Catastrophic Epilepsies of Childhood

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Abstract

The tragedy of epilepsy emerges from the combination of its high prevalence, impact upon sufferers and their families, and unpredictability. Childhood epilepsies are frequently severe, presenting in infancy with pharmacoresistant seizures; are often accompanied by debilitating neuropsychiatric and systemic comorbidities; and carry a grave risk of mortality. Here, we review the most current basic science and translational research findings on several of the most catastrophic forms of pediatric epilepsy. We focus largely on genetic epilepsies and the research that is discovering the mechanisms linking disease genes to epilepsy syndromes. We also describe the strides made toward developing novel pharmacological and interventional treatment strategies to treat these disorders. The research reviewed provides hope for a complete understanding of, and eventual cure for, these childhood epilepsy syndromes.

Contents

INTRODUCTION

Epilepsy has plagued humankind since the earliest written descriptions of medical conditions (Magiorkinis et al. 2010). Indeed, abnormal bursts of neural hyperactivity (i.e., seizures), the defining feature of epilepsy disorders, are seen across the animal kingdom (Grone & Baraban 2015) and could be an inevitability in even the simplest neural circuits (Jirsa et al. 2014).

Unfortunately, the most severe forms of epilepsy are often those arising early in infancy and childhood. Although catastrophic is no longer deemed a clinical classification of these epilepsy syndromes, it remains an apt descriptor. Like adult seizure disorders, developmental epilepsies are diverse in their etiologies. They are generally classified as arising from genetic or structural/metabolic causes or being of unknown origin. Importantly, genetic epilepsies are those in which a mutation results directly in epilepsy, whereas structural/metabolic epilepsies are those in which epilepsy is a secondary result of a disorder of cellular or anatomical origin which itself may be genetic in cause or may be acquired, such as by stroke, trauma, or infection. Pinpointing genetic causes of epilepsy has led to a better understanding of the disease process: linking mutations to altered protein function, to disturbed cellular and neural network activity, and finally to the behavioral outcomes of epilepsy. Understanding structural/metabolic childhood epilepsies, such as those arising from stroke or trauma or as a secondary effect of other genetic disorders, has also broadened with the development of new model systems and integration of cutting-edge technology.

With this enhanced knowledge of epilepsy mechanisms, it is vital that researchers translate these findings into effective treatments. Many pediatric epilepsy patients exhibit frequent seizure events that are disruptive, damaging, and lead to a poor quality of life. Antiepileptic drugs (AEDs) are often ineffective at reducing the seizure burden in these children. The devastation of childhood epilepsy disorders extends beyond seizures and frequently includes comorbidities that can alter cognitive processing and disrupt the quality of life for both the patient and their family members. These deficits can include, but are not limited to, severe developmental delay or deficits in sensory processing, movement, behavior, mood, and sleep. Even when seizures are well controlled with AEDs, these comorbidities often remain unchecked. Although the origin of comorbidities may be similar (e.g., genetic mutation affecting neural physiology), mechanisms linking insult to seizures and insult to comorbidities can be distinct. This review provides a discussion focused largely on the most severe (or "catastrophic") genetic childhood epilepsies. We take a mechanistic approach to describe the basic and translational research that informs our understanding of the links between

genes, cellular function, circuit processing, and clinical epilepsy phenotypes. We discuss how this research is guiding development of novel pharmacological and interventional therapeutic strategies. Finally, we outline the near-future goals for research toward cures for these childhood epilepsies.

PROGRESS TOWARD UNDERSTANDING THE MECHANISMS OF PEDIATRIC EPILEPSIES

Classification of epilepsies can be confusing to clinicians and scientists well versed in the field, and off-putting to educated outsiders. The confusion, however, may be an inevitability of describing diseases based on either clinical outcomes or genetics, when the complexity of genetic, epigenetic, cellular, and neural circuit interactions can transform a single mutation change into a diverse array of neuroclinical manifestations (**Figure 1**). For example, infantile spasms (IS), a.k.a. West Syndrome, can be caused by mutations of the genes Aristaless-related homeobox (*ARX*) or syntaxin binding protein 1 (*STXBP1*, a.k.a. Munc18) and is associated with other neurological syndromes such as developmental delay or autism, with or without comorbid epilepsy. It is important to consider that epilepsy syndromes exist on a spectrum such that many patients may fit imperfectly into multiple categories of the disease. Many of the pediatric syndromes we discuss are classified as epileptic encephalopathies (EEs) using terminology described by the International League Against Epilepsy (Berg et al. 2010). Generally, EEs are progressive epilepsies in which seizures are accompanied by, and may contribute to, cognitive and behavioral deficits.

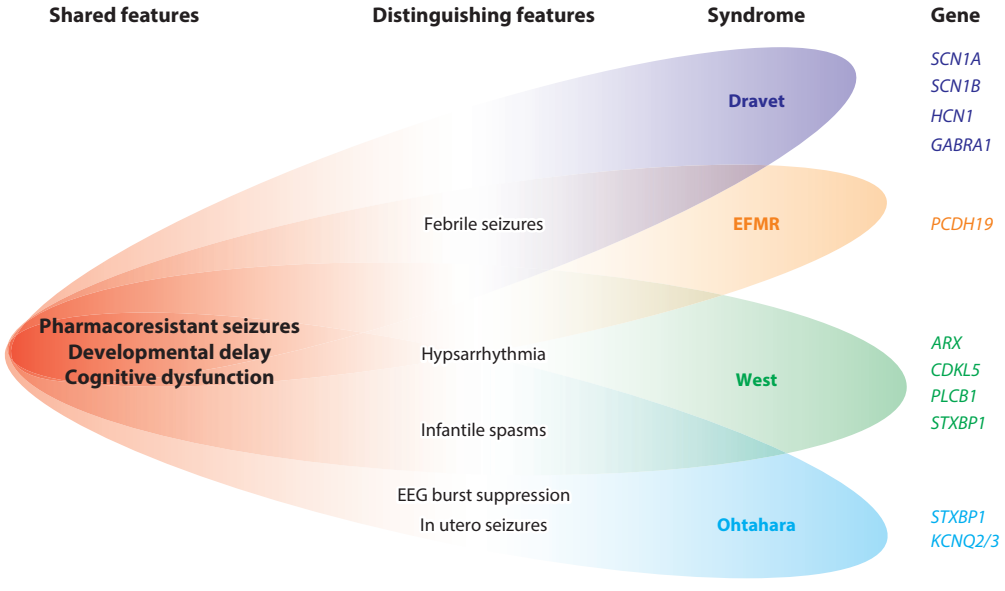

Figure 1

The complexity of genetic pediatric epilepsy stems in part from the large number of genes involved and shared features across syndromes. This figure illustrates partial lists of severe pediatric epilepsy syndromes and causative genes. Understanding the mechanistic basis of disease mutations is often difficult owing to the convergence of major symptoms of these syndromes.

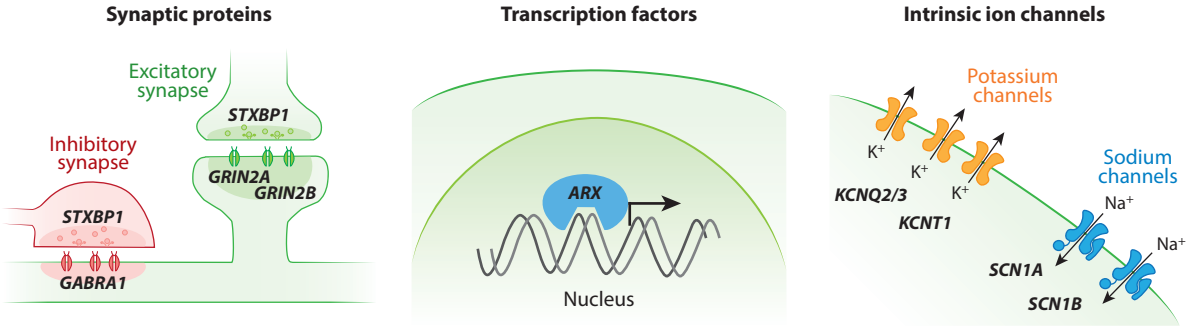

Figure 2

Pediatric epilepsy syndrome disease genes impact a variety of cellular processes. The example genes (*italicized*) illustrated alter pre- and postsynaptic function, control of gene transcription, and intrinsic cellular excitability.

Genetic Epilepsies

It has been almost three decades since the first human epilepsy-related gene was discovered (Shoffner 1990, The European Chromosome 16 Tuberous Sclerosis Consortium 1993). In the intervening decades, technological advances have made gene and whole-genome sequencing for more epilepsy patients possible and economically feasible. These advances, coupled with teams sharing data across many different sites and countries, allow for screening of large patient cohorts, resulting in the recent explosion in the number of epilepsy gene mutations identified in severe pediatric epilepsies (Epi4K Consortium & Epilepsy Phenome/Genome Project 2013, EuroEPINOMICS-RES Consortium et al. 2014, Oliver et al. 2014, Epilepsy Phenome/Genome Project & Epi4K Consortium 2015, Kwong et al. 2015). These studies also highlight the complexity of the disease, as mutations in genes coding for ion channels, ligand-gated receptors, solute transporters, synaptic trafficking proteins, kinases, transcription factors, and adhesion molecules have been identified (**Figure 2**). In the following section, we review some of what we have learned about these single-gene mutations and pediatric epilepsy.

Dravet syndrome, a.k.a. severe myoclonic epilepsy of infancy. Dravet syndrome (DS), or severe myoclonic epilepsy of infancy (SMEI), is characterized by febrile seizures in infancy, followed by frequent and severe afebrile seizures, developmental delay, and a host of cognitive deficits, as well as a high risk of sudden unexplained death in epilepsy (SUDEP) (Auvin et al. 2016). DS has received growing research interest in recent years owing to the development of multiple transgenic animal models of the disease: transgenic mice (Yu et al. 2006), zebrafish (Baraban et al. 2013), and patient-derived induced pluripotent stem cells (iPSCs) (Higurashi et al. 2013, Jiao et al. 2013, Liu et al. 2013, Sun et al. 2016). DS and related generalized epilepsy with febrile seizures plus (GEFS+) disorders are canonically associated with the gene *SCN1A* (Escayg et al. 2000, Claes et al. 2001), mutations of which alter the physiology of the α1 pore-forming subunit of the voltage-gated sodium channel $Na_V1.1$ (Lossin et al. 2002). To date, more than 600 de novo mutations in this gene have been identified. Understanding how mutations alter protein function is vital to our understanding of the underlying pathophysiology and development of new therapies.

Initial characterization of SCN gene family mutant mice revealed epilepsy phenotypes similar to DS and alterations in GABAergic interneuron function that result in decreased neuronal excitability but showed normal intrinsic properties in excitatory pyramidal neurons (Yu et al. 2006). These findings suggest that DS and *SCN1A*-linked epilepsies result from a specific dysfunction

of inhibitory interneurons (interneuronopathy), resulting in circuit hyperexcitability. Many studies have followed this line of research. The cell subtype–specific deletion of the *SCN1A* gene in parvalbumin-expressing (PV+) interneurons in mice results in a propensity toward both febrile and spontaneous afebrile seizures (Dutton et al. 2013). Mice heterozygous for the mutant allele exhibited behavioral and social deficits, some of which could be rescued with AEDs that increase inhibitory neurotransmission (Han et al. 2012, Ito et al. 2013). Genetic haploinsufficiency of *SCN1A* was sufficient to reduce the excitability of both PV+ and somatostatin-expressing interneurons in the cortex, leading to disinhibition of cortical microcircuits (Tai et al. 2014). Transgenic knockin mice with human missense point mutations also exhibited defects in interneuron activity that resulted in network hyperexcitability, further suggesting decrements in inhibitory synaptic activity as a mechanism for the human condition (Hedrich et al. 2014). This research illustrates the complexity of a single gene mutation embedded in a complex neural network. Indeed, focal knockdown of *SCN1A* expression is sufficient to alter network activity in the form of oscillations and impaired learning and memory during training in certain tasks without inducing seizures (Bender et al. 2013, 2016). However, single unit recordings of identified cortical interneurons of different subtypes showed normal activity levels during circuit activity in the preseizure period (De Stasi et al. 2016), suggesting that further network changes may be required during a period of epileptogenesis to transition the brain from a state of diminished interneuron hypoexcitability to epilepsy.

Other lines of evidence have emerged that complicate the interneuron-specific hypothesis. Excitatory neurons generated from DS patients using iPSC technologies exhibit increased sodium current density and propensities toward hyperexcitability (Jiao et al. 2013, Liu et al. 2013). As the de novo *SCN1A* mutation in question caused complete loss-of-function of the $Na_V1.1$ channel, the increase in excitability associated with excitatory neurons suggests a secondary or compensatory mechanism of control over sodium currents occurs even in the absence of altered inhibitory input. Interestingly, other iPSC studies report that only interneuron physiology is affected (Sun et al. 2016), similar to results from mouse work. This suggests that findings could be mutation-specific or that culturing techniques could lead to individual neuron physiological phenotypes different from the human condition. Further studies of knockout mouse models highlight the complexity of these genotype/phenotype relationships. For example, cellular physiology and behavioral phenotypes are dependent on both the age and the background strain of the animal, with seizures prominent in some backgrounds but absent in others (Mistry et al. 2014, Rubinstein et al. 2015). These findings suggest the involvement of other mechanisms capable of modulating neural excitability in the presence of $Na_V1.1$ channel dysfunction and could lead toward a deeper understanding of the wide range of clinical outcomes associated with *SCN1A* mutations. Indeed, some human patients with de novo *SCN1A* mutations and DS have been found to carry mutations in other genes—for instance, patients carrying *SCN1A* and a voltage-gated calcium channel subunit mutation exhibit seizure phenotypes distinct from DS patients with only $Na_V1.1$ dysfunction (Ohmori et al. 2008, 2013).

In addition to our growing understanding of the links between disease mutations and the core features of DS, animal models provide new insight into the causes of SUDEP associated with this disorder. *SCN1A* is expressed in the heart as well as the brain, and transgenic knockin mice expressing a human *SCN1A* mutation linked to DS exhibit altered electrical activity in vivo and in isolated cardiomyocytes (Auerbach et al. 2013). Interestingly, global and brain-specific deletion of SCN1A in mice results in SUDEP following tonic-clonic seizures, whereas heart-specific deletion did not, despite altered cardiac physiology in all cases (Kalume et al. 2013). These data indicate that altered parasympathetic control to the heart may underlie increased risk of SUDEP in DS. Recent work by Aiba & Noebels (2015) has shed light on a potential causative

factor in cardiorespiratory arrest after seizure. They discovered that brainstem nuclei exhibit increased susceptibility to spreading depression (SD) in *SCN1A* mice. SD waves propagate slowly through neural circuits, causing widespread cellular depolarization, loss of synaptic efficacy, and neural dysfunction that can be transient or permanent. This study links the cortical depression following ictal activity and cardiorespiratory collapse with the onset of brainstem SD. As these studies illustrate, understanding the primary mechanisms of the disease, and the intermediate steps linking mutation to morbidity to mortality, is essential for developing treatments that will not only improve patients' quality of life but save lives as well.

SCN1B encodes the voltage-gated Na^+ channel β1 subunit (Isom et al. 1992). Although most broadly known as a modulator of $Na_V1.1$ channel activation, β1 is involved in a diverse array of protein-protein interactions intra- and extracellularly, with alternate splice variants being transmembrane bound or soluble and secreted (Kazen-Gillespie et al. 2000, Qin et al. 2003, Patino et al. 2011). The consequence of the broad variety of activities associated with β1 is a variety of outcomes for patients with *SCN1B* mutations who exhibit a spectrum of epilepsies, including DS (Wallace et al. 1998, Patino et al. 2009). Recent work uncovered numerous key roles for β1 in neural development and cellular physiology that could serve as underlying mechanisms for these epilepsy phenotypes. *SCN1B* knockout mice, which phenocopy many traits of human DS, exhibit altered neural patterning during developmental stages prior to the onset of hyperexcitability (Brackenbury et al. 2010, 2013). In addition to altered $Na_V1.1$ activity, *SCN1B* deficits also result in hyperexcitability due to loss of β1 interactions with voltage-gated K^+ channels (Marionneau et al. 2012). Novel cell type–specific changes to excitability have also been reported in a transgenic knockin mouse expressing a human epilepsy-related mutation of *SCN1B*, in which pyramidal cells of the subiculum and cortical layer 2/3 exhibit underdeveloped dendrites and hyperexcitability (Reid et al. 2014). Interestingly, these mice do not show deficits to interneuron physiology. This β1 mutation also alters the subcellular distribution of the subunit, eliminating its association with nodes of Ranvier and $Na_V1.1$, suggesting deficits in the cell-cell adhesion function of β1 (Kruger et al. 2016). These new data add complexity to the story of DS, imply alternate mechanisms and loci of seizure generation, and suggest reasons for the diverse outcomes exhibited by patients with *SCN1B* mutations. Similar to *SCN1A*, *SCN1B* is expressed in cardiac tissue. *SCN1B* knockout mice exhibit abnormal Na^+ currents and Ca^{2+} transients in cardiomyocytes, as well as arrhythmias in the hearts of cardiac-specific knockouts (Lin et al. 2015). Data linking brainstem or parasympathetic activity and cardiac function to SUDEP in *SCN1B* mutant mice have not yet been reported, but these studies will be of great interest for understanding convergence or divergence of mechanisms of SUDEP between DS models of different genetic etiology.

STXBP1 (discussed in detail below) is involved in presynaptic vesicle cycling. $GABA_A$ receptor α1, encoded by *GABRA1*, originally described in relation to juvenile myoclonic epilepsy (Cossette et al. 2002), resides on the postsynaptic membrane and initiates the synaptic response to GABAergic input. Mutations of either gene can result in epilepsy with clinical features similar to DS (Carvill et al. 2013a,b, 2014; Schubert et al. 2014). Finally, mutations to *HCN1* (encoding a hyperpolarization-activated, cyclic nucleotide–gated channel) were first discovered in patients with idiopathic generalized epilepsy (Tang et al. 2008). *HCN1* is known as a target for physiological changes to cellular excitability following seizures (Brewster et al. 2002). New findings implicate *HCN1* in an epilepsy syndrome with similarities to DS (Nava et al. 2014).

Epilepsy and mental retardation limited to females. Epilepsy and mental retardation limited to females (EFMR) is a DS-like syndrome caused by mutations of the X-chromosome gene *PCDH19* (Dibbens et al. 2008). This disorder strikes in female infants with febrile and spontaneous seizures, developmental delay, and other cognitive deficits (Depienne et al. 2009). Cadherins

and protocadherins, such as that encoded by *PCDH19*, are transmembrane cell adhesion proteins that signal bidirectionally by binding complementary proteins (often other members of the cadherin superfamily) embedded in the membranes of neighboring cells and linking to intracellular signaling pathways (for a review, see Halbleib & Nelson 2006).

Taken together, these genes represent a broad variety of cellular processes, from both sides of the synapse to intrinsic ion channels to cell-cell adhesion molecules. The convergence of symptoms in epilepsy syndromes associated with wide-ranging genes indicates the vitality and delicacy of neural circuit function but also gives hope for developing therapies that take advantage of shared signaling pathways to be effective across epilepsy syndromes.

Infantile spasms, a.k.a. West syndrome. IS is typically characterized by the onset of clusters of brief seizures during infancy. In some children these seizures resolve, but most patients show evolution of IS into different types of epilepsy, such as Lennox-Gastaut syndrome (LGS, discussed below). The prevalence of developmental delay and intellectual disability is high in patients with IS, and the etiology is complex and potentially linked with several different genes.

Mutations of the X-chromosome *ARX* gene have been linked to certain forms of IS (Strømme et al. 2002) as well as mental retardation and autism (Bienvenu et al. 2002). ARX is a transcription factor important for interneuron development and migration. Like *SCN1A*-linked epilepsies, *ARX*-related syndromes are considered interneuronopathies. Human *ARX* mutation transgenic knockin mice exhibit interneuron-specific deficits in cell survival, spasm-like myoclonus, seizures, and cognitive deficits mirroring the human condition (Price et al. 2009). Recent studies have begun to elucidate the transcriptional regulators upstream and downstream of ARX and their involvement in interneuron development and function (Hadziselimovic et al. 2014, Stanco et al. 2014, Vogt et al. 2014). For example, human mutations disrupt protein-protein interactions and consequently alter ARX's functional ability to regulate transcription (Polling et al. 2015). Understanding of the basic roles of ARX transcriptional control in development has already begun to guide translational research. Olivetti and colleagues (2014) demonstrated that treating transgenic *ARX* mutant mice with estradiol, which regulates synaptic transmission but also is a potent genetic and epigenetic modulator during development, reversed the interneuron loss and seizure phenotypes.

CDKL5 (initially known as *STK9*) is an X-linked gene encoding a serine/threonine kinase linked to IS (Kalscheuer et al. 2003), severe developmental delay, and Rett syndrome (Tao et al. 2004, Weaving et al. 2004). *CDKL5* knockout mice exhibit altered electrophysiological responses and behavior but, perplexingly, no spontaneous seizures (Wang et al. 2012). Although these mice are more susceptible to induced seizures (Amendola et al. 2014), putative compensatory mechanisms that protect them from *CDKL5*-related epilepsy make the role of this protein in epilepsy difficult to deduce. However, recent work uncovered key functions of *CDKL5* that suggest a path from mutation to neural dysfunction. The protein plays a key role in enhancing interactions between the cell adhesion protein netrin 1 and the synaptic scaffolding protein PSD95 (Ricciardi et al. 2012). Mutations of *CDKL5* disrupted binding with PSD95 and modulation by palmitate cycling, leading to decrements in dendritic spine formation and growth (Zhu et al. 2013). Such an outcome would greatly alter neural circuit processing and excitability. Importantly, *CDKL5* dysfunction also results in dysregulation of other protein signaling cascades, including the AKT-mTOR (protein kinase B–mechanistic target of rapamycin) pathway (Wang et al. 2012, Fuchs et al. 2014), which is crucial for neural development and excitability, and represents a potential therapeutic target in epilepsy (for a complete review, see Crino 2016). Pharmacological approaches to improve neurological deficits in *CDKL5* mouse models also include targeting the inhibiting kinase GSK3β (Fuchs et al. 2015) and treatment with insulin-like growth factor 1, a modulator of the AKT-mTOR pathway (Della Sala et al. 2014). Both represent potential targets for future IS therapies.

PLCB1 (phospholipase C-beta-1) is an essential component of activity-dependent neurodevelopment and a key link in G protein–coupled receptor signaling pathways (De Camilli et al. 1996). This protein is particularly important in neuromodulation, linking muscarinic acetylcholine (Kim et al. 1997) and metabotropic glutamate receptors (Hannan et al. 2001) with the downstream targets of intracellular signaling cascades. Kurian et al. (2010) discovered human mutations of *PLCB1* linked to IS.

Ohtahara syndrome. Ohtahara syndrome (OS), a.k.a. epileptic encephalopathy with suppression burst (EESB) or early infantile epileptic encephalopathy (EIEE), is one of the earliest forms of EE to manifest itself in patients, with a high volume of short-duration seizures beginning as early as the first postnatal weeks. The burst suppression epithet refers to the EEG pattern of bursts of large spikes alternating with suppressed electrical activity that typifies the syndrome. Seizures are often refractory to AEDs, and OS patients have poor prognosis, often developing IS or LGS and frequently exhibiting cognitive and motor deficits (see Beal et al. 2012 for a review). The most commonly known gene linked to OS is *STXBP1* (Saitsu et al. 2008).

STXBP1 is an integral component of the machinery of synaptic vesicle fusion and neurotransmitter release (Fisher et al. 2001, Ma et al. 2013). The fundamental importance of this protein to neural function has made it the subject of intense study. Although a great deal is known about the basic mechanisms of its function, the role of STXBP1 in epilepsy is still not fully understood. *STXBP1* mutations linked to OS decrease the capability of the protein to bind to syntaxin and participate in the process of exocytosis (Saitsu et al. 2008, Shen et al. 2015). As with DS, researchers have used several emerging technologies to investigate the role of STXBP1 in epilepsy. The epilepsy phenotypes of the human mutation were recapitulated in a zebrafish morpholino knockdown model (Schubert et al. 2014). Our group recently generated a stable zebrafish *STXBP1* knockout line using CRISPR/Cas9 gene editing. These mutants exhibited epilepsy as well as deficits in behavior, cardiac function, and metabolism (Grone et al. 2016). Neurons induced from human embryonic stem cells engineered to carry *STXBP1* deletions showed altered presynaptic protein levels and impaired synaptic transmission (Patzke et al. 2015).

Malignant migrating partial seizures in infancy. Malignant migrating partial seizures in infancy (MMPSI) is another form of severe EE that often begins within the first six months of life. The partial seizure (which initially affects only a specific part of the brain) phenotype is a differentiating characteristic of MMPSI. As with other catastrophic pediatric epilepsies, seizures are pharmacoresistant and usually accompanied by profound developmental delay. Only recently have genetic studies discovered human mutations linked with MMPSI, particularly to the sodium-activated potassium channel gene *KCNT1* (Barcia et al. 2012). *KCNT1* mutations have also been linked to families with childhood-onset autosomal dominant nocturnal frontal lobe epilepsy with intellectual and psychiatric comorbidities (Heron et al. 2012). Identified MMPSI-linked *KCNT1* mutations result in a hyperactivation of potassium currents and could also alter the protein-protein binding sites of the channel involved in neurodevelopmental signaling. Recent work demonstrated an interesting mechanism by which *KCNT1* mutations caused enhanced channel cooperativity, rather than changes to single-channel activation or conductance, resulting in enhanced K^+ currents and thus altered cell excitability (Kim et al. 2014).

Many early-onset EEs have a genetic basis but do not clearly fit into one well-defined syndrome. Genes critical to neuronal function have recently been implicated in early-onset EE; links between human mutations of these genes and epilepsy phenotypes are as of yet poorly understood. Rather than list all genes connected to EE, we briefly highlight a small number whose links to epilepsy are more established and mechanistically clear.

Potassium channels are directly involved in neuronal excitability and thus provide fertile ground for mutations resulting in a variety of epilepsies. Mutations of the *KCNQ2* and *KCNQ3* genes were initially identified as causative for benign familial neonatal epilepsy (Biervert et al. 1998, Charlier et al. 1998, Schroeder et al. 1998, Singh et al. 1998). These genes encode proteins in the K_V7 family, which carry the M-current and play a key role in controlling neuronal excitability (Wang et al. 1998). Expanded genetic analysis has revealed the commonality of such mutations in EE patients in which seizures may resolve but cognitive deficits remain (Weckhuysen et al. 2012, Kato et al. 2013). Further mechanistic work has shown that human mutations resulting in channel loss-of-function (Miceli et al. 2013), gain-of-function (Miceli et al. 2015), and subcellular redistribution (Abidi et al. 2015) can all cause network hyperexcitability and epilepsy. This mechanistic work is currently guiding pharmacological studies exploring the use of the KCNQ2/3 channel activator and anticonvulsant retigabine and related compounds to suppress epilepsy in mouse models (Miceli et al. 2013, Kalappa et al. 2015). Importantly, such pharmacological therapy may be more or less effective depending on how the gain- or loss-of-function is induced by a patient's specific mutation. This emphasizes the importance of genetic screening for patients and developing strategies of personalized medicine for the treatment of severe epilepsy disorders.

Neuronal excitability is also sensitive to mutations of synaptic genes. NMDA receptor genes are cornerstones of long-term synaptic potentiation (LTP), a canonical molecular mechanism of memory formation. *GRIN2A*, which encodes the NMDA receptor subunit GluN2A, is involved in EE (Endele et al. 2010) and other childhood epilepsies (Lesca et al. 2013). *GRIN2A* epilepsy mutations result in overactivation of the receptor (Yuan et al. 2014). *GRIN2B*, encoding the NMDA receptor GluN2B subunit, is linked to multiple types of epilepsy and shows receptor overactivation in IS (Lemke et al. 2013, 2014). Synaptic Ras-GTPase interacting protein (SYNGAP1) is a key regulator of LTP that prevents receptor insertion and synapse enlargement until synapse activation (Araki et al. 2015). *SYNGAP1* mutations can disturb dendritic spine structure, particularly during critical stages of development (Clement et al. 2012, Aceti et al. 2015). Previously linked to autism spectrum disorders and intellectual disability, *SYNGAP1* mutations have also recently been discovered in patients with EE (Carvill et al. 2013a,b; Mignot et al. 2016).

Nongenetic Epilepsies

Pediatric epilepsies resulting from metabolic or structural abnormalities are generally categorized as nongenetic. Although these could have a genetic basis, seizures are thought to arise secondarily to alterations of neural function caused by the primary metabolic dysfunction or anatomical irregularities. The so-called nongenetic epilepsies are not the major focus of this review and have been reviewed well elsewhere from both clinical (Auvin et al. 2016) and basic science perspectives (Wong & Roper 2016). We only briefly highlight some of the severe nongenetic epilepsies for which progress is being made at the basic science and translational levels.

Tuberous sclerosis complex (TSC) genes *TSC1* and *TSC2* were some of the first identified as being positively associated with epilepsy syndromes (The European Chromosome 16 Tuberous Sclerosis Consortium 1993, van Slegtenhorst et al. 1997). TSC is a developmental disorder affecting many systems, characterized neurologically by cortical tubers (i.e., regions of disorganized cells visible on neuroimaging). Mutations to *TSC1* or *TSC2* result in dysregulation of the vital mTOR intracellular signaling cascade. Patients with TSC exhibit a wide range of neuropsychiatric deficits including epilepsy, autism, and intellectual disability; mTOR inhibitors are a promising avenue for the development of new treatments for a variety of neurological syndromes (Crino 2016).

The genetic basis for Angelman syndrome, mutations to the gene *UBE3A*, was also an early discovery for the field of epilepsy genetics (Kishino et al. 1997). Encoding a ubiquitin ligase,

UBE3A interacts with specific substrate proteins intracellularly, labeling them for degradation. Altered UBE3A function results in dysregulation of the levels and thus activity of these substrate proteins. Angelman syndrome patients frequently exhibit a complex set of epilepsy and cognitive disabilities, which can include movement, mood, social, and intellectual changes (for a review, see Sell & Margolis 2015). Recent work has shown that GABAergic neuron–specific disruption of maternal *UBE3A* is sufficient to induce both interneuron dysfunction and epileptic phenotypes in mouse models (Judson et al. 2016).

LGS is an EE complex in both symptomology and etiology (see Auvin et al. 2016 for a review). Patients exhibit a variety of seizure types and cognitive regression. Other forms of pediatric epilepsy, such as IS, or brain injuries can result in the development of LGS as the child ages. With heterogeneous causes and manifestations, there is likely no single mechanism underlying LGS, but recent discoveries of genes associated with IS and LGS may help distinguish genotypes that lead to LGS outcomes from those that result in only IS (Epi4K Consortium & Epilepsy Phenome/Genome Project 2013, Janve et al. 2016).

DEVELOPING NEW THERAPEUTIC STRATEGIES

Gene Therapy

Several pathways have been targeted with gene therapy to reduce seizures in epilepsy models, including using genes to increase growth factor production, increase responses to GABA, and decrease intrinsic excitability (for a review, see Simonato et al. 2014). Most of these studies focused on models of acquired rather than genetic epilepsies. But the efficacy of these approaches against pharmacoresistant forms of epilepsy, such as temporal lobe epilepsy, raises hope that such techniques can be effective more broadly against pediatric epilepsy syndromes. There is a growing understanding of the roles that microRNAs play in epilepsy (Henshall 2014). Epilepsy phenotypes can be altered bidirectionally through antagonism or overexpression of microRNAs (Jimenez-Mateos et al. 2015). In work toward developing therapy for pediatric syndromes, Prabhakar and colleagues (2015) used a gene therapy approach in TSC. They exposed newborn *TSC1* transgenic conditional knockout mice to adeno-associated virus encoding a wild-type version of the gene. Treatment prolonged the lives of mutant mouse pups, decreased neuronal abnormalities, and improved motor behavior. The importance of the mTOR pathway, modulated by TSC1, in multiple forms of pediatric epilepsies makes these data highly encouraging for future implementation of this therapeutic strategy toward other severe epilepsy syndromes.

Cell Therapy

Successful preclinical cell therapies for epilepsy have focused on increasing GABAergic interneuron density in neural circuits to disrupt the initiation and propagation of seizures (for a review, see Hunt & Baraban 2015). In mouse models, this has largely been accomplished using embryonic progenitor cells from the medial ganglionic eminence (MGE), a developmental structure that births many forebrain interneurons (Anderson et al. 1997). These cells are experimentally ideal in that they maintain the ability to migrate away from the transplant site, intercalate into the existing neural circuitry, and mature into select subtypes of interneurons that provide selective inhibition to native pyramidal neurons but not interneurons (Alvarez-Dolado et al. 2006, Baraban et al. 2009). Transplantation of MGE progenitor cells into *KCNA1* knockout mice, which exhibit severe early-onset epilepsy, dramatically reduced seizure frequency and duration (Baraban et al. 2009). Interneuron transplantation has since been applied successfully to other forms of acquired

and genetic epilepsy (Calcagnotto et al. 2010, Hunt et al. 2013, Howard et al. 2014). Further development of this strategy for pediatric genetic epilepsies in mice, many of which result in early mortality, may require conditional mouse mutants to prolong survival or enhanced progenitor cells to more rapidly integrate into the host circuit.

New Animal Models

Genetic mouse models have brought a new age of discovery and understanding for many human disorders. Although mechanistic insights are essential to guide the development of treatments, mouse models remain expensive to produce and maintain, and many that carry catastrophic disease mutations have high early mortality rates. Drug discovery in these types of mice can be extremely costly and time-consuming. Fortunately, alternative model systems now exist. For example, zebrafish with an *scn1lab* haploinsufficiency mimicking patients with DS epilepsy have proven useful for large-scale phenotype-based drug screening (Baraban et al. 2013, Dinday & Baraban 2015, Griffin et al. 2016). These screens have isolated new potential anticonvulsant drugs that could have greater efficacy against pharmacoresistant pediatric epilepsies. Interestingly, these screens revealed strong positive outcomes of two known drugs that were not commonly used for treating epilepsy, namely clemizole, a US Food and Drug Administration–approved antihistamine (Baraban et al. 2013), and fenfluramine, a serotonin reuptake blocker (Dinday & Baraban 2015, Zhang et al. 2015). Discovery of these drugs has already guided the creation and testing of chemical derivatives and modulation of new physiological pathways and has led to the successful treatment of pediatric epilepsy patients (Griffin et al. 2017).

The continued development of other high-throughput screening techniques will be key to finding cures for the diverse epilepsy disorders that plague patients. Patient-derived iPSCs, differentiated into neurons and cultured sparsely or as organoids, are a highly attractive model for testing therapies that modulate neuronal excitability or neurodevelopment. These systems have been used to examine the role of numerous epilepsy genes in neural differentiation and circuit formation (see Parent & Anderson 2015 for a review), most recently *PCDH19* (Compagnucci et al. 2015). Examination of iPSC-derived neural cultures has provided new information on the cellular physiology of DS (Liu et al. 2013, Sun et al. 2016). In TSC, modulation of the mTOR signaling pathway in iPSC-derived neurons reversed defects in both cell hyperexcitability and circuit connectivity (Costa et al. 2016). Currently, the cost of producing iPSC-derived neurons in large quantities and the time it takes for induced neurons to exhibit mature properties and responses to AEDs (Odawara et al. 2016) are limiting factors. However, these technologies will continue to become more common and effective and will surely be a vital tool in the development of future pediatric epilepsy cures.

CONCLUSIONS

The combined effects of pharmacoresistant seizures and cognitive dysfunction render severe (or catastrophic) pediatric epilepsy syndromes devastating to patients and their families and caretakers. However, an ongoing revolution in genetic research has pinpointed many of the genes linked with these disorders. This in turn has led to discovery of pathways leading from gene to symptom; each new step discovered provides a target around which therapies can be designed. By bringing to bear a wide range of technical approaches and model systems, our understanding of pediatric epilepsies and their potential treatments is expanding faster than ever before. Thus, there is great hope for truly translating cutting-edge epilepsy research to the bedside and bringing more effective treatments and cures to those most in need.

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