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THE BIOLOGY OF EPILEPSY GENES

Jeffrey L. Noebels
Department of Neurology, Baylor College of Medicine, One Baylor Plaza, Houston, Texas, 77030; email: jnoebels@bcm.tmc.edu

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■ **Abstract** Mutations in over 70 genes now define biological pathways leading to epilepsy, an episodic dysrhythmia of the cerebral cortex marked by abnormal network synchronization. Some of the inherited errors destabilize neuronal signaling by inflicting primary disorders of membrane excitability and synaptic transmission, whereas others do so indirectly by perturbing critical control points that balance the developmental assembly of inhibitory and excitatory circuits. The genetic diversity is now sufficient to discern short- and long-range functional convergence of epileptogenic molecular pathways, reducing the broad spectrum of primary molecular defects to a few common processes regulating cortical synchronization. Synaptic inhibition appears to be the most frequent target; however, each gene mutation retains unique phenotypic features. This review selects exemplary members of several gene families to illustrate principal categories of the disease and trace the biological pathways to epileptogenesis in the developing brain.

Epilepsy genes are isolated from two principal sources: the cloning of the inherited disorders in human, mouse, and fly, and the incidental finding of epilepsy phenotypes following targeted mutagenesis. In the past decade, the number of identified genes linked to inherited epilepsies has risen along a steady growth curve with a doubling time of about three years, with no zenith in sight. Neither the predictably large number nor the steep rate of discovery is surprising. Instead, it is the functional diversity, at multiple levels, that sets the epilepsies apart from most other neurological diseases. From intrinsic membrane proteins directly responsible for cellular excitability to nuclear transcription factors distantly regulating the fate of developing networks, the pathways implicate mechanisms that range from the instantaneous control of firing behavior to early maturational steps that selectively stabilize the strength and plasticity of specific neural circuits.

As each mutation is identified, the initial steps are directed at describing the altered functions of the molecule, the cell types expressing the mutant gene, and the downstream networks secondarily altered during development. The intrinsic plasticity of these biological parameters will distinguish each disorder at the neuropathological level; however, this may or may not be revealed in clinically relevant ways, such as differences in natural history, severity, or therapeutic drug response.

Now that many epileptogenic mutations have been identified, we can begin the next level of analysis, that is, to assess the degree of convergence of these genetically heterogeneous pathways and to learn how and how much the diverse defects overlap. Do the seizures emerge at common periods of development? Do they integrate common elements of use-dependent plasticity? Do they share profiles of anticonvulsant sensitivity and vulnerability to seizure-induced brain damage? Understanding the commonalities of different genetically defined epilepsies at a network level may ultimately permit a narrowed focus on optimal repair strategies.

TRACING THE FUNCTIONAL PATHWAYS OF EPILEPTOGENESIS

Whether they act early or late in brain development, the genes are only starting points to define the changes that force the brain down a path of heightened excitability and epilepsy. The mutations themselves provide few clues to the central questions that have long defined and continue to perplex the field, namely, what triggers an individual seizure, why it remains focal or spreads throughout the brain, and why it stops. The millisecond timescale of these events means that precise answers remain in the electrophysiological domain. Furthermore, with so many different genetic mechanisms for epileptogenesis now described, a single, unifying answer to all of them appears unlikely. The effective stimulus for a network impaired by a pH homeostasis defect may not be the same as one for a channelopathy or transmitter imbalance. However, a gene-by-gene approach can tell us why, and when, certain networks are selectively at risk and not others. It also provides a set of essential tools, namely, a system of gene mutations at multiple steps of epileptogenesis, to analyze the natural history of each and to learn whether, how, and when the pathways converge on a smaller number of common synaptic regulatory control points.

A previous review assigned cellular sites of action based on location of the expressed proteins of the initial dozen genes, organizing them into a pre- or postsynaptic model (Noebels 1996). Since many genes change expression patterns and assume multiple roles during neuronal, and glial, development, a more elastic framework based on functional rather than "positional" information may provide better insight into their role in epileptogenesis. Inherited epilepsies can be divided into functional categories: those linked to primary defects of membrane and synaptic signaling, to neuronal plasticity and metabolism, and to network development. Although not exclusive, these categories serve as a durable reference point both for functional analysis and in framing future repair strategies.

GENES FOR FAST NEURONAL SIGNALING

Voltage- and Ligand-Gated Channelopathies

Multiple examples of ion channel mutations linked to paroxysmal network synchronization have now been identified, including the pore-forming and regulatory

subunits of Na^+, K^+, and Ca^{2+} channels, along with channels gated externally by GABA, glutamate, Ach, 5HT, and neuropeptide Y (NPY). Preliminary analysis of these mutations in heterologous systems has provided essential biophysical data; however, there are still broad gaps in our understanding of how these channelopathies sculpt the excitability of individual circuits. The missing information depends crucially on discovering whether, and when, in a developing neuron the mutant subunit leads to altered activity-dependent plasticity in the expression of other genes.

SODIUM CHANNELOPATHIES—STILL A PUZZLE Of 13 expressed sodium channel genes, mutations in 3 subunits (Nav1.1, 1.2, β1) have been associated with epileptic phenotypes; other subunits remain interesting candidates owing to their localization (Hartmann et al. 1999) or functional behavior (Grieco et al. 2002), although persistent sodium current favoring neuronal oscillation may be a feature of all sodium channel genes (Taddese & Bean 2002). Site-directed mutagenesis of these channel subunits has illustrated the precise dependence of specific biophysical properties on various internal sequence motifs, and reductions in channel inactivation of only a few percent promote aberrant repetitive firing. Based on these models, analysis of the first set of human epilepsy mutations from large family pedigrees yields data consistent with the neurological phenotype (Spampanato et al. 2001, Sugawara et al. 2001a, Wallace 1998). When human subunits are transfected into mammalian cells, a slow ramp depolarization protocol reveals that the mutations lead to inappropriate activation of sodium current, and test pulses show defects in membrane repolarization due to delayed channel openings, which indicates incomplete inactivation rather than altered single-channel conductance (Lossin et al. 2002). These subunits are arranged in distinct but only partially overlapping distributions on neurons; Nav1.1 localizes to somatodendritic compartments, whereas Nav1.2 resides primarily on axonal membranes, including the hillock (Gong et al. 1999). The β1 subunit interacts with both α subunits, and mutation of the extracellular domain also prolongs current flow by reducing inactivation (McCormick et al. 1999). These mutant kinetic properties and the channel distribution make intuitive sense in terms of their ability to enhance bursting in individual neurons, allowing rapid recruitment of cells into a hypersynchronous neuronal ensemble.

A second set of sodium channelopathies is not as well behaved. One mutation in the gene for Nav1.1 accelerates recovery from inactivation (Spampanato et al. 2001), and another shows a reduction of current by prolonging inactivation (Alekov et al. 2001). These data could reflect a disparity between oocyte and neuronal expression systems; however, other evidence also suggests that epilepsy may arise from reducing sodium currents. In severe myoclonic epilepsy of infancy (SMEI), a clinically more severe infantile seizure disorder, sporadic mutation of Nav1.1 is linked to diffuse EEG abnormalities and febrile, clonic, myoclonic, and partial seizures (Claes et al. 2001, Sugawara et al. 2001b). The majority of cases are hemizygous for nonsense and frameshift mutations that lead to truncation of the pore-forming protein and a predicted loss of channel function.

How might reduction of Nav1.1 current density lead to a hyperexcitable neurological phenotype—one that is more malignant than those owing to mutations prolonging channel openings? Reduced current has also been noted in other sodium channelopathies linked to episodic heart and muscle disorders; however, the absence of positive signs of prolonged cellular depolarization (no LQT, no myotonia) in these phenotypes (Baroudi et al. 2002, Jurkatt-Rott et al. 2000) distinguishes them from the hyperexcitability of epileptic brain. Mice heterozygous for Nav1.2 subunit deletion are normally developed without cellular hyperexcitability or behavioral seizures (Planells-Cases et al. 2000). Although voltage clamp protocols do not necessarily predict in vivo repetitive firing behavior, this unexpected finding suggest that, unless the truncated channel protein interacts allosterically to enhance native wild-type currents, epilepsy may arise by an alternative downstream pathway of reorganized gene expression in the developing circuit. Analysis of deletion mouse models will be required to determine whether a reduced gene dose for this key channel subtype is accompanied by a change in the number or positioning of Nav family members or related proteins in certain cells, resulting in a paradoxically seizure-prone network. Alternatively, loss of excitability may disturb a critical period of activity dependence at the network level, since early (albeit transient) experimental silencing of sodium channels in developing cortical and hippocampal circuits leads to subsequent increased transmitter release, anatomical reorganization, and seizures (Catalano & Shatz 1998, Galvan et al. 2000, Murthy et al. 2001).

Additional questions regarding downstream plasticity arise when the spatial and temporal parameters of the clinical phenotypes are considered. The disorders appear at various ages and display a mixed seizure phenotype, both in a single affected individual and as the gene travels through the pedigree. This pattern of generalized epilepsy with febrile seizures has been noted in large pedigrees with sodium channelopathies and termed GEFS^{+}. Although the exact circuits mediating the motor activity during different seizure types, such as clonic, tonic, myoclonic, and astatic, are not known, they are functionally distinct. When the same channel mutation creates different seizure types within a single individual, it suggests that the mutant channel lowers the seizure threshold in multiple but independently triggered circuits. Nav1.1 and $\beta 1$ channels are widely expressed, and the selectivity of the epileptic neuronal substrate must emerge from other determinants. A Nav1.1 channelopathy might create an imbalance between excitatory versus inhibitory neurons or may alter integrative properties in more complex ways—for example, by shifting the electrotonic profile and firing behaviors of small, compact cells with somatic inputs proximal to the spike initiation zone differently than those of large, highly compartmentalized neurons with distal inputs. Similarly, variation in the seizure type among members of the same pedigree may be accounted for by differing modifier loci, and, in this sense, functional expression of the channelopathy is more penetrant in some neural circuits than others.

Other issues remain before the epilepsy of sodium channelopathies can be considered solved. What mechanisms account for the temporal changes in seizure type and the sometimes substantial delay in developmental onset of the seizures?

One possibility is that the mechanism of a second seizure type is not entirely the same as the first. Both febrile and other seizure types in immature brain are potent inducers of pro- (and anti-) epileptogenic gene expression (Brewster et al. 2002, Sanchez et al. 2001), and this plasticity provides a dynamic substrate for differential circuit excitability as the seizure history develops.

POTASSIUM CHANNELOPATHIES—FEWER THAN PREDICTED With a fivefold larger number of genes distributed across many subfamilies, K^+ channelopathy is categorically far more complex owing to the diverse distribution and combinatorial possibilities of the subunit proteins. Each subunit has a specific expression pattern and generates a preferred channel subtype in the brain. It is interesting to speculate whether or not these attributes increase the likelihood or phenotypic diversity of clinical K^+ channel disorders. Although only a few examples from different subtypes have been isolated so far, each is inherently instructive.

Like other channelopathies, different mutations within the same subunit lead to diverse clinical phenotypes, and not all mutations are epileptogenic. For example, human mutations of *KCNA1* differentially affect assembly, targeting, and kinetics of the channel and may lead to partial temporal lobe epilepsy, episodic ataxia, neuromyotonia, or myokymia. The phenotypes correlate to some degree with the reduction in channel current (Rea et al. 2002) and may depend on other variables as well. For example, human mutations associated with temporal lobe epilepsy severely reduce K^+ currents, whereas a mutation associated with neuromyotonia alone does not alter current amplitude (Eunson et al. 2000, Zuberi et al. 1999). However, mice deleted for the same Kv1.1 channel show both limbic seizures (Smart et al. 1998, Rho et al. 1999) and neuromyotonia (Zhou et al. 1998). Somewhat paradoxically, overexpression of Kv1.1 can result in an unanticipated epileptic phenotype, which is likely due to coordinate changes in the expression of other subunit family members (Sutherland et al. 1999).

Epileptic K^+ channelopathies prolong neuronal depolarization in distinct ways, and the specific subtypes of K^+ channels altered lead to very different excitability patterns depending on the cell type studied. For example, Kv1.1 channels normally activate at low voltages and deactivate slowly. Kv1.1 is diffusely but differentially expressed, and, in limbic circuits, channels are prominently localized to presynaptic terminals (Wang et al. 1994). In layer V pyramidal neurons, Kv1.1 mutants show no significant differences in intrinsic membrane properties or action potential shape, which suggests little effect on repolarization in the somatic compartment. However, presynaptic excitability in some interneurons is altered because the frequency of spontaneous inhibitory, but not excitatory, postsynaptic currents is elevated, which may increase inhibitory drive (van Brederode et al. 2001). Similar evidence for a preferred effect on inhibitory synaptic terminals has been obtained in cerebellar circuits, where GABAergic basket cells (although not involved in epileptogenesis) also express Kv1.1 at the preterminal axonal arborization. Spontaneous inhibitory postsynaptic currents (IPSCs) onto Purkinje cells in mutants are elevated twofold in frequency. Because the spontaneous firing patterns of the interneuron are unaltered,

prolonged repolarization may facilitate impulse propagation through a branch point where failure could ordinarily occur (Zhang et al. 1999). Thus, some forms of inhibition are enhanced in mutant Kv1.1 networks.

In contrast, Kv3.2 channels activate at more positive voltages seen only during an action potential and have fast deactivation rates that facilitate high-frequency bursting (Rudy & McBain 2001). Because Kv3.2 is preferentially expressed in a subset of "fast-spiking" cortical interneurons (Tansey et al. 2002), loss of this channel impairs bursting and disinhibits cortical circuits, which contributes to the epilepsy identified in mice deleted for this gene (Lau et al. 2000). A mutation in the human orthologue has not yet been reported.

KCNQ2/3 channels differ with those above both in distribution and mode of activation. Discovery of these genes resulted from cloning a human neonatal convulsion syndrome (see Leppert & Singh 1999) and opened two doors: first, the identification of a family of novel brain K^+ channels that could be modulated by the m1 muscarinic receptor and activated by the anticonvulsant drug retigabine (reviewed by Jentsch 2000, Rogawski 2000); and second, the channels define a molecular origin for an inherently important clinical epilepsy syndrome considered to be benign because seizures appear in the newborn but remit in early childhood. Understanding the molecular plasticity employed by the brain to overcome loss of this source of M current may point the way to therapeutically relevant strategies for other seizure syndromes.

Kcnq2/3 heteromultimers are outwardly rectifying at voltages above −60 mV and sensitive to intracellular ATP and calmodulin (Schroeder 1998, Wen & Levitan 2002). All combinations of Kcnq1-4 homomers as well as Kcnq2/3 heteromers are inhibited by muscarinic activation; however, Kcnq1 and 4 are not ubiquitously available in brain to rescue Kcnq2/3 mutations. *KCNQ2* gene expression overlaps with *KCNQ3* in excitatory pyramidal neurons in the middle layers of neocortex and the hippocampal formation, defining a region of vulnerability (Saganich et al. 2001). Immunocytochemistry of Kcnq2 shows strong labeling of inhibitory neurons (Cooper et al. 2001).

Differential expression of splice variants may play a role in the temporal onset of the disorder, since the long splice variant expressed in differentiated neurons is functionally blocked by coexpression of a short form found in fetal brain (Smith et al. 2001). Seizure remission is not due to a programmed downregulation of *KCNQ2/3* genes, since expression normally persists in adult brain. Clinical improvement does coincide with a developmental increase in the strength of other inhibitory pathways [for example, the conversion of GABA from depolarizing to hyperpolarizing transmission (reviewed in Holmes et al. 2002)]; however, this cannot explain the subsequent reoccurrence of seizures later in life in some individuals with this disorder. A mouse model (Watanabe et al. 2000) may clarify this excitability change.

Mutations of regulatory subunits of K^+ channels are also linked to disease. Hemizygous deletion of the cytoplasmic beta subunit gene *KCNAB2,* encoding the major regulatory subunit of Shaker-type channels in the brain, contributes to mental retardation and multiple seizure types in the 1p36 contiguous gene-deletion

syndrome (Heilstadt et al. 2002). Loss of the $\beta 2$ subunit prolongs membrane repolarization, and its deletion in mice also produces seizures (McCormack et al. 2002). The GABA δ subunit also lies within the 1p36 critical deletion region (Windpassinger et al. 2002), making it a second susceptibility gene for seizures in this syndrome. Because absence of the δ subunit alone has not been linked to epilepsy, the genes may act cooperatively to potentiate excitability.

CALCIUM CHANNELOPATHIES—COMPLEX RELEASE DEFECTS Inherited disorders of voltage-gated Ca^{2+} channels are epileptogenic but in entirely different ways. By decreasing inward depolarizing currents, epileptic calcium channelopathies do not directly lower thresholds for spike electrogenesis and bursting but instead alter synaptic strength and promote synchronization by secondary changes in circuit behavior.

Mutations in 4 of the 24 voltage-gated Ca^{2+} channel subunit genes have been associated with epilepsy. In spontaneous mouse mutants, $\alpha 1$a (Cav 2.1, *tottering, leaner, rocker, rolling*), $\beta 4$ (*lethargic*), $\alpha 2\delta$ (*ducky*), and $\gamma 2$ (*stargazer, waggler*) subunits each produce generalized absence seizures involving ethosuximide-sensitive thalamocortical spike-wave synchronization (see Burgess & Noebels 1999 and Crunelli & Leresche 2002 for review of this seizure phenotype; Barclay et al. 2001, Zwingman et al. 2002). The first few reported human mutations include a truncated Cav2.1 subunit with an absence seizure phenotype (Jouvenceau et al. 2001) and missense $\beta 4$ subunit mutations associated with other seizure patterns, including absence (Escayg et al. 2000).

Mutations of Cav2.1 in human and mouse reduce P/Q-type calcium currents owing to defective membrane targeting (*tg*) (Leenders et al. 2002) and/or kinetics (tg^{la}, tg^{rol}) (Mori et al. 2000, Wakamori et al. 1998). The effects may be unequal at excitatory and inhibitory synapses (Caddick et al. 1999). The presence of absence seizures in the Cav2.1 deletion mouse (Jun et al. 1999) confirms that reduced current leads to the synchronous discharge.

Selective network excitability in calcium channelopathies Two forms of molecular plasticity may help explain the spatial and temporal aspects of calcium channelopathy phenotypes: temporal switching and spatial reshuffling. The first defines a developmental shift in the functional reliance of the neuron from one channel pore subunit to another, whereas the latter describes the assembly of novel channel complexes comprised of subunits that remain following loss of an accessory subunit.

The first form of molecular plasticity is channel subunit switching. Optical imaging of Ca^{2+} entry at presynaptic terminals in hippocampus reveals that N-type channels rescue transmitter release impaired by P/Q channel mutations (Qian & Noebels 2000). At many central synapses, release normally depends on both P/Q and N-type channels, whereas a subset may rely on either one or the other. After N-type blockade at the CA3-CA1 synapse in +/+ mice, release is reduced by about one half; whereas in *tg* mice, release fails at this synapse. This means that synapses relying primarily on N-type release are functionally spared in *tg* brain,

whereas those where P-type release predominates are severely impaired. This selective rescue of transmitter by an intact alpha subunit family member pinpoints the impaired circuitry within the *tg* brain. The developmental implications of this "rescue-of-function" hypothesis are striking because they predict the appearance of spike-wave discharges in the immature mouse. Specifically, developing thalamic terminals normally convert their release dependence from a combination of both N- and P-type channels to pure P-type during the second postnatal week (Iwasaki 2000), coincident with the appearance of spike-wave seizures (Noebels 1984). This developmental switch defines the first molecular mechanism that can explain the delayed temporal appearance of a seizure disorder and may provide a general model for the clinical phenotype of other channelopathies.

The second form of molecular plasticity is channel subunit reshuffling. A slightly different mechanism operates in the functional rescue of the $\beta 4$ subunit mutation in *lethargic* mice (Burgess et al. 1997). $\beta 4$ is the predominant Ca^{2+} channel accessory subunit in brain and interacts with two sites on both N- and P-type $\alpha 1$ subunits (Walker & De Waard 1998). Loss of $\beta 4$ in *lethargic* brain allows $\alpha 1$ subunit interactions with other β subunit family members, notably $\beta 1$ and $\beta 3$ (Burgess et al. 1999). β subunit reshuffling rescues calcium currents in brain regions where expression overlaps but leaves circuits lacking complementary β subunit expression vulnerable, although channels with novel β subunit combinations may also display distinctive physiology.

A third mechanism contributes to selective excitability increases following mutation of subunits normally associated with high voltage–activated threshold calcium currents, namely, a downstream effect on low voltage–activated currents through T-type calcium channels. Patch clamp analysis of thalamic neurons from three mice (*tg*, *lh*, and *stg*) with mutated Ca^{2+} channel subunits, none of which are confirmed to directly interact with the $\alpha 1$ subunits forming T-type channels, reveals striking increases in low voltage–activated calcium currents (Zhang et al. 2002). These currents strongly favor rebound bursting and spike-wave synchronization in the thalamocortical circuit, which suggests a complex substrate for epileptogenesis in these models.

The transmembrane $\gamma 2$ subunit is one of 7 expressed in brain (Burgess et al. 2001) and interacts directly with calcium channel $\alpha 1$ subunits (Kang et al. 2001). Loss of $\gamma 2$ leads to the spike-wave seizure phenotype in the *stargazer* mouse (Letts et al. 1998). Relay neurons in *stg* thalamic slices show alterations of both high- and low-voltage calcium current subtypes. A second function of this subunit is related to its intracellular PDZ binding domain, allowing interactions with PSD proteins that regulate AMPA receptor clustering at cerebellar granule cell synapses (Chen et al. 2000a, Hashimoto et al. 1999). Through unknown downstream steps, the $\gamma 2$ mutation also leads to further changes in excitability in *stg* neurons, including increases in a mixed cationic current Ih in neocortical pyramidal cells that favors hyperexictability (Di Pasquale et al. 1997).

Null mutations of several other α or β calcium channel subunit genes have not yet been linked to epileptic phenotypes, and deletion of a gene responsible

for thalamic T-type current, α1G, raises the threshold for induced spike-wave generation (Kim et al. 2001).

Transmitter Release Machinery—Activity Dependent Network Changes

Defects in the precise mobilization of neurotransmitter for release may alter dynamic network behavior, and, accordingly, the large protein families that mediate vesicle trafficking and exocytosis (35 SNARES, 60 Rabs, and 53-coat complex subunits in the human genome) (Bock et al. 2001) include several genes for epilepsy. Seizures appear in mice deleted for the vesicle-anchoring phosphoproteins synapsins 1 and 2, which is the first model to confirm that a primary disorder of release machinery may lead to epilepsy. Loss of these proteins diminishes the size of the presynaptic vesicle pool and disrupts synaptic depression (Rosahl et al. 1995). This phenotype was the first to focus attention on a pivotal issue, namely, the potential for an excitability imbalance due to a differential contribution of release machinery at inhibitory versus excitatory synapses. In cultured hippocampal neurons of synapsin 1–deficient mice, the quantal content of IPSCs is significantly reduced, and release is suppressed compared to excitatory synapses (Terada et al. 1999). The selectivity of this defect could also relate to the firing patterns characteristic of different cell types rather than the transmitter phenotype per se because a defective vesicle supply may preferentially impact terminals requiring high availability at moments of rapid activity, which is typical of interneurons that fire in high frequency bursts. Synapsin III shows a similar selectivity but with an opposite effect on exocytotic vesicle recycling at inhibitory synapses, and mice deficient in this gene do not have a seizure phenotype (Feng et al. 2002).

Another synaptic vesicle protein, Sv2A, also regulates synaptic strength by altering the mobility of the releasable pool. *Sv2A*-deficient mice, alone or combined with *Sv2B* nulls, show a severe seizure phenotype (Crowder et al. 1999, Janz et al. 1999). In contrast to synapsin mutants, neurons showed sustained release of transmitter in response to brief activation. Not all disruptions of the exocytotic pathway are equally epileptogenic, as evidenced by the lack of epilepsy reported in mouse mutants deleted for several other vesicle-related proteins, such as synaptotagmin (Fernandez-Chacon et al. 2001), synaptobrevin/VAMP (Schoch et al. 2001), Rab3a (Leenders et al. 2001), RIM1alpha (Castillo et al. 2002), amophiphysin 1 (Di Paolo et al. 2002), and synaptic adhesion/NCAM (Polo-Parada et al. 2001).

At an earlier stage in vesicle biogenesis, incomplete vesicle assembly can also lead to an epileptic phenotype. The *mocha* mouse encodes the AP3δ subunit of an adaptor complex that facilitates incorporation of the Znt3 zinc transporter into synaptic vesicles. Lack of the δ subunit leads to loss of vesicular zinc sequestration, severe EEG hypersychronization, and seizures (Kantheti et al. 1998). *ZNT3*$-/-$ mice also lack vesicular zinc and show a selective increase in seizure susceptibility to kainate, but not to other convulsants (Cole et al. 2000).

GABA Transmission—A Major Target for Epileptogenesis

Chloride-mediated synaptic inhibition is governed by cells that are as diverse as excitatory neurons but designed to behave in entirely distinct ways. The activation kinetics of interneurons are faster owing to distinct forms of AMPA receptors, their action potential firing patterns are more rapid owing to specific K^+ channels, and their patterns of use-dependent plasticity vary according to the molecular pathway used for calcium homeostasis (Miles 2000). Divergent synaptic projections with specific spatiotemporal activity patterns and receptor subtypes allow different types of cortical interneurons to act within their own layers, extend to others, and reach within or across modules (Golshani et al. 1997, Gupta et al. 2000). Within this pathway there are numerous molecular control points regulating transmission that may synchronize firing patterns.

PRESYNAPTIC REDUCTION OF GABA LEVELS Multiple genes that regulate the strength of GABAergic transmission are now associated with epilepsy phenotypes (Figure 1). Mutations of some genes cause a global reduction of inhibition, whereas others affect only selected cell subsets. One group of epileptogenic genes responsible for GABA levels includes *GAD65*, one of two enzymes directly responsible for synthesis of a releasable pool of GABA (Kash et al. 1997), and the neuronal glutamate transporter *EAAT1*, which supplies substrate glutamate for GABA synthesis (Sepkuty et al. 2002). Loss of the gene for tissue nonspecific alkaline phosphatase (*TNAP*) reduces pyridoxine-dependent GABA synthesis (Waymire et al. 1995), and

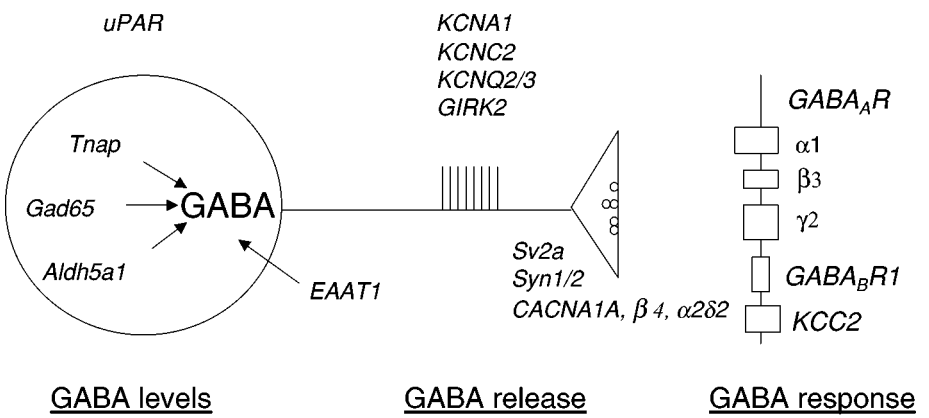

Figure 1 Site of action of 21 genes influencing central inhibitory synaptic transmission by alterations in interneuron number, excitability, GABA levels, strength of evoked presynaptic release, and postsynaptic response at GABA receptors. Targeted deletion of these genes in mice and their spontaneous mutation in human produce epileptic phenotypes. The central synaptic inhibitory pathway is the most commonly affected among known epilepsy gene mutations. See text for details.

succinic semialdehyde dehydrogenase deficiency due to *Aldh5a1* deletion modifies levels of GABA and its metabolite GHB (gamma hydroxybutyrate) (Hogema et al. 2001). These genes combine with others altering the number or release behavior of inhibitory interneurons (described below) to alter GABA availability.

GABA RECEPTOR SUBUNIT SYNDROMES GABA(A) receptors are heteropentameric protein complexes with a central chloride-conducting pore; the $\alpha 1\beta 2\gamma 2$ subunit complex predominates in most brain regions. An extensive, differentially expressed GABA(A) receptor subunit gene family (α 1-6, β1-4, γ1-3, and δ, ε, π, θ) allows for regional brain diversity. A missense mutation of the GABAR(A) α1 subunit leads to a rare dominant form of a relatively common epilepsy syndrome arising in adolescence: Juvenile Myoclonic Epilepsy (Cossette et al. 2002). Heterologous expression of the mutant subunit shows a sharply reduced binding affinity and response for GABA. The α1 subunit is diffusely expressed in forebrain (Pirker et al. 2000), but deletion of this gene in mice has no reported epileptic phenotype (Kralic 2002). This finding might be due to selective compensation in some cells by remaining α subunits, consistent with other disease examples where loss of a subunit is less deleterious than assembly of a receptor complex bearing a mutant subunit.

Functional compensation of null mutations of GABA receptor subunits by alternative family members is not uniformly effective, however, nor predictable. For example, transcriptional silencing of the GABAR β3 subunit gene in the Angelman Syndrome, a childhood mental retardation syndrome, is associated with seizures [a nearby ubiquitin processing gene, UBE3a, also contributes to the epileptic phenotype, and its imprinted expression in selected brain regions may add specificity to the β3 excitability effect (Jiang et al. 1998)]. Deletion of β3 in mice is accompanied by major regional reductions of GABA(A) receptors, thalamic disinhibition, and a severe seizure disorder (Delorey et al. 1998, Nusser et al. 2001, Sohal et al. 2000). Apparently β1, -2, or -4 subunits are unavailable for compensation in this syndrome.

Gamma subunit mutations are also less forgiving. Despite a striking reduction in GABA response, mutations of the γ2 subunit are linked to human epilepsy syndromes that are quite distinct clinically from those of α or β GABA subunits. Two types of mutations have been identified, and each shows a mixed, rather than single, seizure phenotype. Point mutation of γ2 at K289M is linked to a syndrome of childhood generalized tonic clonic epilepsy with febrile seizures (Baulac et al. 2001), and at R43Q it is linked to a pedigree with generalized absence epilepsy and febrile seizures (Wallace et al. 2001). Both of these mutations are predicted to alter extracellular domains of the receptor, and analysis of the GABA sensitivities shows reduced function through distinct mechanisms; R43Q decreases the amplitude consistent with a numerical reduction of membrane receptors, whereas K289M alters deactivation kinetics (Bianchi et al. 2002). Truncation mutations in the same gene lead to retention of the nonfunctional subunit in the endoplasmic reticulum, diminished GABA response, and epilepsy (Harkin et al. 2002, Kananura et al. 2002).

In mice, targeted deletion of the GABA $\gamma 2$ subunit is lethal soon after birth; however, the mutants exhibit abnormal episodes of hyperactivity (Gunther et al. 1995). While unconfirmed electrophysiologically, such limb movements are characteristic of neonatal seizure activity. Neurons from this mutant lose benzodiazepine sensitivity; however, $\gamma 2$ is not required for a stable GABA(A) receptor complex because the null mutant retains flunitrazepam responses in the neurons studied. It is premature, however, based on heterologous expression studies, to conclude that GABA signaling is uniformly preserved in this brain, since it remains likely that a subset of cells that does not show overlapping expression of other γ family members may show a more profound loss of GABA sensitivity.

Defects in the slower component of GABAergic signaling are also epileptogenic. Two genes encode subunits of the heterodimeric GABA(B) receptor, which couples G protein signaling to modulate Ca^{2+} and K^+ ion channels with presynaptic effects (Billinton et al. 2001). Mice deleted for the neuronal GABA(B1) receptor gene show clonic and rare absence or tonic/clonic seizures (Schuler et al. 2001). This deletion also leads to a deficiency of GABA(B2) receptors and a reduction in both pre- and postsynaptic GABAR(B) responses. A polymorphism in GABA(B1) has also been associated with a human temporal lobe epilepsy phenotype (Gamabardella et al. 2002).

Generalization of these data would support the long-held view that a simple reduction of GABA-mediated IPSPs allows escape from cortical inhibitory control and leads inexorably to seizures, but this statement is not yet fully confirmed by genetic models. Deletion of several GABA(A) receptor subunits, including $\alpha 1$ (Kralic et al. 2002), $\alpha 5$, or $\gamma 3$ (Collinson et al. 2002, Culiat et al. 1994), and δ (Peng et al. 2002) are reportedly not associated with an epileptic phenotype. It is unclear whether this outcome is due to difficulty in ascertainment of subtle seizures, to the presence of background modifier genes, or to selective functional rescue of the receptor by other GABA subunits. Alternatively, upregulation of other inhibitory pathways may mask a latent epilepsy phenotype; or perhaps these GABA subunits predominate on cell types that lie outside the epileptogenic circuit or mediate different dynamic forms (tonic versus phasic) of synaptic inhibitory signaling (Stell & Mody 2002).

Mechanisms underlying the variable developmental onset of GABAergic epilepsy syndromes have not been addressed but might be predicted to appear only after an initial neonatal delay, since GABA is depolarizing in many neural networks during early brain development (but see Wells et al. 2000). Deletion of the chloride transporter *KCC2*, which mediates the conversion of GABAergic transmission from excitatory to inhibition, also produces an epileptic phenotype (Woo et al. 2002). Similarly, GABA receptor subunits and glutamate dehydrogenase (GAD) itself show variations in cellular expression during early development (Golshani et al. 1997) and thus may entrain different circuit properties. Once seizures begin, there is substantial reorganization of GABA receptor subunit expression (Brooks-Kayal et al. 1998).

Glutamate Receptors—Epileptogenic Gains of Function

Activity-dependent plasticity of glutamate receptors is an essentially inescapable feature of epileptic brain once seizures begin; however, evidence for primary genetic errors in this pathway in human remains scant. Because receptor deletion mutants are less viable, only a few relevant examples have been directly linked to epileptogenesis by gene targeting studies: one that alters the editing of an AMPA receptor subunit, and a pair of genes involved in glutamate transport.

Mutations of the AMPA-sensitive, calcium-impermeant glutamate receptor demonstrate a novel candidate mechanism linking receptor pore properties to epileptogenesis. Mutation of the GluRB subunit to excise a pre-mRNA editing site permits formation of heteromeric AMPA receptors missing the critical pore-lining arginine site that confers both calcium impermeability and a threefold attenuation of single-channel conductance. Immature excitatory cortical neurons normally lack the GluR subunit but acquire it during postnatal development (Kumar et al. 2002). Mice bearing this mutation assemble AMPA receptors with high calcium permeability and a neurological phenotype of severe seizures and cell death (Brusa et al. 1995). A mutant null for the relevant editing enzyme, ADAR2, also shows seizures and can be rescued by Q/R site substitution (Higuchi et al. 2000). Editing enzyme defects may impact additional genes that include the A-I editing site (Seeburg 2002). Coincidentally or not, most of these genes, including 5HTR, Kv1.1, nAchR, and the drosophila calcium channel mutant *cacophony* (Kawasaki et al. 2002), have been linked to seizure or excitability phenotypes. A similar mechanism involving an RNA helicase mutation that contributes to sodium channel mRNA editing in the drosophila sodium channel mutant *para* also results in an excitability disorder (Reenan et al. 2000). The A-I editing process may be a potent, naturally occurring epileptogenic mechanism located upstream of several key excitability molecules.

Impaired glial uptake of glutamate in targeted *EAAT2* glutamate transporter deficient mice leads to excitotoxicity and seizures (Tanaka et al. 1997), whereas seizures in mice deleted for the neuronally expressed *EAAT1* family member may arise from insufficient glutamate available for GABA synthesis (Sepkuty et al. 2002).

Cholinergic Receptors

Pentamers assembled in a (2α-3β) subunit stoichiometry form the majority of brain nicotinic receptors, and five mutations in these two subunits have been linked to a partial myoclonic epilepsy syndrome termed autosomal dominant frontal lobe epilepsy (ADNFLE). Expression studies (reviewed by Bertrand et al. 2002) controlling for heterozygous gene dosage show that receptors reconstituted with mutant subunits are more sensitive to Ach, with or without changes in desensitization or calcium permeability. The receptors are widely distributed on both excitatory and inhibitory interneurons lying in and outside of the frontal lobe. The hypersynchronization may be related to excessive disinhibition by Ach release within specific cortical layers (Christophe et al. 2002). Neither the subcellular

topography, nor the modulatory function of cholinergic inputs, provide substantial clues into the basis for frontal localization of the epilepsy.

Serotonin Receptors

Targeted deletion of the serotonin 5HT2c receptor gene is associated with spontaneous seizures and a reduced threshold for audiogenic seizures (Brennan et al. 1997, Tecott et al. 1995). One mechanism for the altered excitability may include the role of this receptor in modulating a persistent sodium current. Activation of the 5HT2c receptor in cortical neurons reduces both the rapidly inactivating and persistent Na^+ channel currents through a protein kinase C (PKC)-dependent mechanism, thus lowering dendritic excitability (Carr et al. 2002). Loss of inhibition of these currents in 5HT2c−/− brain may enhance seizure susceptibility.

GENES FOR NEURONAL METABOLISM AND PLASTICITY This category currently contains a long list of genes with a broad range of function that may act in early, and perhaps throughout, brain development to enhance circuit excitability (Noebels 2001). There is as yet little information on how these different genomic "start sites" for epilepsy converge upon major pathways regulating neuronal synchronization.

GENES FOR NETWORK DYSPLASIA

Cortical dysplasias resulting from aberrant patterns of brain development are a frequent substrate for inherited seizure syndromes. The malformations may be microscopic or visible by magnetic resonance imaging and originate from diverse signaling defects affecting migration, proliferation, differentiation, and segmentation. Not all disruptions of cortical circuits are epileptogenic. Several striking examples are described here; demonstration of more intricate dysplasias awaits the experimental merger of mutagenesis models with transgenic techniques to selectively visualize cellular subtypes and the fine structure of synaptic projections in the brain (Heintz 2001, Oliva et al. 2000).

Proliferation and Cell Size

Deletion of *NeuroD/Beta2*, a neuronal bhlh transcription factor, selectively blocks postnatal proliferation of granule cells in the dentate gyrus. These mice show a hippocampal formation entirely devoid of a granule cell layer, but with a preserved pyramidal cell layer and theta rhythm generation, and exhibit frequent partial motor seizures in adulthood (Liu et al. 2000). A second but more severe defect leading to this hippocampal phenotype is demonstrated by deletion of citron-kinase, a Rho effector regulating cytokinesis (Di Cunto et al. 2000). *Citron-K*-deficient mice lack granule cells and develop fatal seizures before adulthood.

Neuronal hypertrophy is found in the neocortex of patients with temporal lobe epilepsy (Bothwell et al. 2001), and mutations of genes that control cell growth confirm an association between neuron size and epilepsy. The *pten* tumor suppressor gene encodes a lipid phosphatase that negatively regulates cell survival

mediated by the phosphatidyl inositol 3′ kinase-PKB/Akt signaling pathway (Wu et al. 1998). Selective (Cre-loxP-mediated) neuronal inactivation of *pten* in brain regions including neocortex and hippocampus is associated with cell autonomous neuronal hypertrophy and severe seizures (Kwon et al. 2001, Backman et al. 2001). No increases in cell number are evident in this model; however, cell proliferation may be perturbed in human *pten* mutations associated with macrocephaly and seizures (Marsh et al. 1999).

Migration, Segmentation, and Patterning

Inhibitory interneurons are both modified and reduced in specific human focal cortical dysplasias (Spreafico et al. 2000, Thom et al. 2002, White et al. 2001), and recent models of disrupted neocortical inhibition due to early migration failure of neuroblasts demonstrate a distinct subtype of epileptogenesis. Cortical interneurons originating in the lateral ganglionic eminence (LGE) depend on several molecules to activate signals critical for departure of these cells from their proliferative zone. Loss of repulsion signals results in retention of the cells near the site of origin, failure to pursue the migratory trajectory, and delayed or reduced arrival in the adult cortex. Neocortical GABAergic neurons are entirely absent in mutant mice with deletions of *Dlx-1* and *Dlx-2*, two homeobox genes expressed in the LGE; however, these mice are nonviable. UPA is a protease that cleaves a repulsion signal, HGF/SF, into its active form, and blocking this activation by targeted deletion of the UPA receptor, *UPAR*, results in a 60% reduction of cortical interneurons (Powell et al. 2001). *UPAR*−/− mice display frequent myoclonic seizures throughout adulthood (Powell et al. 2003).

The subcortical band heterotopia syndrome is a profound disturbance of cell migration featuring an excess production of neurons arranged in a laminar heterotopic band beneath the cortical mantle, cognitive impairment, and seizures (see review by Feng & Walsh 2001). This phenotype is linked to mutation of *DCX*, the gene encoding doublecortin, a cytoplasmic protein that interacts with the transmembrane cell adhesion molecule neurofascin and interferes with movement and proliferation of early neuroblasts (Kizhatil et al. 2002). Functional imaging and depth recordings of *DCX*-deficient patients reveal aberrant synchronization within the inner layer (Pinard et al. 2000, Bernasconi et al. 2001). Analysis of a genetically unrelated phenocopy, the recessive *tish* rat, reveals functional interconnectivity between normotopic and heterotopic cells (Schottler et al. 2001), and depth recordings in this model also show epileptiform EEG synchronization occurring in both external and inner gray matter layers (Chen et al. 2000b). The relative balance in the number and efficacy of excitatory and inhibitory neurons within the outer and inner laminae have not been defined.

Similar issues remain to be explored in the *filamin* gene (*FLN1*) mutation linked to periventricular nodular heterotopia (Fox et al. 1998). Filamin interacts with F-actin during motility-related cytoskeletal reorganization, and mutation results in a subset of neurons clustered at the ventricular zone. Although this phenotype suggests an earlier migratory arrest, some of the network defects, both inside and

outside the ectopic cortex, may overlap with those of doublecortin and other gene mutations where neurons do not mature in their normal cortical environment. Analysis of mutant human *FLN1* neurons and chemically induced heterotopias confirms that key intrinsic excitability changes occur when cells develop outside of their natural lamination pattern; such molecular rearrangements may provoke specific patterns of aberrant receptor expression and loss of repolarizing K^+ currents that favor epilepsy (Castro et al. 2001, Battaglia et al. 2002).

Mutations in the human *reelin* gene (*RELN*) are linked to a lissencephalic cortical neuronal migration defect with seizures (Hong et al. 2000). *RELN* encodes a secreted protein that binds to multiple receptors, including the very low density lipoprotein receptor (VLDLR), apolipoprotein E receptor 2 (ApoER2), integrins, and protocadherins. A similar loss of function in the *reeler* mouse has not been associated with seizures. In contrast, mice lacking the neuronal-specific activator of cyclin-dependent kinase 5, *p35*, show seizures and a severe migration defect notable for a reversal of the radial sequence of cortical lamination resembling that of *reeler* mice (Chae et al. 1997). Cellular dysmorphology, laminar dispersion, and altered inhibitory axonal innervation patterns are also seen (Wenzel et al. 2001). Hypotheses concerning the role of orientation and lamination patterns versus intrinsic excitability properties may be testable by comparing these two disparate genes causing reversal of cortical neuronal migration order.

Genetic disruption of homeobox genes related to specification, regionalization, and terminal differentiation of the neocortex result in epileptic phenotypes. In a mutant mouse deleted for *OTX-1* with spontaneous seizures, analysis of layer V cortical pyramidal neurons suggests that a selective loss of large projecting neurons leads to a complex rearrangement of local circuitry characterized by an excess of NMDA-mediated excitation (Sancini et al. 2001). Also within this category, mutation of the human *ARX* gene is associated with a variable syndrome of myoclonic seizures, infantile spasms, and mental retardation types in a neurological syndrome featuring epilepsy and mental retardation (Stromme et al. 2002).

Epigenetic Dysregulation

Transcription factors and protein silencers act together to control the activation and repression of the genetic differentiation program (Robertson & Wolffe 2000). Mutation of genes acting in this pathway are now linked to epilepsy; however, tracing their molecular pathogenesis will prove unusually complex because they may engender aberrant expression of hundreds of other genes throughout brain development (Tucker et al. 2001), and even a single factor can both activate and repress transcription (Latchman 2001).

Two examples are worth noting at the DNA and RNA levels. Rett Syndrome, an X-linked disorder including mental retardation and seizures, is associated with mutations of the *MECP2* gene. The gene encodes a 486–amino acid neuronal protein containing several active regions, including a domain that binds to methylated CpG dinucleotides present in promoter regions and a transcriptional repression domain that interacts with corepressor complexes, including histone deacetylase,

to mediate transcriptional repression by remodeling chromatin structure. Transgenic expression of a human pathogenic mutation in the mouse increases histone acetylation and produces myoclonic seizures (Shabazaian et al. 2002). Human Rett cortex demonstrates regressive changes, including reduced cortical thickness, neuronal size, dendritic arborization, and synaptic density, which suggests that a proliferative phase of synaptic and dendritic elaboration may have been inhibited owing to a failure of *MECP2* to silence genes involved during this remodeling period (Johnston 2001). The extent of abnormal gene expression in the brain of *MECP2*-deficient mice, however, appears more subtle than predicted (Tudor et al. 2002).

Deletion of the *jerky* gene in mice leads to a limbic seizure phenotype, and, although functional characterization is not complete, this may arise through a defect in translational processing. The Jerky protein is a brain-specific constituent of translationally inactive messenger ribonucleoprotein (mRNP) particles. Based on its similarity to centromere binding protein-B, Jerky may act in the cytoplasm to inhibit a subset of mRNAs, and loss may lead to early dysregulation of neuronal genes (Liu et al. 2002). A mutation in the human homologue, JH8, has been identified in a case of childhood absence epilepsy (Moore et al. 2001).

SEIZURE SUSCEPTIBILITY AND EPILEPTOGENESIS

Seizure susceptibility loci, that is, mutations in genes where no spontaneous seizures are reported and yet the threshold to convulsant stimuli is lowered, far outnumber the genes reviewed here. These may or may not be related to an epilepsy phenotype and are best considered separately. The distinction is based on two concerns, clinical and genomic. First, spontaneous electrographic seizures may be brief, infrequent, age dependent, or behaviorally silent, and therefore unwitnessed. Assays for seizure threshold evaluate specific chemical or anatomical pathways, meaning that different modes of stimulation, even within the same mutant, often yield distinct, and occasionally reciprocal, results. Second, the mutations are rarely evaluated on multiple genetic backgrounds, even though loci modifying stimulus threshold are present in inbred mouse strains (Frankel et al. 2001). Thus an allele's effect on the excitability phenotype is empiric, and even a lowered threshold for triggering a seizure does not mean that epilepsy will ever spontaneously occur. Identification of such genes is nonetheless crucial to understanding the complex inheritance of human epilepsy as well as discrepancies in the phenotypic patterns of epilepsy observed between mouse and man.

CONVERGENCE OF EPILEPTOGENIC MOLECULAR PATHWAYS

After genetic delineation of pathways for epileptogenesis, the next level of analysis is whether, where, and when these diverse pathways functionally intersect. Does the molecular proximity of the site of convergence matter? Do all epileptogenic genes ultimately disturb inhibition?

Heteromeric subunits within a single-gene superfamily of voltage-gated ion channels are a clear example of convergence at close range. For example, individual mutations of the four genes encoding individual subunits of the calcium channel, each of which is critical for proper function of the complex, lead to remarkably similar, but not identical, phenotypes. This is likely to be a general statement for other channelopathies. Longer-range convergence is detectable across gene families, for example linking a transmitter to its postsynaptic targets. NPY is coreleased at a subset of inhibitory interneurons and potently inhibits synaptic release by two separate receptor mechanisms: NPYR1 (acting on a GIRK channel) and NPYR2 (acting on a Ca^{2+} channel) (Sun et al. 2001). Both of these downstream targets are also directly linked to epileptogenesis. Loss of NPY signaling alters network synchronization, and NPY-deficient mice have prolonged severe convulsive episodes (Erickson et al. 1996, Vezzani et al. 1999). In this example, each of the mutations have entirely distinct neurological and seizure phenotypes. It would appear that mutation at almost any molecular step in a neural pathway is capable of altering brain function in a unique way.

Pathway analysis should motivate linkage in other experimental models to test for convergent function that could shape epileptogenesis. For example, both calcium channels and potassium Kcnq2/3 channels interact with calmodulin, and loss of the alpha subunit of Ca^{2+}/calmodulin-dependent kinase II is also related to spontaneous seizures (Butler et al. 1995). In contrast, seizures have not been reported as a phenotype in any of the muscarinic receptor deletion mutants on the backgrounds studied, despite the linkage of reduced Kcnq2/3-mediated M currents and epilepsy. With continued hypothesis testing, pivotal points will be clarified that will allow predictive statements about the role of interacting proteins in up- and downstream pathways.

SUMMARY

Mutations in genes regulating most major categories of cellular function now identify the point of origin of many inherited epilepsies. The primary affected network is defined by the cellular expression of the mutant gene and its overlap with functionally compensatory interacting proteins; however, based on the precision with which use and disuse shape the developing neural network, the pathogenic circuit for seizures may often extend beyond these borders. The alterations induced by a majority of genes for epileptogenesis, regardless of their expression in interneurons, undermine inhibitory processes in the brain.

The isolation of gene mutations associated with human epilepsy and targeted deletion of genes in mutant mice have profoundly expanded the molecular substrate of epilepsy research, enabling biological model-building of developmental pathways of neurologic disease. It is too early to fully grasp the dimensions of activity-dependent plasticity in the developing brain before and after seizures begin; however, conditional transgenic models will help delineate which of the biological defects arise in early development or can produce epilepsy at any time,

and promoter-driven gene modification can be used to identify necessary and sufficient networks for many seizure phenotypes. More, rather than fewer, mutations in gene pathways will be required to resolve principle sites of convergence. These sites will ultimately help answer the two most important clinical questions regarding downstream molecular mechanisms of epilepsy: Which mechanisms are reversible? Which, if identified early, can be prevented?

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