Epilepsy Benchmarks Area I: Understanding the Causes of the Epilepsies and Epilepsy-Related Neurologic, Psychiatric, and Somatic Conditions

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Abstract

The 2014 NINDS Benchmarks for Epilepsy Research included area I: Understand the causes of the epilepsies and epilepsy-related neurologic, psychiatric, and somatic conditions. In preparation for the 2020 Curing Epilepsies Conference, where the Benchmarks will be revised, this review will cover scientific progress toward that Benchmark, with emphasize on studies since 2016.

Keywords

causes of the epilepsies, causes of epilepsy, what causes seizures, epilepsy benchmarks, NINDS Benchmarks for Epilepsy Research, epilepsy comorbidities, progress in epilepsy research

Introductory Vignette by Lizbeth Carmichael. Epilepsy, Depression, and SUDEP—A Parent's Perspective

My son John developed epilepsy in his late teens, and despite medications, his seizures remained severe and uncontrolled. John was a talented and creative musician and a caring and thoughtful brother and son. He had many friends, and he desperately wanted an independent life. As John's epilepsy progressed, he also experienced declining mental health. John, who was normally a very peaceful individual, had periods of severe irritability and rage. He also became very anxious at

times, and this was a sign of an impending seizure. John heard voices and developed paranoia, hallucinations, and depression. Our family was told to see specialists, but we found that the communication and coordination of care between epileptologists and mental health professionals was impossible, even when he was hospitalized and referrals were made. Ultimately, his mental health issues were not understood or addressed and contributed significantly to his decline. John died of sudden unexpected death in epilepsy (SUDEP) in 2012. Our family's wish is that those around John had been more attuned to the mental health comorbidities that he was experiencing, and that his medical issues were jointly managed as the outcome for him might have been different.

Significant comorbidities often accompany epilepsy and can be more debilitating than the seizures themselves. A better understanding of the underlying mechanisms of epilepsy-associated comorbidities and appropriate clinical care is critical for increased quality of life for those impacted by epilepsy and their families.

Lizbeth Carmichael. Forever John's Mom. Citizens United for Research in Epilepsy (CURE).

Introduction

In this review, we provide an update on preclinical and clinical advances into our understanding of the many etiologies of the epilepsies, as well as progress in assigning etiology to epilepsy-related neuropsychiatric and somatic comorbidities. Since the most recent summary in this area,[1] expansion in our knowledge of epilepsy genetics and autoimmune epilepsies has continued to result in fewer individuals being labeled with epilepsy of unknown etiology. With the advent of next-generation sequencing technologies, the number of "epilepsy genes" continues to expand. Assigning a causative role to such genes requires verification in not only larger cohorts with statistical rigor but also a number of criteria that take into account normal variation, determination of how a genetic change leads to altered molecular function, and the demonstration of an epilepsy or epilepsy-related phenotype in genetically manipulated model organisms.[2] Similar considerations apply for autoimmune epilepsies, for which the relative epileptogenic effects of T-cell infiltration and circulating antibodies continue to be clarified.

Preclinical models of genetic, autoimmune, and brain injury-related epilepsies have been essential to advance our knowledge into upstream and downstream cellular and neurophysiological perturbations that may promote hypersynchrony and the transition to the ictal state. It is only with this type of knowledge that we will be able to better inform treatment of epilepsy related to these types of epilepsy. Incomplete penetrance and variable phenotypes in both humans and animal models strongly implicate genetic modifiers of susceptibility, which need to be identified and validated so as to appreciate mechanisms by which epilepsy may be therapeutically modulated.

In parallel with efforts to address the causes of epilepsy and epileptogenesis, there has been an expansion in efforts designed to unravel the genesis of epilepsy's various psychiatric comorbidities. Generally, these are etiologically related to broad network dysfunction that may be secondary to the underlying epileptogenic lesion (genetic, structural, or unknown) and actively modulated by the burden of ongoing seizures (if present) and antiseizure medications. Animal models of monogenic epilepsies provide the most tractable route to assigning etiology to epilepsy-associated comorbidities, albeit with some limitations in the ability to assess psychiatric comorbidities in various models. Incorporating optogenetic and chemogenetic strategies in these models affords the ability to definitively test whether specific network abnormalities affect seizure risk or impact limbic function or cognitive function or both.

We conclude our review with a set of general recommendations for future research into the causes of epilepsy spectrum disorders that will guide our understanding into epilepsy prevention (area II), treatment options (area III), and the adverse consequences of seizures themselves (area IV).

Key Advances in Area I

Epilepsy Genetics

Advances in our understanding of the genetics of the epilepsies have continued to accrue since the last Benchmarks update and have been reviewed in several excellent publications.[3-6] Many new variants associated with epilepsy are identified as "de novo dominant," meaning that they are present in the heterozygous state in sporadically affected individuals. At a cellular level, these genes encode proteins that display a broad range of functions that extend well beyond ion channels, including cell adhesion (eg, *PCDH19*), DNA binding and chromatin remodeling (eg, *CHD2*), and neurotransmitter release (eg, *STXBP1*).[7] The importance of genetic etiologies in focal epilepsy in particular has become even more clear, with the involvement of *DEPDC5* and associated GATOR1-complex mTOR repressors in epileptogenic cortical malformations being notable examples.[8]

De novo postzygotic (somatic) mutation has been increasingly recognized to play a role in focal epilepsy, largely involving the mTOR pathway in the pathogenesis of lesional epilepsies such as focal cortical dysplasia and hemimegalencephaly, with a majority of cases explained by this mechanism.[9-11] Extending the discovery of somatic mutation to a new pathway and, interestingly, to both focal cortical dysplasia (type I) and nonlesional focal epilepsy was a report on mosaic variants in the gene *SLC35A2*, which encodes an UDP-galactose transporter previously associated in nonmosaic form with developmental and epileptic encephalopathy.[12] The discovery of these 2 distinct pathways may point to very different targeted therapies after further study, which is promising but also demands attention to precision in classifying individuals with focal epilepsy and establishing a molecular diagnosis before pursuing experimental therapy.

Although most newly discovered pathogenic variants each seem to be causative in only a small number of individuals, taken together their combined impact is substantial. From the perspective of practicing epileptologists, we now benefit from a relatively high rate of identifiable genetic causes in neonatal and early childhood epilepsies, particularly in those individuals with comorbid intellectual disability, so that more routine usage of next-generation sequencing methods in this population may be warranted.[13,14] Much more research is needed, however, to separate out the effects of seizures, genetic changes, and treatments on the intellectual impairments that are found in the epileptic encephalopathies.[15]

Animal models have permitted important insights into the specific mechanisms by which genetic aberrations may promote hyperexcitability. In additional to conventional "knockout" mice, mutants with conditional gene deletions (permitted via *Cre*-LoxP technology) have helped dissect the individual contributions of specific neuronal populations to seizure generation. For example, mice with a conditional deletion of *Lgi1* in parvalbumin-positive interneurons alone are devoid of spontaneous seizures, while conditional deletions of *Lgi1* in forebrain glutamatergic neurons result in frequent early-life seizures and premature death,[16] just as in *Lgi1* knockout mice.[17] These results not only provide guidance to future gene replacement strategies but also show that while Lgi1 is an extracellularly secreted protein that is expressed in both GABAergic and glutamatergic neurons, restoring Lgi1 expression in glutamatergic neurons may be more likely to ameliorate seizures. The lack of spontaneous seizures in mice with heterozygous deletions of *Lgi1* (recapitulating the haploinsufficiency of *LGI1* mutation-related lateral temporal lobe epilepsy [TLE]) illustrates an important point with regard to gene dosage in animal models. Similar findings exist with other epilepsy genes, including *KCNQ2*,[18] *CDKL5*,[19] and *DEPDC5*.[20] Heterozygous *DEPDC5* variants are found in cases of familial focal epilepsy as well as focal cortical dysplasia–associated epilepsy.[20,21] Mice or rats with homozygous germ line deletions of *Depdc5* had embryonic lethality,[22-24] which is itself etiologically nonspecific and may even reflect placental pathology.[25] In contrast, rats with heterozygous deletions of *Depdc5* do not display spontaneous seizures.[24] Mice with a conditional brain-specific homozygous deletion of *Depdc5* display extremely rare seizures, together with macrocephaly, impaired survival, and biochemical evidence of mTOR1 complex activation.[22] Thus, it appears that for certain genetic variants strongly associated with epilepsy in humans, mice with corresponding gene deletions or transgenic "knock-ins" of variants seen in individuals with the specific epilepsy syndrome may not display spontaneous seizures or even reflex audiogenic seizures, a common expression of epilepsy in mice. This phenomenon may reflect the influences of variations in genetic background or fundamental differences in mechanisms of genetic epileptogenesis between mice and humans.

Confirming the epilepsy-inducing or epilepsy-modifying effects of specific variants may be greatly aided through the use of other vertebrate models, such as zebrafish (*Danio rerio*).

Classically employed as a model to study embryology and development, zebrafish has now been adopted to study a variety of neurological disorders, including epilepsy. This species is amenable to exon deletion via homologous recombination, and specific single-nucleotide variants can be introduced via CRISPR-Cas9 technology.[26-28] As with mice, stereotyped spontaneous or induced seizures can be identified by video tracking and/or electroencephalography. The small size and rapid development of zebrafish also permit high-throughput drug screening[29] that may be individualized to identify a treatment for a specific variant.[30]

Despite the impressive array of genetic advances, the translation of these findings into gene-related or pathway-based clinical treatments has had mixed results.[31] There are genetic diagnoses for which specific antiepileptic therapies are either indicated or relatively contraindicated (eg, GLUT1 deficiency, pyridoxine dependency, *SCN1A*-related epilepsy), and mTOR inhibitors are now known to be at least partially effective for tuberous sclerosis complex–associated epilepsy.[32] By contrast, the use of quinidine for *KCNT1*-related epilepsy, initially thought to be promising following the report of a single case,[33] has not been shown to reduce seizure frequency in subsequent studies.[34] Overall, these and other findings suggest that simply modulating a causative pathway featuring a rational drug target can lead to variable responses. More work is clearly necessary to bring genetic discoveries from the bench successfully to therapeutic application at the bedside.

Interneuronopathy-Related Epilepsies

Interneuronopathies can be broadly defined as those conditions in which epilepsy or neuropsychiatric comorbidities arise as a consequence of either developmental or functional changes in interneurons. Alterations in interneuron migration or numbers have been identified in multiple epilepsy mouse models, including mice with deletions of *Cntnap2*,[35] *Wwox*,[36] and *Syngap1*,[37] as well as in certain models of acquired epilepsy,[38,39] and after traumatic brain injury.[40,41] Epilepsy that occurs in Dravet syndrome associated with pathogenic variants in *SCN1A* may also be classified in this category based on evidence that interneurons in *Scn1a* heterozygous mice display a selective decrease in excitability, and selective deletions of *Scn1a* in interneurons are sufficient to recapitulate the spectrum of Dravet-related phenotypes.[42-44] The term "interneuronopathy" was first used in the setting of a very severe genetic epilepsy syndrome (X-linked lissencephaly with ambiguous genitalia, XLAG) caused by pathogenic variants in *ARX*, with significant reductions in interneuron density in hippocampal and cortical regions observed in this condition.[45-47]

A more detailed understanding of interneuron development and migration patterns will be critical for developing novel treatments for these specific genetic epilepsy syndromes and will guide our explorations into the therapeutic potential of either transplantation[48,49] and/or optogenetic/chemogenetic manipulations of interneurons.

Tumor-Related Epilepsies

The incidence of epilepsy in individuals with brain tumors ranges from 70% to 80% in glioneuronal tumors (including gangliogliomas and dysembryoplastic neuroepithelial tumors) to 20% to 35% in individuals with brain metastases.[50] Epileptogenesis associated with gliomas, the most common malignant primary brain tumor, has been a focus of intense research, with 2 nonmutually exclusive mechanisms explored extensively.

For some neurodevelopmental tumors such as ganglioglioma, a genetic profile has become apparent in the form of a BRAF V600E variant, suggesting the possibility of treatment with BRAF inhibitors.[51] Furthermore, in some tumors, malignant glial cells release excessive amounts of glutamate through the cystine/glutamate transporter (*SLC7A11*), a gene whose expression is upregulated in at least half of all glial tumors.[52] SLC7A11-mediated glutamate release results in hyperexcitability that spreads to adjacent tissues,[53] and in preclinical studies, a currently available SLC7A11 inhibitor (sulfasalazine, utilized in the treatment of Crohn disease) resulted in improved seizure frequency and prolonged survival.[54] Mutations in isocitrate dehydrogenase (*IDH1*) are a strong predictor of epilepsy in patients with low-grade glial tumors.[55] Mutant IDH1 converts isocitrate to 2-hydroxyglutarate (instead of α-ketoglutarate), which is structurally similar to glutamate and sufficient to lengthen burst duration in cultured rat cortical neurons in an NMDA-receptor-dependent fashion.[55]

A second potential mechanism involves the dysregulation of chloride homeostasis in peritumoral cortical neurons through the aberrant downregulation of *KCC2* (potassium chloride cotransporter) and upregulation of *NKCC1* (sodium potassium chloride cotransporter) within these cells.[56] Under these conditions, γ-aminobutyric acid (GABA) binding to ionotropic receptors results in depolarization, and inhibitors of NKCC1 (which reverse altered chloride gradients) in preclinical glioma models improve seizure susceptibility.[57] It remains to be seen whether similar mechanisms of epileptogenesis may be involved in epilepsies related to meningiomas or metastatic lesions, for which preclinical models are less well developed. Clearly, cortically based or invading tumors seem to possess the greatest risk of epilepsy.[50]

Autoimmune Epilepsies

As of 2019, antibodies to at least 11 different antigens have been associated with epilepsy occurring in the context of encephalitis. Antibodies against extracellular antigens raise neuronal excitability and impose synaptic dysfunction either by disrupting specific protein interactions (eg, LGI1, NMDAR), enhancing receptor internalization (AMPAR), or by functioning as an antagonist (GABA-BR).[58] In contrast, antibodies against intracellular antigens are thought to produce epilepsy as a consequence of direct cytotoxic T-cell infiltration (eg, amphiphysin, GAD-65). The clinical presentation of autoimmune encephalitides is highly variable (signs and symptoms of limbic or motor dysfunction may or may not be present), and seizures may be the presenting symptom, a late symptom, or absent entirely.[59]

Establishing a direct causative link between individual antibodies and their specific mechanisms of epileptogenesis has been possible through experiments in which patient-derived antibodies are infused into mouse or rat models. For example, hippocampal specimens from mice that received intracerebroventricularly infused LGI1 antibodies over 14 days displayed reduced synaptic expression of the voltage-gated potassium channel KV1.1 (*KCNA1*) together with increases in presynaptic-release probability and postsynaptic current amplitudes, as well as diminished long-term potentiation and impairments in learning and memory.[60] These mice did not develop spontaneous seizures, suggesting that at least in mice, either longer durations of anti-LGI1 antibody exposure or higher antibody titers may be necessary for seizure generation. In contrast, similar infusions of anti-NMDAR antibodies in mice produced spontaneous seizures without impairments in memory or motor function.[61]

Recent genome-wide association studies have revealed that particular human leukocyte antigen (HLA) haplotypes may increase the risk of specific antibody-mediated encephalitides,[59,62,63] just as with other autoimmune conditions such as type I diabetes mellitus or ankylosing spondylitis; these HLA associations provide pathophysiological insights into the genesis of these antibodies. Fortunately, only a minority of patients who display acute symptomatic seizures during active encephalitis go on to develop epilepsy.[58] Early immunomodulatory therapy appears to be critical to avoid future drug resistance, while other factors, such as medical complications or hypoxia, may also contribute to long-term seizure risk.[58,59]

Epilepsy-Related Conditions

Adults have a median of 2 chronic medical conditions, but this number rises to 6 in individuals older than 65 years.[64] Thus, "comorbidities" are a central aspect of all chronic medical conditions, and epilepsy is no exception. In epilepsy, comorbidities can be broadly divided into those which affect mental health (including sleep), general physical health (including trauma), and reproductive health.[65,66] Together, these comorbidities contribute tremendously to overall disability, impairments in quality of life, and premature mortality.[67,68] Outside of chance or artifactual comorbidities that may reflect various forms of bias,[64] 4 main mechanisms of comorbidity have been proposed[69]: (1) independent comorbidity (etiologically unrelated to epilepsy), (2) consequent comorbidity (a direct consequence of epilepsy), (3) iatrogenic comorbidity (treatment related), and (4) shared risk factor (in which epilepsy and its comorbidity independently arise from a single etiology). Importantly, shared risk factors may epidemiologically resemble a bidirectional association (in which each condition causes the other).

Psychiatric comorbidities in epilepsy have received the greatest emphasis. Epilepsy is associated with significantly higher rates of mood and anxiety disorders,[70,71] psychosis,[72]

fatigue,[73] and autism spectrum disorder.[74] These entities are each independently associated with varying degrees of intellectual disability. Cross-sectional and/or prospective human data provide a framework for mechanistic hypotheses into their etiology; ultimately, these hypotheses require verification in animal models. Unfortunately, this schema is inherently limited since many psychiatric endophenotypes are either absent entirely (eg, suicidality) or difficult to measure (eg, depressed mood, psychosis) in animal models.

Depression, or major depressive disorder, has and will continue to be a major focus of comorbidity research. Individuals with epilepsy are twice as likely to develop depression over their lifetime,[70] and either entity can occur first.[75] The severity of depression is associated with the risk of epilepsy.[76] Depression and suicidality tend to be more prominent in individuals with TLE compared with those who have genetic generalized epilepsies,[77,78] and within TLE, depression severity correlates with pharmacoresistance but does not correlate with the side[57] or the extent of hippocampal atrophy,[79] if present. Improvements in depression that follow temporal lobectomy are strongly associated with improvements in seizure control.[80] To date, there has been no high-quality evidence to suggest that antidepressants (in conjunction with standard anticonvulsant therapy) are sufficient to either impact epilepsy risk or reduce seizure frequency.[81] On the other hand, behavioral interventions such as cognitive behavioral therapy or mindfulness training have been shown to improve both seizure control and quality of life.[82] Overall, this body of evidence argues strongly for the presence of shared noniatrogenic neurobiological risk factors that simultaneously raise the risk of depression and epilepsy.

What are these risk factors? Genetic or epigenetic factors may play only a modulatory role since major depression and epilepsy display little to no evidence of genetic overlap (unlike autism and epilepsy).[78] The roots of epilepsy–depression comorbidity may be related to changes in network functional connectivity. In major depression, such functional rearrangements are broad, bilateral, and vary by depression subtype.[83,84] At least within TLE circuits,[85] hyperexcitability within the anterior hippocampus (corresponding to the ventral hippocampus in rodents) may be one such anatomical substrate for comorbidity. In mice, ventral hippocampal injections of kainic acid produce epileptic seizures together with memory impairments and anhedonic behavior; these behavioral comorbidities were not observed in mice that received dorsal kainic acid injections.[86] Hypersynchrony in the anterior/ventral hippocampus region may contribute to depressive symptoms by compromising functional connectivity to ipsilateral frontal regions.[87]

Testing these hypotheses in preclinical models is now possible with optogenetics, in which an anatomically or molecularly defined neuronal population is genetically or virally transduced to express an excitatory or inhibitory ion channel that is activated by light of a specific wavelength. Bilateral optogenetic activations of ventral hippocampal afferent pathways in nonepileptic mice are sufficient to produce depression and anxiety-like symptoms.[88,89] Similarly, the optogenetic inhibition of mossy cells within the dentate gyrus (simulating mossy fiber loss) is sufficient to produce impairments in object memory in mice.[90] Aside from these focal network derangements, aberrations in a variety of other neuromolecular axes have been proposed as substrates that may raise seizure risk and compromise mood, including disturbances in neurotransmitter signaling (glutamate, GABA, serotonin), dysfunctional hypothalamo–pituitary–adrenal axis signaling, and a host of cellular and secreted mediators of neuroinflammation.[57,91]

Looking Forward: Opportunities and Challenges

Given the progress over the past several years and the remaining gaps in knowledge in the field, we have identified some ambitious but feasible future priorities in epilepsy research that we believe should guide our scientific efforts in this area over the next decade. First, it is notable that a large portion of this update has been devoted to genetic advances, given the substantial work in this area. We also recognize that many patients worldwide have epilepsy primarily caused by infection, head injury, birth trauma, hypoxic–ischemic insult, or any of a number of other perturbations of nervous system function. We support an increased focus on investigating the underlying causes and mechanisms of all forms of epilepsy, including these acquired forms of epilepsy, in order to improve our ability to prevent and treat these conditions successfully.

We also support further work on the cognitive and behavioral deficits that accompany epilepsy through experimental animal models, including further use of chemogenetic and optogenetic strategies to study specific cellular populations in the pathogenesis of epilepsy and related conditions. An important question with direct clinical relevance centers on the transition to the ictal state: Since seizures occur only in discrete episodes in most instances, we need a better understanding of what allows them to arise at any particular time and what limits transition to an ictal state at other times.[92]

We support continued attention on interneuron pathology, central neuronal signaling pathways, and autoimmune factors as underlying mechanistic factors in both genetic and acquired epilepsy syndromes. Further, invoking another less well-studied cell type in the nervous system, we support evaluation of the role of glia in epileptogenesis and seizure propagation. The pathogenesis of infection-related epilepsy, including virus-induced epilepsy and parasite-induced epilepsy, the latter of which is a leading cause of epilepsy worldwide but lacks a relevant animal model, needs further exploration. In general, the links between the brain and immune system and the relationship between inflammation and neural excitability should be critical targets of investigation. Despite the large volume of new advances in epilepsy genetics, we believe there needs to be further characterization of genes associated with the most prevalent early-life syndromes and further research on the use of "rational" therapy design to modulate known pathogenic pathways.

Although some work has been devoted to understanding the causality behind some of the most common epilepsy-related comorbidities, much more is required. We would support further research aimed at disentangling the effects of seizures, genetic changes, and antiseizure medication in contributing to the intellectual impairments that are present in patients with epileptic encephalopathies. In addition, we believe that further timely study of epilepsy etiologies in elderly individuals, who represent a second peak of epilepsy incidence after early childhood, could be highly impactful. Recent findings related to hippocampal hyperexcitability in individuals with Alzheimer disease[93] and the discovery of associations between lifestyle risk factors and late-onset epilepsy[94] provide tantalizing suggestions of important etiological connections in older adults who had multiple medical conditions.

"Doctor, what is causing my seizures?" At the current time, in a significant majority of individuals, including those without a definite brain lesion, an encephalitic prodrome, evidence for a familial epilepsy syndrome, or a comorbid neurodevelopmental syndrome, the answer to this question remains unknown. Fortunately, 65% of individuals will experience seizure freedom with 1 or more currently available antiseizure medications.[95] To improve the lives of all individuals affected by epilepsy, however, we must address the fundamental causes of epilepsy and its associated conditions. As demonstrated in the introductory vignette, we also have a responsibility to translate our scientific advances toward the treatment of epilepsy and fcognitive and psychiatric comorbidities in a coordinated fashion.

Authors' Note

B.S.C. and V.K. contributed equally to this manuscript. The opinions expressed in this publication are those of the author(s) and do not necessarily reflect the views of the National Institute of Health (NIH) or the American Epilepsy Society (AES).

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References

1. Caplan R, Mefford H, Berl M, et al. 2014 Epilepsy Benchmarks Area I: understanding the causes of the epilepsies and epilepsy-related neurologic, psychiatric, and somatic conditions. *Epilepsy Curr*. 2016;16(3):182-186.
2. Helbig I, Riggs ER, Barry CA, et al. The Clingen Epilepsy Gene Curation Expert Panel—bridging the divide between clinical domain knowledge and formal gene curation criteria. *Human Mutat*. 2018;39(2):1476-1484.
3. Myers KA, Johnstone DL, Dyment DA. Epilepsy genetics: current knowledge, applications, and future directions. *Clin Genet*. 2019;95(7):95-111.
4. Nolan D, Fink J. Genetics of epilepsy. *Handb Clin Neurol*. 2018; 148(1):467-491.
5. Symonds JD, Zuberi SM, Johnson MR. Advances in epilepsy gene discovery and implications for epilepsy diagnosis and treatment. *Curr Opin Neurol*. 2017;30(9):193-199.
6. Epi4K consortium, Epilepsy Phenome/Genome Project. Ultrararare genetic variation in common epilepsies: a case–control sequencing study. *Lancet Neurol*. 2017;16(2):135-143.
7. Wang J, Lin ZJ, Liu L, et al. Epilepsy-associated genes. *Seizure*. 2017;44(6):11-20.
8. Baulac S.mTOR signaling pathway genes in focal epilepsies. *Prog Brain Res*. 2016;226(6):61-79.
9. D'Gama AM, Woodworth MB, Hossain AA, et al. Somatic mutations activating the mTOR pathway in dorsal telencephalic progenitors cause a continuum of cortical dysplasias. *Cell Rep*. 2017; 21(13):3754-3766.
10. Sim NS, Ko A, Kim WK, et al. Precise detection of low-level somatic mutation in resected epilepsy brain tissue. *Acta Neuropathol*. 2019;138(6):901-912.
11. Baldassari S, Ribierre T, Marsan E, et al. Dissecting the genetic basis of focal cortical dysplasia: a large cohort study. *Acta Neuropathol*. 2019;138(6):885-900.
12. Winawer MR, Griffin NG, Samanamud J, et al. Somatic SLC35A2 variants in the brain are associated with intractable neocortical epilepsy. *Ann Neurol*. 2018;83(6):1133-1146.
13. Berg AT, Coryell J, Saneto RP, et al. Early-life epilepsies and the emerging role of genetic testing. *JAMA Pediatr*. 2017;171(9): 8638-8671.

14. Shellhaas RA, Wusthoff CJ, Tsuchida TN, et al. Profile of neonatal epilepsies: characteristics of a prospective US cohort. *Neurology*. 2017;89(9):893-899.

15. Klassen T, Davis C, Goldman A, et al. Exome sequencing of ion channel genes reveals complex profiles confounding personal risk assessment in epilepsy. *Cell*. 2011;145(7):1036-1048.

16. Boillot M, Huneau C, Marsan E, et al. Glutamatergic neuron-targeted loss of LGI1 epilepsy gene results in seizures. *Brain*. 2014;137(2):2984-2996.

17. Fukata Y, Lovero KL, Iwanaga T, et al. Disruption of LGI1-linked synaptic complex causes abnormal synaptic transmission and epilepsy. *Proc Natl Acad Sci U S A*. 2010;107(8):3799-3804.

18. Kim EC, Patel J, Zhang J, et al. Heterozygous loss of epilepsy gene KCNQ2 alters social, repetitive, and exploratory behaviors. *Genes Brain Behav*. 2019:e12599.

19. Wang IT, Allen M, Goffin D, et al. Loss of CDKL5 disrupts kinome profile and event-related potentials leading to autistic-like phenotypes in mice. *Proc Natl Acad Sci U S A*. 2012;109: 21516-21521.

20. Myers KA, Scheffer IE. DEPDC5 as a potential therapeutic target for epilepsy. *Expert Opin Ther Targets*. 2017;21(6):591-600.

21. Baldassari S, Picard F, Verbeek NE, et al. The landscape of epilepsy-related GATOR1 variants. *Genet Med*. 2019;21(2): 398-408.

22. Yuskaitis CJ, Jones BM, Wolfson RL, et al. A mouse model of DEPDC5-related epilepsy: neuronal loss of Depdc5 causes dysplastic and ectopic neurons, increased mTOR signaling, and seizure susceptibility. *Neurobiol Dis*. 2018;111:91-101.

23. Dickinson ME, Flenniken AM, Ji X, et al. High-throughput discovery of novel developmental phenotypes. *Nature*. 2016;537(8): 508-514.

24. Marsan E, Ishida S, Schramm A, et al. Depdc5 knockout rat: a novel model of mTORopathy. *Neurobiol Dis*. 2016;89(7): 180-189.

25. Perez-Garcia V, Fineberg E, Wilson R, et al. Placentation defects are highly prevalent in embryonic lethal mouse mutants. *Nature*. 2018;555(7697):463-468.

26. Griffin A, Krasniak C, Baraban SC. Advancing epilepsy treatment through personalized genetic zebrafish models. *Prog Brain Res*. 2016;226(4):195-207.

27. Samarut E, Chalopin D, Riche R, Allard M, Liao M, Drapeau P. Individual knock out of glycine receptor alpha subunits identifies a specific requirement of glra1 for motor function in zebrafish. *PLoS One*. 2019;14(5):e0216159.

28. Pena IA, Roussel Y, Daniel K, et al. Pyridoxine-Dependent epilepsy in zebrafish caused by ALDH7A1 deficiency. *Genetics*. 2017;207(5):1501-1518.

29. Nieoczym D, Socala K, Gawel K, Esguerra CV, Wyska E, Wlaz P. Anticonvulsant activity of pterostilbene in zebrafish and mouse acute seizure tests. *Neurochem Res*. 2019;44(5):1043-1055.

30. Tessadori F, Roessler HI, Savelberg SMC, et al. Effective CRISPR/Cas9-based nucleotide editing in zebrafish to model human genetic cardiovascular disorders. *Dis Model Mech*. 2018;11:dmm035469.

31. Perucca P, Perucca E. Identifying mutations in epilepsy genes: impact on treatment selection. *Epilepsy Res*. 2019;152:18-30.

32. French JA, Lawson JA, Yapici Z, et al. Adjunctive everolimus therapy for treatment-resistant focal-onset seizures associated with tuberous sclerosis (EXIST-3): a phase 3, randomised, double-blind, placebo-controlled study. *Lancet*. 2016;388: 2153-2163.

33. Bearden D, Strong A, Ehnot J, et al. Targeted treatment of migrating partial seizures of infancy with quinidine. *Ann Neurol*. 2014; 76(3):457-461.

34. Mullen SA, Carney PW, Roten A, et al. Precision therapy for epilepsy due to KCNT1 mutations: a randomized trial of oral quinidine. *Neurology*. 2018;90:e67-e72.

35. Penagarikano O, Abrahams BS, Herman EI, et al. Absence of CNTNAP2 leads to epilepsy, neuronal migration abnormalities, and core autism-related deficits. *Cell*. 2011;147(1):235-246.

36. Hussain T, Kil H, Hattiangady B, et al. Wwox deletion leads to reduced GABA-ergic inhibitory interneuron numbers and activation of microglia and astrocytes in mouse hippocampus. *Neurobiol Dis*. 2019;121:163-176.

37. Jacob J. Cortical interneuron dysfunction in epilepsy associated with autism spectrum disorders. *Epilepsia*. 2016;57(2):182-193.

38. Wei D, Yang F, Wang Y, et al. Degeneration and regeneration of GABAergic interneurons in the dentate gyrus of adult mice in experimental models of epilepsy. *CNS Neurosci Ther*. 2015; 21(1):52-60.

39. Cameron S, Lopez A, Glabman R, et al. Proportional loss of parvalbumin-immunoreactive synaptic boutons and granule cells from the hippocampus of sea lions with temporal lobe epilepsy. *J Comp Neurol*. 2019;527(14):2341-2355.

40. Cantu D, Walker K, Andresen L, et al. Traumatic brain injury increases cortical glutamate network activity by compromising GABAergic control. *Cereb Cortex*. 2015;25(8):2306-23020.

41. Koenig JB, Cantu D, Low C, et al. Glycolytic inhibitor 2-deoxyglucose prevents cortical hyperexcitability after traumatic brain injury. *JCI Insight*. 2019;5:126-506. doi:10.1172/jci.insight.126506.

42. Cheah CS, Yu FH, Westenbroek RE, et al. Specific deletion of NaV1.1 sodium channels in inhibitory interneurons causes seizures and premature death in a mouse model of Dravet syndrome. *Proc Natl Acad Sci U S A*. 2012;109(36):14646-14651.

43. Favero M, Sotuyo NP, Lopez E, Kearney JA, Goldberg EM. A transient developmental window of fast-spiking interneuron dysfunction in a mouse model of Dravet syndrome. *J Neurosci*. 2018; 38(36):7912-7927.

44. Yu FH, Mantegazza M, Westenbroek RE, et al. Reduced sodium current in GABAergic interneurons in a mouse model of severe myoclonic epilepsy in infancy. *Nat Neurosci*. 2006;9: 1142-1149.

45. Kato M, Dobyns WB. X-linked lissencephaly with abnormal genitalia as a tangential migration disorder causing intractable epilepsy: proposal for a new term, "interneuronopathy". *J Child Neurol*. 2005;20(4):392-397.

46. Price MG, Yoo JW, Burgess DL, et al. A triplet repeat expansion genetic mouse model of infantile spasms syndrome, arx(GCG)10+7, with interneuronopathy, spasms in infancy, persistent seizures, and adult cognitive and behavioral impairment. *J Neurosci*. 2009;29(27):8752-8763.

47. Kitamura K, Itou Y, Yanazawa M, et al. Three human ARX mutations cause the lissencephaly-like and mental retardation with epilepsy-like pleiotropic phenotypes in mice. *Hum Mol Genet*. 2009;18(19):3708-3724.

48. Casalia ML, Howard MA, Baraban SC. Persistent seizure control in epileptic mice transplanted with gamma-aminobutyric acid progenitors. *Ann Neurol*. 2017;82(4):530-542.

49. Hammad M, Schmidt SL, Zhang X, Bray R, Frohlich F, Ghashghaei HT. Transplantation of GABAergic interneurons into the neonatal primary visual cortex reduces absence seizures in stargazer mice. *Cereb Cortex*. 2015;25(9):2970-2979.

50. Englot DJ, Chang EF, Vecht CJ. Epilepsy and brain tumors. *Handb Clin Neurol*. 2016;134:267-285.

51. Koh HY, Kim SH, Jang J, et al. BRAF somatic mutation contributes to intrinsic epileptogenicity in pediatric brain tumors. *Nat Med*. 2018;24(11):1662-1668.

52. Robert SM, Buckingham SC, Campbell SL, et al. SLC7A11 expression is associated with seizures and predicts poor survival in patients with malignant glioma. *Sci Transl Med*. 2015;7(289): ra86.

53. Buckingham SC, Campbell SL, Haas BR, et al. Glutamate release by primary brain tumors induces epileptic activity. *Nat Med*. 2011;17(10):1269-1274.

54. Sleire L, Skeie BS, Netland IA, et al. Drug repurposing: sulfasalazine sensitizes gliomas to gamma knife radiosurgery by blocking cystine uptake through system Xc-, leading to glutathione depletion. *Oncogene*. 2015;34(49):5951-5959.

55. Chen H, Judkins J, Thomas C, et al. Mutant IDH1 and seizures in patients with glioma. *Neurology*. 2017;88(5):1805-1813.

56. Conti L, Palma E, Roseti C, et al. Anomalous levels of Cl⁻ transporters cause a decrease of GABAergic inhibition in human peritumoral epileptic cortex. *Epilepsia*. 2011;52(9): 1635-1644.

57. Mazarati A, Sankar R. Common mechanisms underlying epileptogenesis and the comorbidities of epilepsy. *Cold Spring Harb Perspect Med*. 2016;6(7):a022798.

58. Geis C, Planaguma J, Carreno M, Graus F, Dalmau J. Autoimmune seizures and epilepsy. *J Clin Invest*. 2019;129(3):926-940.

59. Britton J. Autoimmune epilepsy. *Handb Clin Neurol*. 2016;133: 219-245.

60. Petit-Pedrol M, Sell J, Planaguma J, et al. LGI1 antibodies alter Kv1.1 and AMPA receptors changing synaptic excitability, plasticity and memory. *Brain*. 2018;141(11):3144-3159.

61. Taraschenko O, Fox HS, Pittock SJ, et al. A mouse model of seizures in anti-N-methyl-D-aspartate receptor encephalitis. *Epilepsia*. 2019;60(3):452-463.

62. Binks S, Varley J, Lee W, et al. Distinct HLA associations of LGI1 and CASPR2-antibody diseases. *Brain*. 2018;141(8): 2263-2271.

63. Mueller SH, Farber A, Pruss H, et al. Genetic predisposition in anti-LGI1 and anti-NMDA receptor encephalitis. *Ann Neurol*. 2018;83(4):863-869.

64. Keezer MR, Sisodiya SM, Sander JW. Comorbidities of epilepsy: current concepts and future perspectives. *Lancet Neurol*. 2016; 15(1):106-115.

65. Barnard S, French J. Collaboration of care for women with epilepsy in their reproductive years. *J Womens Health (Larchmt)*. 2019;28(3):339-345.

66. Wu D, Chen L, Ji F, Si Y, Sun H. The effects of oxcarbazepine, levetiracetam, and lamotrigine on semen quality, sexual function, and sex hormones in male adults with epilepsy. *Epilepsia*. 2018; 59(7):1344-1350.

67. Sajobi TT, Jette N, Fiest KM, et al. Correlates of disability related to seizures in persons with epilepsy. *Epilepsia*. 2015;56(9): 1463-1469.

68. Koch-Stoecker SC, Bien CG, Schulz R, May TW. Psychiatric lifetime diagnoses are associated with a reduced chance of seizure freedom after temporal lobe surgery. *Epilepsia*. 2017;58(6): 983-993.

69. Noebels JL. Single-gene determinants of epilepsy comorbidity. *Cold Spring Harb Perspect Med*. 2015;5(11):a022756.

70. Fiest KM, Dykeman J, Patten SB, et al. Depression in epilepsy: a systematic review and meta-analysis. *Neurology*. 2013;80(6): 590-599.

71. Tellez-Zenteno JF, Patten SB, Jette N, Williams J, Wiebe S. Psychiatric comorbidity in epilepsy: a population-based analysis. *Epilepsia*. 2007;48(12):2336-2344.

72. Clancy MJ, Clarke MC, Connor DJ, Cannon M, Cotter DR. The prevalence of psychosis in epilepsy; a systematic review and meta-analysis. *BMC Psychiatry*. 2014;14:75.

73. Kwon OY, Ahn HS, Kim HJ. Fatigue in epilepsy: a systematic review and meta-analysis. *Seizure*. 2017;45:151-159.

74. Tuchman R, Hirtz D, Mamounas LA. NINDS epilepsy and autism spectrum disorders workshop report. *Neurology*. 2013;81(18): 1630-1636.

75. Hesdorffer DC, Ishihara L, Mynepalli L, Webb DJ, Weil J, Hauser WA. Epilepsy, suicidality, and psychiatric disorders: a bidirectional association. *Ann Neurol*. 2012;72(2):184-191.

76. Josephson CB, Lowerison M, Vallerand I, et al. Association of depression and treated depression with epilepsy and seizure outcomes: a multicohort analysis. *JAMA Neurol*. 2017;74(5): 533-539.

77. Mula M, Jauch R, Cavanna A, et al. Interictal dysphoric disorder and periictal dysphoric symptoms in patients with epilepsy. *Epilepsia*. 2010;51(7):1139-1145.

78. Park SJ, Lee HB, Ahn MH, et al. Identifying clinical correlates for suicide among epilepsy patients in South Korea: a case–control study. *Epilepsia*. 2015;56(12):1966-1972.

79. Hecimovic H, Santos J, Price JL, et al. Severe hippocampal atrophy is not associated with depression in temporal lobe epilepsy. *Epilepsy Behav*. 2014;34:9-14.

80. Hamid H, Liu H, Cong X, et al. Long-term association between seizure outcome and depression after resective epilepsy surgery. *Neurology*. 2011;77(22):1972-1976.

81. Ribot R, Ouyang B, Kanner AM. The impact of antidepressants on seizure frequency and depressive and anxiety disorders of patients with epilepsy: is it worth investigating? *Epilepsy Behav*. 2017;70(1):5-9.

82. Haut SR, Gursky JM, Privitera M. Behavioral interventions in epilepsy. *Curr Opin Neurol*. 2019;32(2):227-236.

83. Akil H, Gordon J, Hen R, et al. Treatment resistant depression: a multi-scale, systems biology approach. *Neurosci Biobehav Rev.* 2018;84:272-288.

84. Drysdale AT, Grosenick L, Downar J, et al. Resting-state connectivity biomarkers define neurophysiological subtypes of depression. *Nat Med.* 2017;23(2):28-38.

85. Bertram EH. Neuronal circuits in epilepsy: do they matter? *Exp Neurol.* 2013;244:67-74.

86. Zeidler Z, Brandt-Fontaine M, Leintz C, Krook-Magnuson C, Netoff T, Krook-Magnuson E. Targeting the mouse ventral hippocampus in the intrahippocampal kainic acid model of temporal lobe epilepsy. *eNeuro.* 2018;5(7):ENEURO.0158-18.2018.

87. Kemmotsu N, Kucukboyaci NE, Cheng CE, et al. Alterations in functional connectivity between the hippocampus and prefrontal cortex as a correlate of depressive symptoms in temporal lobe epilepsy. *Epilepsy Behav.* 2013;29(3):552-559.

88. Bagot RC, Parise EM, Pena CJ, et al. Ventral hippocampal afferents to the nucleus accumbens regulate susceptibility to depression. *Nat Commun.* 2015;6:7062.

89. Parfitt GM, Nguyen R, Bang JY, et al. Bidirectional control of anxiety-related behaviors in mice: role of inputs arising from the ventral hippocampus to the lateral septum and medial prefrontal cortex. *Neuropsychopharmacology.* 2017;42(8):1715-1728.

90. Bui AD, Nguyen TM, Limouse C, et al. Dentate gyrus mossy cells control spontaneous convulsive seizures and spatial memory. *Science.* 2018;359(6377):787-790.

91. Kanner AM. Can neurobiological pathogenic mechanisms of depression facilitate the development of seizure disorders? *Lancet Neurol.* 2012;11(12):1093-1102.

92. Karoly PJ, Ung H, Grayden DB, et al. The circadian profile of epilepsy improves seizure forecasting. *Brain.* 2017;140(8):2169-2182.

93. Lam AD, Deck G, Goldman A, et al. Silent hippocampal seizures and spikes identified by foramen ovale electrodes in Alzheimer's disease. *Nat Med.* 2017;23(6):678-680.

94. Johnson EL, Krauss GL, Lee AK, et al. Association between midlife risk factors and late-onset epilepsy: results from the atherosclerosis risk in communities study. *JAMA Neurol.* 2018;75(11):1375-1382.

95. Golyala A, Kwan P. Drug development for refractory epilepsy: the past 25 years and beyond. *Seizure.* 2017;44:147-156.