Single-Gene Determinants of Epilepsy Comorbidity

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Common somatic conditions are bound to occur by chance in individuals with neurological disorders as prevalent as epilepsy, but when biological links underlying the comorbidity can be uncovered, the relationship may provide clues into the origin and mechanisms of both. The expanding list of monogenic epilepsies and their associated clinical features offer a remarkable opportunity to mine the epilepsy genome for coordinate neurodevelopmental phenotypes and examine their pathogenic mechanisms. Defined single-gene-linked epilepsy syndromes identified to date include all of the most frequently cited comorbidities, such as cognitive disorders, autism, migraine, mood disorders, late-onset dementia, and even premature lethality. Gene-linked comorbidities may be aggravated by, or independent of, seizure history. Mutations in these genes establish clear biological links between abnormal neuronal synchronization and a variety of neurobehavioral disorders, and critically substantiate the definition of epilepsy as a complex spectrum disorder. Mapping the neural circuitry of epilepsy comorbidities and understanding their single-gene risk should substantially clarify this challenging aspect of clinical epilepsy management.

Comorbid conditions are prevalent in epilepsy and actually exceed the disability caused by seizures themselves (Lin et al. 2012); over a lifetime, their diagnosis and treatment more than doubles the overall economic burden of the disorder (Cramer et al. 2014). Classically, the term “comorbidity” was introduced by Feinstein to denote cases in which “a distinct additional clinical entity” occurred during the clinical course of a patient presenting with an index disease. A search for the cause of a contemporaneous problem and whether it is connected to a common pathogenic mechanism is a routine task in neurological diagnosis, and has a significant impact on health care. Yet in the

epilepsy clinic, the biological underpinnings of comorbidity are often poorly understood, and by virtue of the early and profound impact seizures may exert on normal brain development, often believed to arise as a result of the seizures themselves. This need not be so. Although the clinical history in epilepsy typically defines the initial symptom as primary, comorbidities can arise before, during, or after onset of the first seizure, and their temporal appearance may have little bearing on whether the two are connected by a common biological mechanism. An essential task for the clinician, therefore, is to develop a working hypothesis that relegates the conjugal relationship to one of three etio-

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logical categories: (1) an independent comorbidity (shared but unrelated concurrent dysfunction in different brain pathways), (2) a consequent comorbidity (direct result of the primary disease), or (3) an iatrogenic comorbidity (treatment-related). Uncertainty among these alternatives is a major determinant of unfavorable medical outcomes, and may lead to an incorrect diagnosis, polypharmacy and its complications, or an erroneous prognosis.

ACQUIRED VERSUS INBORN: ISOLATING THE ROOTS OF SEIZURE COMORBIDITY

Seizure disorders, in all of their protean manifestations, are common throughout the life span and arise from both acquired and genetic lesions. The same is true of a number of neurodevelopmental and adult-onset cognitive, psychiatric, and neurological syndromes, which, even when coexpressed in the context of epilepsy, are considered disorders in their own right. This means that multiple independent etiologies of the syndromic elements are always a leading possibility. Alternatively, they may be a shared downstream sequelae of a single common etiology; for example, acquired brain injuries account for up to one-third of individuals with epilepsy, yet can lead to cognitive and psychiatric syndromes throughout the life span whether seizures are present or not.

Acquired seizure disorders arise from neural injuries that are highly variable in pathobiology, timing, and severity. These range from neonatal hypoxia characterized by diffuse pancellular patterns of cell death and inflammation, along with encephalitides, hemorrhagic stroke, and penetrating brain trauma, to the opposite extreme, such as adult-onset autoimmune disorders with precisely defined, antigen-specific molecular lesions of membrane channels and glutamatergic and GABAergic synaptic neurotransmission (Lancaster and Dalmau 2012). Each of these extrinsic insults may occur at almost any stage of brain development, disrupt entirely different patterns of brain function, and with the distinct exception of autoimmune processes, are of little value in localizing the circuitry of the functional

defect, particularly when they are not exactly correlated with the actively discharging epileptic networks. Dissecting causal mechanisms underlying acquired seizure comorbidities is a challenge because it can rarely be determined with confidence that the comorbid disturbance might not have emerged regardless of the seizures and subsequent medication. Short of a complete resolution once the seizures are controlled, the codependent relationship is uncertain, and, in the case of migraine (Hoffmann et al. 2014) and some mood disturbances (Oncu et al. 2014; Selle et al. 2014), remains unproven, because the two disorders are often treatable by the same antiepileptic drug (AED) even in the absence of the other.

In contrast, inherited epilepsies offer a far more tractable framework to analyze comorbidity, namely, whether mutation of a single gene can produce seizures along with a coordinate, nonepileptic phenotype. The discovery of mutations in single genes that give rise to both seizures and comorbid conditions provides compelling evidence for genetically interdependent mechanisms, and a clear path to dissect the underlying biology, because they should each display relatively stereotyped natural histories. Genes linked to epilepsy and coordinate phenotypes indicate that a single molecular lesion can alter immature neuronal circuits at multiple stages, with a profound pleiotropic impact on early brain development (Fig. 1).

Figure 1. A monogenic basis for epilepsy comorbidity. Single genes contribute to distinct biology at multiple levels of brain development. Mutations, even within the same gene, can lead to highly selective patterns of pathophysiology.

In epilepsy patients, the functional effect of these gene mutations can alter both the dynamic and the static behavior of neural circuits, and the distinction has profound clinical significance. When epileptiform activity disrupts neural network signaling and produces a comorbid deficit that is promptly regained once seizures are eliminated, the encephalopathic deficit is considered “epileptic” in origin. Epileptic pseudodementia (Tatum et al. 1998), migraine (Rogawski 2012), and depression (Kanner 2011) are important examples. The active contribution of interictal electroencephalogram (EEG) discharges to persistent cognitive decrements in the absence of seizures is an interesting but still unresolved issue (Holmes 2014). However, when either the mutated gene itself or the damage that seizures produce result in prolonged interictal disruption of cortical function, and the comorbid symptoms persist despite effective seizure control, a more complex and potentially instructive relationship is present.

In this group, the biological nature of the gene defect in neural circuitry largely determines the spectrum of the comorbid phenotypes. This enables a series of questions for subsequent investigation. Does the causative gene for epilepsy lead directly to the pleiotropic appearance of a second disorder as a result of the early onset or severity of the seizures themselves, or are they each the product of seizure-independent downstream mechanisms? Does the molecular lesion affect overlapping cell types across widespread brain regions, or distinct cellular compartments in specific cortical networks? Are the seizures sufficiently severe to trigger cell death, or is there a window of opportunity where early recognition and therapeutic cellular and molecular remodeling could reshape the outcome? These issues are of extraordinary significance for therapeutic targeting, because they determine whether stopping or preventing the seizures could ameliorate the entire syndrome, which otherwise will continue whether seizures are controlled or not. Because the answers may differ for each epilepsy gene, the value of individual clinical gene profiles will increase as each becomes better understood.

This article provides illustrative examples of gene-linked comorbidities in epilepsy, including cognitive disorders of early and later life, autism, mood (mania, depression, bipolar, ADHD, schizophrenia), migraine, and premature death genes. These genes clearly strike more than one brain network, resulting in a complex clinical phenotype. A focus on these mechanistic pathways, as studied in mouse models and in humans, will hopefully lead to novel therapies and personalized management of persons with complex epilepsy comorbidities.

COORDINATE PHENOTYPES OF SINGLE EPILEPSY GENES

The study of monogenic epilepsies has highlighted several broad issues. First, virtually every known inherited epilepsy syndrome can be caused by more than one gene, and, second, each gene typically causes more than one syndrome. This means that for any broadly defined clinically epilepsy syndrome, for example, epileptic encephalopathy, we expect an innate spectrum of distinct comorbidities depending on the gene in question. An interesting example is presented by two genes for the childhood syndrome of autosomal dominant frontal lobe epilepsy (ADNFLE), the nicotinic cholinergic receptor nAChR4 (Steinlein et al. 1995), and the sodium-sensitive potassium channel KCNT1, where human mutations are associated with epilepsy and severe intellectual disability and developmental delay (Heron et al. 2012b; Kim and Kaczmarek 2014). Despite a similar seizure phenotype, intellectual disability only occurs in the Slack channel mutations (Steinlein 2014).

Third, the phenotypic seizure spectrum of any single gene for epilepsy is itself typically broad, leading to mild and severe seizure phenotypes, with either early or late onset. The heterogeneity of seizure severity and age of onset are well-known features of mutations in voltage-gated ion channels, the largest and best-studied category of inherited epilepsy to date, and depend on properties of the specific mutation within the gene (Zuberi et al. 2011), the epistatic genetic complexity of each individual (Klassen et al. 2011), or both. The sheer number of

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specific genes with multifunctional intragenic domains, and the array of mutations (gain or loss of function) found within each of them represent a major challenge to prognosis, and much research remains to decipher the clinical utility of individual gene profiles.

Nevertheless, a prominent group of genes have been discovered in epilepsy syndromes that are solid biomarkers of other neurodevelopmental and psychiatric conditions, such as cognitive disorders, autism, attention-deficit hyperactivity disorder (ADHD)/mood disturbances, and migraine. The genetic overlap with early-onset cognitive disorders and autism is particularly notable (Betancur 2011). Other genes reveal phenotypic overlap with movement disorders (dyskinesias) (Heron et al. 2012a), ataxias (Matsuura et al. 2000; Ortolano et al. 2014), and late-onset dementias (Lopera et al. 1997). The latter illustrate how a seizure disorder can appear alongside or in the wake of another neurological deficit during its neurodegenerative trajectory. In general, as circuits fail within the brain, they may progress through a stage where an inhibitory imbalance predominates, leading to network dysrhythmia and seizures. These genes bridge the traditionally narrow perspective of epilepsy as a static monomorphic hyperexcitability disorder with the broader view of a collection of more dynamic synchronization disorders that mark different stages of brain disease arising from errors of cell proliferation, cell migration, and synaptogenesis on the one hand, and inflammation, cell death, and homeostatic repair on the other.

seizures, a common occurrence in childhood absence epilepsy. Experimentally, these have been reproduced in monogenic-engineered single-gene mouse models (Price et al. 2009), or by combining two different genes (Serikawa and Yamada 1986). The glucose transporter gene *GLUT1* is another leading example of a monogenic complex seizure phenotype. This membrane transporter mediates glucose uptake across the blood–brain barrier, is present throughout the brain, and loss-of-function mutations give rise to diverse neurological syndromes with multiple seizure types in children (Pearson et al. 2013). Various *GLUT1* mutations are found in individuals with childhood absence epilepsy, generalized seizures, and movement disorders, sometimes even without accompanying seizures. Paroxysmal dyskinesia occurs in some individuals along with a range in severity of intellectual impairment. Several seizure types have been documented in mice homozygous for *Glut1* deletion (Wang et al. 2006), validating the complex seizure phenotype of this gene. Lennox–Gastaut syndrome is another epileptic encephalopathy with multiple seizure types (Camfield 2011) and emerging gene candidates (Lund et al. 2014; Terrone et al. 2014).

Developmental Epileptic Encephalopathies

Gene discovery in this complex neurodevelopmental phenotype has accelerated to a once unimaginable pace with the advent of clinical exome analysis for de novo mutations in infantile and childhood epilepsy accompanied by cognitive delay. Beginning with ARX (Stromme et al. 2002), over 100 genes for early-onset seizures with intellectual disability are listed in the Online Mendelian Inheritance in Man (OMIM) database. The extent and heterogeneity of this major comorbid genetic overlap is of scant surprise, because microcircuits in the hippocampus and entorhinal cortex, essential for proper memory storage and retrieval, are also extremely low-threshold initiation sites for seizures when lesions are placed experimentally in limbic circuitry (Kleen et al. 2012). The diverse molecular contribution to neuronal synchrony in these circuits means that not each gene model

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Mixed Seizure Types

From a strictly mechanistic standpoint, one category of epilepsy comorbidity is underappreciated but actually very common, namely, the coexistence of multiple seizure types that clearly involve distinct cellular networks in the brain. Examples include individuals with multiple seizure types, such as infantile spasms followed by convulsive epilepsy in ARX mutations or staring spells followed by the onset of convulsive

will necessarily perturb seizure threshold and cognitive performance to a similar extent. Early gene lesions in immature brain may be either less injurious and more easily reversed or severe, depending on the mutant allele. Benign neonatal familial seizures as a result of missense mutations in the *KCNQ2* potassium channel gene (Singh et al. 1998) were modeled in mice and found to leave little trace of hippocampal reorganization (Singh et al. 2008). Subsequently, it was recognized that dominant negative mutations in the same gene gave rise to the far more severe cognitive deficits of Ohtahara syndrome (Saitsu et al. 2012). A similar monogenic phenotypic spectrum is well known for mutations within the sodium channel gene *SCN1A* underlying uncomplicated generalized febrile seizures and the encephalopathy of Dravet syndrome. Other genes may even show a positive dissociation between epilepsy and cognitive impairment. A striking example of the latter is provided by the *PKR* gene encoding a double-stranded RNA-activated protein kinase whose deletion enhances the late phase of hippocampal long-term potentiation (LTP), increases network excitability, and elevates cognitive performance in behavioral tasks while reducing GABAergic inhibition and the threshold for spontaneous seizures (Zhu et al. 2011).

Deconstructing the Circuitry of Comorbid Cognitive Deficits

Further evidence for the impact of epilepsy within learning and memory circuits can be gained by analyzing conditional rather than genomic gene expression in mouse models. The ability to focally express pathogenic mutations within specific brain networks facilitates the isolation of necessary and sufficient pathways underlying the comorbidity phenotype. For example, Bender et al. (2012) showed that selective reduction of *Scn1a* in subcortical circuits produced cognitive dysfunction in the absence of the epilepsy seen in the genomic deletion model. This powerful strategy to isolate anatomical substrates of normal cognitive function can be extended to explore the role of specific cell types and developmental critical periods using condi-

tional drivers of gene expression, and promises to pinpoint future molecular targets and critical opportunities for therapeutic intervention. It is worth noting, however, that these methods fall short of defining the full extent of participating brain networks in developing brain. Although transgenic expression can be precisely controlled within the confines of specific cell types, the developmental influence of mutant cells on synaptically linked nonmutant networks extends the functional pathophysiology. For example, primary impairment of interneurons is tightly coupled to use-dependent changes in excitatory cells, leaving the contributions of each to the overall phenotype less distinct. In Rett syndrome models, selective deletion of *MECP2* in interneurons produces a disease phenotype, but so does deletion in excitatory neurons (Chao et al. 2010; Zhang et al. 2014). Analysis of the epileptic encephalopathy gene *KCNT1*, a sodium-activated potassium channel (Slack) (Heron et al. 2012), reveals that mutations disrupting the carboxy-terminal protein–protein interactions of Slack with cytoplasmic signaling molecules contribute to intellectual disability, and show molecular interactions with other cognitive genes, such as *FMRP*.

Autism

Depending on the cohort examined, the clinical epidemiology of autism spectrum disorder (ASD) includes epilepsy as a feature in up to one-third of individuals (Matsuo et al. 2010). Of the genes associated so far with autism behavioral features, a growing fraction display epileptic phenotypes in both human and mouse models (Fig. 2). Although the neural circuitry of autism is poorly defined and extends beyond regions traditionally critical for epilepsy, such as the cerebellum, genetic evidence for overlapping biology in the synaptic compartment of forebrain networks is sufficiently compelling to assume that these comorbidities can be functionally linked. The principle mechanisms affected are neurotransmission and DNA methylation/chromatin remodeling. Recent exome sequencing in a large autism cohort revealed 27 gene candidates with de novo loss-of-function mutations and

>1500 with de novo missense variants (Iossifov et al. 2014). Of these six, *CHD8*, *DYRK1A*, *ANK2*, *GRIN2B*, *DSCAM*, and *CHD2* were identified in three or more people with autism. A second study (De Rubeis et al. 2014) added *ADNP*, *SCN2A*, *SYNGAP1*, and *TBR1*. Still other candidates include *NRX1*, *CNTN4*, *DCLK2*, *CNTNAP2*, *CATNAP4*, *TRIM32*, *MBD5*, *ASTN2*, *CNTN5*, *GABRG1*, *SYN1*, and *CHRNA7*.

More than a few of these genes produce robust epilepsy and social interaction deficits when deleted in mouse models. *SYNGAP1*, a synaptic Ras GTPase-activating protein, is interesting because the primary functional defect in *Syngap1*-deficient epileptic mice appears to reside in excitatory neurons (Ozkan et al. 2014). *CNTNAP2* and family members are membrane proteins involved in ion channel localization that lead to autism and epilepsy (Penagarikano et al. 2011). Initially believed to reside primarily in excitatory cells, *CNTNAP4* has recently been found to be enriched in interneurons (Karayannis et al. 2014). Recent work with the gene *PRICKLE1*, which contributes to both autism and epilepsy phenotypes, reveals an interaction of Prickle protein with synapsin 1, a second exocytosis-related protein linked to epilepsy (Paemka et al. 2013). The evaluation of variants within the presynaptic protein interactome provide an opportunity to functionally integrate variants contributing to risk, as well as a model for further phenotypic diversity based on finely sculpted perturbations of neurotransmitter release.

Fragile X syndrome (FXS), because of a silencing of the gene and loss of FMR protein, is among the most common monogenic cause of autism, responsible for 2%–6% of all ASD cases, and includes cognitive impairment, seizures, hyperactivity, attention deficit, and impulsivity as leading features of the syndrome (Kidd et al. 2014). Epilepsy prevalence is elevated in cases with *FMR1* mutations, with a range of 14%–44%. Seizures are typically both generalized and partial, a majority resolve during childhood, and many FXS children without overt seizures show abnormal EEG centrottemporal spikes resembling benign focal epilepsy of childhood. Several candidate mechanisms triggered by the loss of fragile X mental retardation protein

(FMRP) have been proposed to cause the epilepsy of FXS, centering on dysregulation of excitatory mGluR and inhibitory GABA receptor pathways. Although spontaneous seizures (epilepsy) have not been reported in the *Fmr1*-deletion mouse model of FXS, these mice display dendritic pathology, defective synaptic plasticity, and a lowered threshold for evoked audiogenic seizures, and have proven useful in attempts to rescue hyperexcitability in this disorder (Bianchi et al. 2012; Dolan et al. 2013).

Other genetic syndromes display autism/epilepsy comorbidity. Angelman syndrome includes autism, hyperactivity, and epilepsy, and is typically caused by silencing of a region of imprinted genes on chromosome 15 that includes *UBE3a* and *GABA_B3*, both of which lead to epilepsy and behavioral deficits when deleted in mouse single-gene models (DeLorey et al. 1998; Jiang et al. 1998). Tuberous sclerosis is one of the largest identifiable causes of epilepsy and autism and is frequently associated with ADHD-like symptoms, which affect 30%–60% of children with Tourette syndrome (TS) (Curatolo et al. 2008; D'Agati et al. 2009) children. Mammalian target of rapamycin (mTOR) signaling is directly involved in TS cellular pathology, autism, and epilepsy, and represents a potential key molecular pathway joining these phenotypes (Lipton and Sahin 2014). Despite their strong clinical coincidence, nearly 70% of autism syndromes and early-onset epilepsy share a strong comorbidity with ADHD (Lo-Castro and Curatolo 2014); ADHD genes, with the exception of *CHRNA7*, *GRIN2A*, and *SNAP25* show little overlap with known epilepsy loci (Li et al. 2014).

In a study of patients with childhood-onset epilepsy (Matsuo et al. 2010), nearly half (46%) of clinical autism features arose after the onset of seizures. The finding that some of these features can be partially reversible by antiepileptic therapy requires significant further clinical research (Camacho et al. 2012).

Depression

With a lifetime prevalence of nearly 35%, the clinically heterogeneous disorder of depression is the leading, most common psychiatric com-

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plication of epilepsy (Tellez-Zenteno et al. 2007), yet there is little firm evidence for comorbidity caused by the mutation of any single gene. Substantial human and animal investigation has focused on the limbic system as a shared anatomical substrate for epilepsy and depression, but the models are primarily based on chemical interventions and suffer from the difficulty in equating motor behavior profiles with depression-like human symptomatology (Nestler and Hyman 2010; Epps and Weinshenker 2013). Imaging studies reveal an overlap in structural, hypometabolic, and serotonergic receptor-binding changes in limbic brain regions where chronic epilepsy patients show abnormalities, in particular, the left orbitofrontal and anterior cingulate cortex (Kanner et al. 2012).

Although epidemiologic evidence suggests that up to 50% of the risk for depression is genetic (Nestler et al. 2002), few genes are established for major depressive disorder (MDD) (Gatt et al. 2015). The leading pathogenic models center on monoaminergic, glutamatergic, and GABAergic neurotransmission, and molecules involved in their release and reuptake at synapses, and some genes in these pathways include epilepsy phenotypes. For example, deletion of the glial glutamate uptake transporter GLT1 (Rothstein et al. 1996; Tanaka et al. 1997), a candidate gene for depression, produces epilepsy in mice with a very specific pattern of excitotoxic hippocampal pyramidal cell death. This extensive neurotransmitter overlap may explain what has been considered to be the “bidirectional” risk of depression and epilepsy (Kanner 2011), and likely contributes to the therapeutic overlap of antiepileptic pharmacology (Vasudev et al. 2012; Cipriani et al. 2013; Hernan et al. 2014; Dutta et al. 2015). Genetic associations of human epilepsy with the serotonin pathway remain inconclusive; however, available data from animal experiments suggest that genes in these pathways remain strong candidates for seizure comorbidity (Bragatti et al. 2014; Lacey et al. 2014). In mouse models, epilepsy resistance has been attributed to serotonergic hyperinnervation (Tripathi et al. 2008); seizures downregulate 5HTB receptors (Koh et al. 2007), and deletion of the 5HTC2 receptor

subunit lowers the threshold for audiogenic seizures (Brennan et al. 1997).

Alzheimer's Dementia

It is of historical interest that the first descriptions of senile plaques were actually made in epilepsy patients (Catala and Poirier 2012), and Alzheimer's first report referred to these cases. Although long considered a rare and incidental comorbidity, the risk of epilepsy is now known to rise significantly above age-matched controls without dementia, and is extremely elevated in early-onset familial Alzheimer's Disease (AD) (Amatniek et al. 2006). Individuals with mutations in three known genes for Alzheimer's disease (AD) (*PSEN1*, *PSEN2*, and *APP*) show a dramatic elevation of epilepsy risk (Noebels 2011). Moreover, beginning with the first transgenic mouse model of AD (LaFerla et al. 1995), almost every mouse model of AD displays either convulsive or nonconvulsive seizures.

The evidence that pathological A β accumulation is linked to neural network hyperexcitability and is proepileptogenic continues to accrue. This unexpected finding is one of the more fascinating to emerge recently in the neurobiology of disease. Although there is no data that seizures can initiate the signature cellular plaque and tangle neuropathology of AD, several lines of evidence suggest they accelerate A β accumulation (Cirrito et al. 2005), excitotoxic synaptic dysplasia (Velez-Pardo et al. 2004), and neuronal cell death in overlapping circuits leading to accelerated cognitive decline (Palop et al. 2007; Vossel et al. 2013). Early evidence has emerged that antiepileptic treatment in AD may slow the progression of the disorder (Sanchez et al. 2012). Interestingly, genes that suppress the pathophysiology of A β overexpression and protect against cognitive decline, such as MAPT1 (tau) (Roberston et al. 2011), also prevent epilepsy in ion channel mutant models of epilepsy (Holth et al. 2013; Gheyara et al. 2014).

Deficits of Higher Cortical Function

Genes regulating the physiology of cortical association areas can cause epilepsy in association

with other deficits of higher cortical function including aphasia. *SRPX2*, a human language and epilepsy-associated gene promoting synaptogenesis in language regions of the cerebral cortex is the target of the transcription factor *FOXP2* (Sia et al. 2013). *SRPX2* reduction impairs development of ultrasonic vocalization in mice. Interactors with *SRPX2* have been identified by yeast 2-hybrid analysis of a human brain cDNA library (Royer-Zemmour et al. 2008), including two other known epilepsy genes, urokinase-type plasminogen activator receptor (UPAR or PLAUR) (Powell et al. 2003) and cathepsin B (CTSB) (Pennacchio et al. 1998), involved in extracellular proteolysis in human and rat brain. *GRIN2A* has also been linked to epilepsy in the rolandic region and aphasia (Reutlinger et al. 2010).

Migraine

A clinical relationship between migraine and epilepsy is well established (Rogawski 2012). Genes for a subtype of complicated migraine, familial hemiplegic migraine, have been identified and mutations linked to epileptic phenotypes (Pietrobon and Moskowitz 2013). The P/Q type, high-threshold voltage-gated calcium channel that regulates presynaptic neurotransmitter release was the initial genetic link discovered in human patients (Ophoff et al. 1996). Mouse models of this mutation (Tottene et al. 2009), but not a loss-of-function mutation (Ayata et al. 2000), shows seizures and a striking decreased threshold for the phenomenon of spreading depolarization within cortical pathways, believed to be the substrate of the hemiplegic migrainous deficit. Subsequently, two other genes encoding the Na^+K^+ ATPase $\alpha 2$ subunit and $\text{Na}_v 1.1$ sodium channel have been similarly linked, and mutations in all three of these genes also lead to epileptic phenotypes in human and mouse models (Russell and Ducros 2011). The clinical utility of AEDs in migraine prophylaxis is well known (Hoffmann et al. 2014).

Premature Death

Genes linking seizures, central autonomic disorders, and premature mortality underlying

sudden unexpected death in epilepsy (SUDEP) are vivid examples of inherited comorbidity in epilepsy. Beginning with the finding that *SCN5A*, a cardiac long QT interval syndrome (LQTS) sodium channel gene linked to sudden death is expressed in the amygdala (Hartmann et al. 1999), the limbic nucleus regulating cardiac representation in the forebrain, human mutations in the *KCNQ1* potassium channel (the most common cause of human LQTS and sudden death) were evaluated in mouse models and shown to replicate the SUDEP phenotype (Goldman et al. 2009), pointing to other LQT genes as candidates for shared epilepsy-cardiac arrhythmia phenotypes (Fig. 2). *KCNA1* is a second, non-LQTS potassium channel linked to brainstem and vagal nerve-driven cardiac arrhythmias, severe seizures, and early mortality (Glasscock et al. 2010). Sentrin/SUMO protease protein 2 (*SenP2*), a gene linked to sumoylation and membrane trafficking of these same potassium ion channels in heart and brain, is a new member of this category (Qi et al. 2014). Interestingly, molecular autopsy of human SUDEP cases reveal that mutations of these genes can also form complex risk profiles, suggesting an opportunity for early prognosis and potential for intervention in this life-threatening condition (Klassen et al. 2014).

CONCLUSION

Systematic clinical databases that aggregate gene variants and their human phenotypes (Clinvar) (Landrum et al. 2014) will greatly contribute to our slowly emerging understanding of the genetic landscape of the epilepsy spectrum. Genetic etiologies also play a role in understanding iatrogenic treatment-induced comorbidity, and, in some cases, even absolving the drug of complicity. For example, the appearance of cerebellar abnormalities and rapid decline in motor function in Unverricht–Lundborg disease had been long attributed to phenytoin-related cerebellar degeneration until the gene for this syndrome was identified and shown in animal models to produce mutation-driven cell death in these regions in the absence of the drug (Pennacchio et al. 1996, 1998). More recently,

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concern that the encephalopathy of Dravet syndrome may be aggravated as a postvaccination reaction has been challenged by the observation that patients with *SCN1A* gene mutations show no worse cognitive function when vaccinated before seizure onset or not (McIntosh et al. 2010). In the future, molecular diagnosis may facilitate earlier and even presymptomatic recognition of comorbid neurobehavioral disorders in individuals with seizure disorders. This important change in our approach should accelerate a more holistic etiological understanding and more effective clinical management of epilepsy patients.

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