study authors used the international PDE registry to identify patients with confirmed PDE-ALDH7A1 with at least one sibling with the same disease but with a different age of initial treatment. Primary endpoints were standardized and clinically assessed neurodevelopmental outcomes over several domains. The majority of the siblings who received early treatment on pyridoxine monotherapy performed better than their late-treated siblings in the domain of fine motor skills. Of the siblings who were given early treatment, those

who were on pyridoxine and adjunct LRT performed the best in several neurodevelopmental domains. The important upshot of this study is that early treatment with pyridoxine in combination with LRT has the highest probability of resulting in better neurodevelopmental outcomes [19].

Pyridoxine treatment is well established for pyridoxine-deficient epilepsy. Recent work suggests that it may also be valuable for epilepsy caused by glycosylphosphatidylinositol deficiency (IGD). A prospective open-label multicenter pilot study of patients with IGD enrolled nine patients who received oral pyridoxine at high-dose for 1 year, along with their previous treatments [20[■]]. Six of nine patients experienced seizures, and all of them had developmental delay. With this treatment, seizure frequency decreased by 50% in three patients and up to 90% in one patient [20[■]]. There was no worsening of seizures and there were no adverse side-effects. Further studies are needed to see if pyridoxine should be included in the arsenal of treatments for IGD-related seizures.

Sodium channel blockade

A promising area of genetic epilepsy is the assessment of antiepileptic medications for particular genetic epilepsy syndromes. Examples include the use of cannabidiol for Dravet syndrome [21] and the use of everolimus for tuberous sclerosis [22]. A recent example of this kind of work is a multicenter, retrospective observational study of patients with CDKL5 epilepsy who were treated with a variety of sodium channel blockers (SCB) [23[■]]. Six patients out of 19 with epilepsy (31%) were responders to SCBs (more than 50% reduction), but three patients had significant worsening of seizure frequency (i.e. nonresponders). This study suggests that a subset of patients with CDKL5-related epilepsy may be strong responders to SCB but further studies are needed [23[■]].

While on the topic of sodium channel blockade in genetic epilepsy, we would do well to refer back to the previously mentioned study of neonatal presentation of seizures. In that study, of the 14 patients with genetic epilepsy who had tonic seizures, sodium channel blockers were effective in 13 out of those 14 neonates. This finding suggests that sodium channel blockade ought to be considered earlier in the algorithmic management of neonatal epilepsy, if the seizure semiology is tonic [17[■]].

Ganaxolone and triheptanoin

CDKL5 deficiency disorder (CDD) is an X-linked developmental and epileptic encephalopathy that is often treatment refractory. In an open-label,

phase 2 trial that included patients with CDD, ganaxolone – a neuroactive steroid – was effective in reducing seizure frequency [24]. In a double-blind randomized placebo-controlled phase 3 trial over eight countries, patients with CDD were randomly assigned 1:1 to either enteral adjunctive ganaxolone or an equivalent adjunctive placebo after a 6-week prospective baseline period [25[■]]. Patients were eligible for the study if they had at least 16 major motor seizures per 28-day period in each 4-week period of an 8-week historical period. In this study of 101 patients, the median percentage change over a 28-day period of major motor seizures was –30.7% in the ganaxolone group and –6.9% in the placebo group. Treatment-emergent adverse events and serious adverse events were comparable between the two arms of the study. The authors concluded that ganaxolone significantly reduced the frequency of CDD-associated seizures compared with placebo and was relatively well tolerated, suggested a potential treatment benefit of this drug in this condition. Its long-term potential benefit is being evaluated in the ongoing open-label phase of this trial. This trial was sponsored by Marinus Pharmaceuticals, which is also sponsoring a phase 3 clinical trial called RAISE to test the efficacy of ganaxolone for refractory status epilepticus [25[■]].

Glucose transporter 1 deficiency syndrome (GLUT1DS) is a devastating seizure syndrome with developmental delay. There is no cure, and treatments include the ketogenic diet, glucose, and ASMs. The ketogenic diet is difficult to tolerate for many patients and as a result, there has been a need for alternative therapies that, like the ketogenic diet, can promote ketone body formation as an alternative energy source for the brain. Triheptanoin has been discussed for several years as a possible therapy for GLUT1DS as it is a medium-chain triglyceride approved in the United States in 2020 as a source of calories for the pediatric and adult long-chain fatty acid oxidation disorders. As it is metabolized, triheptanoin goes on to produce C4 and C5 ketone bodies that would serve as a fuel source to the brain [26[■]].

In a randomized, double-blind, placebo-controlled trial of triheptanoin, patients with GLUT1DS, greater than 1 year old and not on a ketogenic diet, were randomized 3:1 to triheptanoin or placebo after a 6-week baseline period [26[■]]. They were given triheptanoin titrated to 35% of total daily calories over a 2-week period and then underwent an 8-week placebo-controlled period before moving to an open-label period. In this cohort of 36 patients (about half children, the other half adolescents and adults), there was a median 12.6% reduction in overall seizure frequency in the triheptanoin arm relative to baseline and a 13.5% difference relative to placebo, without

statistical significance. However, in the small subset of patients with absence seizures only, there was a median 62.2% reduction in seizure frequency in the triheptanoin arm relative to baseline. There was only one patient with absence seizures in the control group so no comparison could be made between the triheptanoin arm and the control arm. There were no statistically significant differences in seizure frequency and no serious adverse events. It should be noted that the study was funded by Ultragenyx Pharmaceutical Inc. The authors concluded that triheptanoin did not significantly reduce seizure frequency in patients with GLUT1DS who are not on the ketogenic diet [26[¶]].

Clinical trials

One-hundred studies were identified using the search term ‘genetic epilepsy’ (including individual terms ‘genetics’ and ‘epilepsy’) to query the clinicaltrials.gov database. We draw attention to the following:

- (1) study of the genetic basis of Ohtahara syndrome (Clinical Trials identifier NCT01858285)
- (2) study of the genetics of neuronal migration disorders (NCT00041600)
- (3) study to predict postneonatal epilepsy (NCT05361070)
- (4) study of population pharmacokinetics of anti-epileptics in children (NCT03196466)
- (5) the BIOJUME study, which is seeking to identify the genetic cause of juvenile myoclonic epilepsy (NCT03400371)
- (6) the TSC-STEPS study to establish the safety and efficacy of early sirolimus in epilepsy from tuberous sclerosis complex (NCT05104983)
- (7) study of the long-term safety of fenfluramine hydrochloride for Dravet syndrome and Lennox–Gastaut syndrome (NCT03936777)
- (8) the MIT-E study of vatiquinone in patients with mitochondrial disease with refractory epilepsy (NCT04378075)
- (9) study of adjunctive ganaxolone in patients with tuberous sclerosis complex-related epilepsy (NCT05323734)
- (10) study of soticlestat as an add-on for Dravet syndrome and Lennox–Gastaut syndrome (NCT05163314)

CONCLUSION

The last 2 years have seen tremendous advances in genetic epilepsy. We have reviewed studies from that time period that have contributed to our

understanding of diagnostic modalities, genotype–phenotype correlation, and therapies for genetic epilepsies. We anticipate that the next few years will continue to see explosive growth in these areas, including immense progress in epileptic gene discovery.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

1. Guerrini R, Balestrini S, Wirrell EC, Walker MC. Monogenic epilepsies: ■ disease mechanisms, clinical phenotypes, and targeted therapies. *Neurology* 2021; 97:817–831.

A comprehensive review of the monogenic epilepsies with their phenotypes and targeted treatments. This article is an excellent introduction to the subject.

2. Zimmern V, Minassian B, Korff C. A review of targeted therapies for mono- ■ genic epilepsy syndromes. *Front Neurol* 2022; 13:1–13.

A summary of the targeted therapies for monogenic epilepsy syndromes, organized by the degree of evidence supporting the use of each therapy.

3. Stefanski A, Calle-López Y, Leu C, *et al.* Clinical sequencing yield in epilepsy, autism spectrum disorder, and intellectual disability: a systematic review and meta-analysis. *Epilepsia (Series 4)* 2021; 62:143–151.

4. Sheidley BR, Malinowski J, Bergner AL, *et al.* Genetic testing for the ■ epilepsies: a systematic review. *Epilepsia (Series 4)* 2022; 63:375–387.

Stefanski *et al.* and Sheidley *et al.* offer complementary insights into the diagnostic yields of various modalities of NGS for genetic epilepsies. Their works suggest that the yield is higher in exome and genome sequencing than with targeted panels.

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14. Stier C, Elshahabi A, Li Hegner Y, *et al.* Heritability of magnetoencephalography phenotypes among patients with genetic generalized epilepsy and their siblings. *Neurology* 2021; 97:64.

An important publication that relies on MEG to characterize the genetically inherited aspects of brain waves and suggests a role for MEG for future characterization of genetic epilepsies.

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A helpful contribution that adds various genetic disorders (qualifying as GEFS+) to the list of epilepsies that can lead to auditory and language disorders.

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- A helpful review of the risk of SUDEP in genetic epilepsies, summarizing the last decades of research in this area.

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While it could be argued that the triheptanoin dose in this trial was under-dosed, it remains an important contribution to our understanding of this possible treatment for GLUT1DS.