Human Molecular Genetics, 2005, Vol. 14, No. 17 ***2491–2500***
doi:10.1093/hmg/ddi250
Advance Access published on July 27, 2005

Sacred disease secrets revealed: the genetics of human epilepsy

Julie Turnbull[1,†], Hannes Lohi[1,†], Jennifer A. Kearney[2], Guy A. Rouleau[3], Antonio V. Delgado-Escueta[4], Miriam H. Meisler[2], Patrick Cossette[3] and Berge A. Minassian[1,*]

[1]Program in Genetics and Genomic Biology, The Hospital for Sick Children, Toronto, Ontario, Canada M5G 1X8, [2]Department of Human Genetics, University of Michigan, Ann Arbor, MI 48109-0618, USA, [3]Center for the Study of Brain Diseases, Centre Hospitalier de l'Université de Montréal, Notre Dame Hospital, Montreal, Quebec, Canada H2L 4M1 and [4]Epilepsy Center of Excellence, Greater Los Angeles VA Healthcare System, Los Angeles, CA 90073, USA

Received June 15, 2005; Accepted July 8, 2005

Neurons throughout the brain suddenly discharging synchronously and recurrently cause primarily generalized seizures. Discharges localized awhile in one part of the brain cause focal-onset seizures. A genetically determined generalized hyperexcitability had been predicted in primarily generalized seizures, but surprisingly the first epilepsy gene discovered, *CHRNA4*, was in a focal (frontal lobe)-onset syndrome. Another surprise with *CHRNA4* was its encoding of an ion channel present throughout the brain. The reason why *CHRNA4* causes focal-onset seizures is unknown. Recently, the second focal (temporal lobe)-onset epilepsy gene, *LGI1* (unknown function), was discovered. *CHRNA4* led the way to mutation identifications in 15 ion channel genes, most causing primarily generalized epilepsies. Potassium channel mutations cause benign familial neonatal convulsions. Sodium channel mutations cause generalized epilepsy with febrile seizures plus or, if more severe, severe myoclonic epilepsy of infancy. Chloride and calcium channel mutations are found in rare families with the common syndromes childhood absence epilepsy and juvenile myoclonic epilepsy (JME). Mutations in the *EFHC1* gene (unknown function) occur in other rare JME families, and yet in other families, associations are present between JME (or other generalized epilepsies) and single nucleotide polymorphisms in the *BRD2* gene (unknown function) and the malic enzyme 2 (*ME2*) gene. Hippocrates predicted the genetic nature of the 'sacred' disease. Genes underlying the 'malevolent' forces seizing 1% of humans have now been revealed. These, however, still account for a mere fraction of the genetic contribution to epilepsy. Exciting years are ahead, in which the genetics of this extremely common, and debilitating, neurological disorder will be solved.

> I am about to discuss the disease called "sacred." It is not, in my opinion, any more divine or more sacred than any other diseases, but has a natural cause … Its origin, like that of other diseases, lies in heredity … The fact is that the cause of this affection is … the brain … My own view is that those who first attributed a sacred character to this malady were like the magicians, purifiers, charlatans, and quacks of our own day … (1)
>
> Hippocrates 470-410 BC

Two and a half millennia ago, the 'father of medicine' described epilepsy (1) and noted its genetic basis. The current decade marks the first unraveling of molecular alterations responsible for epilepsy and its heritability, which we review in this article.

The human brain is possibly the most complex structure in the universe (Fig. 1). The neuronal component consists of more than 20 billion cells, each connected with at least 10 000 others (2). Epilepsy is defined as a propensity to

*To whom correspondence should be addressed at: Program in Genetics and Genomic Biology and Department of Paediatrics (Neurology), The Hospital for Sick Children, Toronto, Canada M5G 1X8. Tel: +1 4168136291; Fax: +1 4168136334; Email: bminass@sickkids.ca
†The authors wish it to be known that, in their opinion, the first two authors should be regarded as joint First Authors.

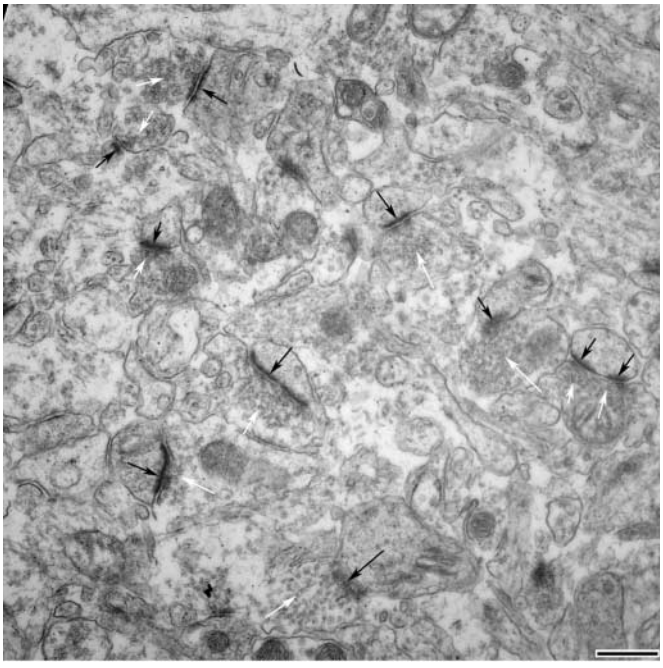

Figure 1. Electron micrograph of mouse neuropil. Several synapses are shown: black arrows point to the postsynaptic density, which is comprised of the neurotransmitter receptors; white arrows point to presynaptic vesicles, which contain the neurotransmitters. Bar = 500 nm. There are at least 200 quadrillion synapses in the human brain. Image courtesy of Dr Cameron Ackerley.

seize; in practice, an individual who has two or more unprovoked seizures is epileptic and will usually continue to have seizures unless successfully treated. Epilepsy affects 1% of people worldwide, in an estimated 40% of whom it is genetically determined (3). Other causes of epilepsy include trauma, stroke and tumors.

In wakefulness, brain activity is in a state of apparent chaos. Like busy workers in a busy city, every neuron is acting and reacting, which in turn generating consciousness and the other characteristics and abilities of the mind. During sleep, specialized neurons in the thalamus with profuse connections to the entire brain (Fig. 2) gradually disrupt the individual activities of cortical neurons and entrain them all into monotonous rhythmic synchronized discharges (4). Therefore, synchronized activity of large numbers of neurons abolishes their normal 'wakeful' functions.

A seizure also consists of synchronized firing of large numbers of neurons. There are two main types of seizures. In primarily generalized seizures, the thalamocortical circuitry is involved early in the attack and results in synchronized firing of neurons brain-wide, unconsciousness and often violent rhythmic shaking of body parts. In focal-onset seizures, the synchronized activity is restricted to one part of the cortex (e.g. to the arm control area of the right hemisphere, resulting in left-arm shaking) and may or may not subsequently spread to recruit the thalamocortical pathways and result in secondary generalization (5).

Firing of an action potential by a neuron results from threshold depolarization of its cross-plasma membrane voltage. This voltage is regulated by numerous ion channels

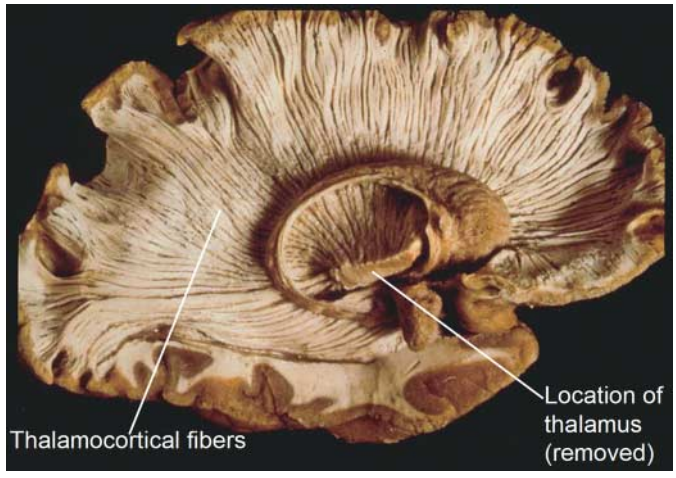

Figure 2. Thalamocortical fibers connect the thalamus to the entire cerebral cortex and allow it to synchronize cortical neuronal firing, in sleep and during generalized seizures.

that open or close, some in response to synaptic neuromediators and others in response to changes in the voltage itself. It is easy to imagine that genetic mutations in singly or groups of channels will result in altered neuronal excitability, which, in certain situations, will cause recurrent firing and driving of a network of neurons into synchrony and a seizure. It is important to remember that 'increased excitability' is not synonymous with seizure, e.g. the increased excitability could be in inhibitory neurons. The final outcome of seizure due to excitability change depends very much on which neurons in which networks are affected.

This review restricts itself to the genetic causes of epilepsies occurring in previously well individuals with no evident underlying brain disorder before the onset of seizures. The first section addresses the roles of excitatory ion channels (Na and Ca), the second, inhibitory channels (K and Cl), and the third, non-ion channel genes. In all cases, so far the resultant epilepsies are autosomal dominant disorders or sporadic syndromes due to *de novo* hemizygous mutations (Table 1).

EXCITATORY ION CHANNEL EPILEPSY GENES

Sodium channel mutations

Nine genes encode α-subunits of voltage-gated Na channels. Four of these are highly expressed in neurons of the central nervous system: *SCN1A* ($Na_v1.1$), *SCN2A* ($Na_v1.2$), *SCN3A* ($Na_v1.3$) and *SCN8A* ($Na_v1.6$). The first evidence for a role of this gene family in epilepsy came from positional cloning of the inherited syndrome generalized epilepsy with febrile seizures plus (GEFS+), a mild disorder with a variable epileptic phenotype including fever-induced seizures. Two families with gene loci mapped to chromosome 2q24 families contained missense mutations in evolutionarily conserved residues of *SCN1A*, changing amino acid residues within or close to transmembrane segments of the protein (6). Since then, 13 additional missense mutations of *SCN1A* have been identified, accounting for ~10% of GEFS+ families tested (Fig. 3A). In functional assays, these missense mutations

Table 1. Epilepsy genes and corresponding syndromes

Genes	Neurological disorder	Chromosome	References
Na channel			
SCN2A	BFNIS (MIM 607745), GEFS+ (MIM 604233)	2q23–q24.3	(15,16)
SCN1B	GEFS+1 (MIM 604233)	19q13.1	(19)
SCN1A	GEFS+2 (MIM 604233), SMEI (607208)	2q24	(6,12)
Ca channel			
CACNB4	IGE (MIM 600669), JME (MIM 606904)	2q22–23	(28)
CACNA1A	EA2 (MIM 108500), FHM(MIM 141500), SCA6 (MIM 183086), IGE (MIM 600669)	19q	(31,33,89)
CACNA1H	CAE (MIM 607682)	16p13.3	(23)
ACh receptor			
CHRNA4	ADNFLE1 (MIM 6000513)	20q13.2–q13.3	(36)
CHRNB2	ADENFL3 (MIM 605375)	1p21	(90,91)
K channel			
KCNQ2	BFNC1 (MIM 125370), BFNC/myokymia (MIM 606437)	20q13.3	(92)
KCNQ3	BFNC2 (MIM 121201)	8q24	(43,44)
KCNA1	EA1 (MIM 160120), partial epilepsy	12p13	(45,93)
$GABA_A$ receptor			
GABRA1	JME (MIM 606904)	5q34	(60)
GABRG2	GEFS+3 (MIM 604233), CAE (MIM 607681)	5q34	(58,59)
GABRD	GEFS+ (MIM 604233)	1p36.3	(63)
Cl channel			
CLCN2	CAE (MIM 607682), EGMA (MIM 607628)	3q26	(66)
Non-ion channel			
LGI1	ADPEAF (MIM 600512)	10q24	(71,94)
EFHC1	JME (MIM 254770)	6p12–p11	(80)
BRD2	JME (MIM 254770)	6p21.3	(85)
ME2	IGE (MIM 600669)	18q21	(86)

BFNIS, benign familial neonatal and infantile seizures; IGE, idiopathic generalized epilepsy; EA, episodic ataxia; FHM, familial hemiplegic migraine; SCA, spinocerebellar ataxia; BFNC, benign familial neonatal convulsions; EGMA, epilepsy with grand mal upon awakening; ADPEAF, autosomal dominant partial epilepsy with auditory features.

produce subtle changes, such as increased persistent current and alterations in voltage-dependent gating, in biophysical parameters of channel activity (7–10). One GEFS+ mutation in the C-terminal cytoplasmic domain of *SCN1A* reduced interaction with the β1-subunit (11).

In addition to inherited mutations, it is now clear that *de novo* mutations of *SCN1A* account for ∼50% of patients with severe myoclonic epilepsy of infancy (SMEI), a severe, early-onset epilepsy accompanied by intellectual deterioration (12). Nearly 200 independent mutations have been identified in affected children, and more than 90% of tested cases were sporadic. Approximately half of the SMEI mutations are nonsense mutations resulting in truncation of the channel protein and loss of channel activity (Fig. 3B). The observation that phenotypic severity is comparable to truncations close to the N-terminus of the protein and those close to the C-terminus indicates that loss of function is the common feature and demonstrates haploinsufficiency for *SCN1A* (13). Many missense mutations in SMEI patients also result in loss of function (14). It now appears that the *SCN1A*-related epilepsies comprise a spectrum of severity ranging from the mildest cases of GEFS+ characterized by childhood seizures without progression, through a wide range of variable phenotypes, to the devastating loss of function mutations in SMEI.

A small number of mutations have been identified in the closely related channel *SCN2A*, located 600 kb downstream from *SCN1A*. One missense mutation of *SCN2A* was found in a GEFS+ family (15), and six missense mutations were identified in patients with benign familial neonatal–infantile seizures, a mild syndrome that presents and remits in the first year of life (16,17) . One truncation mutation of *SCN2A* was identified in a patient with intractable epilepsy resembling SMEI (16,17).

The Na channel β-subunits, β1–β4, are small transmembrane proteins with an extracellular IgG loop (Fig. 3A). Association with the β-subunit influences α-subunit trafficking, stability and channel gating (18). Two different mutations in the β1 gene *SCN1B* have been identified in patients with GEFS+ (Fig. 3A) (19,20). The major effect of the β-subunit mutations seems to delay Na channel inactivation, similar to many of the *SCN1A* missense mutations in GEFS+ patients.

Calcium channel mutations

Ten genes encode α-subunits of voltage-gated Ca channels. Each α-subunit pairs with β- and α2δ-subunits (each of which has four subtypes), as well as a γ-subunit (eight subtypes) in certain instances. The magnitude of combinations linking these subunits allows for vast diversity in the regulation of Ca entry.

Several coding single nucleotide polymorphisms (SNPs) have been found in the *CACNA1H* gene in rare patients with

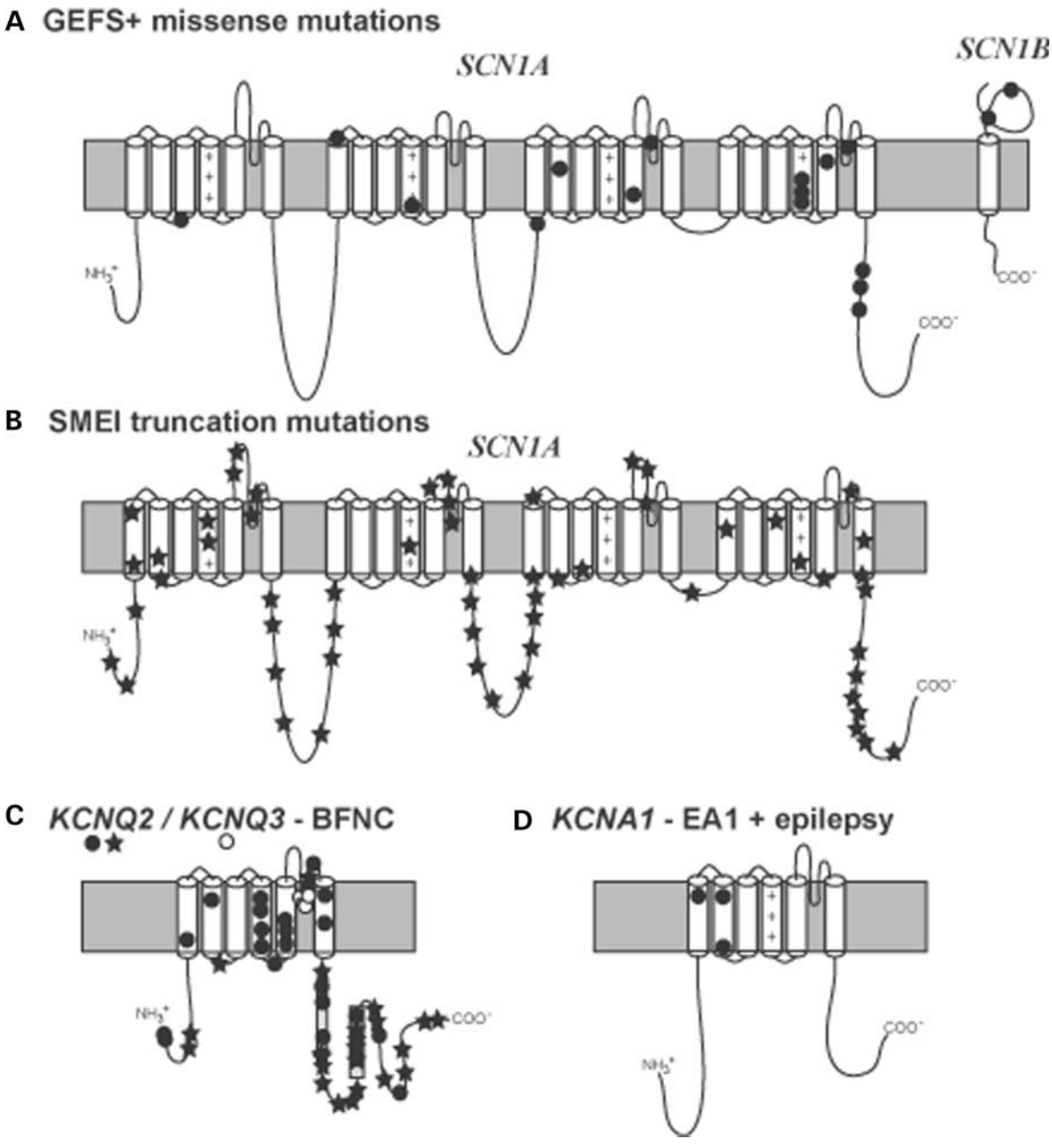

Figure 3. Epilepsy mutations in voltage-gated sodium and potassium channel genes. (**A**) Missense mutations of *SCN1A* and *SCN1B* in families with GEFS+. (**B**) *De novo* truncation mutations of *SCN1A* in patients with SMEI. (**C**) Mutations of *KCNQ2* (filled symbols) and *KCNQ3* (open symbols) in patients with benign familial neonatal convulsions. (**D**) Mutations of *KCNA1* in episodic ataxia 1 patients with seizures.

primarily generalized seizures, and not in a large number of controls. The patients included cases of childhood absence epilepsy (CAE) (21–23), a common pediatric epilepsy with frequent unconscious staring spells without convulsion. *CACNA1H* encodes an α-subunit that determines the $Ca_v3.2$ T-type calcium channel, which is critically linked to the synchronizing activity of the thalamus (4,24) and which is modulated by ethosuximide (25), the drug of choice for CAE. Furthermore, the various epilepsy-associated *CACNA1H* SNPs alter properties of the channel in ways predicted to generate seizures (23,26,27). Together, these results suggest that these SNPs are true mutations, explaining a small fraction of CAE.

A truncating mutation in *CACNB4* was found in a small family segregating juvenile myoclonic epilepsy (JME) (28), a very common epilepsy of adolescence with early morning jerks of the arms and generalized convulsions. The *CACNB4* observation has not yet been confirmed in other JME cases. Other *CACNB4* mutations, and mutations in *CACNA1A*, cause episodic ataxia type 2 and hemiplegic migraine. These disorders are not epilepsies, because they do not involve synchronized firings of large numbers of cortical neurons.

Nonetheless, many affected members in these families do also suffer bona fide seizures, indicating that these Ca channel genes also drive seizures when their properties are altered (28–33).

Mutations in the α4β2 nicotinic acetylcholine receptor

Nicotinic acetylcholine receptors are ligand (acetylcholine)-gated cation (Na and Ca) channels. They are pentamers of two types of subunits (α and β). α4 combined with β2 is the most common arrangement in brain (34). Six missense mutations causing an autosomal dominant nocturnal frontal lobe-onset epilepsy (ADNFLE) have been identified in α4β2, four in α4 (*CHRNA4*) and two in β2 (*CHRNB2*) (35). One of the α4 mutations is the first epilepsy-causing mutation discovered (36).

α4β2 occupies a particular neuronal location, and its mutations appear to cause epilepsy through a particularly interesting mechanism (37), which are worth elaborating (Fig. 4). It is present at the presynaptic side (axonal side) of both glutamatergic and GABAergic synapses. (Glutamate and GABA are the main excitatory and inhibitory neurotransmitters in brain. Glutamate receptors are Ca channels, which take in large amounts of Ca when stimulated. GABA receptors are Cl channels.) (38) The patch of presynaptic membrane occupied by α4β2 at these synapses is itself postsynaptic to a cholinergic synapse. Opening of α4β2 with cholinergic stimulation depends on a strong allosteric effect of extracellular Ca (39). When α4β2 opens, it adds local depolarization to the wave of depolarization arriving to the axon terminus with the action potential. ADNFLE mutations have in common the property of eliminating the allosteric Ca effect on α4β2 (37,40). This has led to the following theory to explain how these mutations cause sleep-induced seizures. Normally, with the recurrent stimulation of cortical neurons by the thalamus during sleep, Ca in glutamatergic synapses is reduced (absorbed by the glutamate receptors) and the Ca effect on α4β2 is diminished. At GABAergic synapses, Ca is not depleted and continues to activate α4β2. In sum, inhibitory GABAergic synapses are active and excitatory synapses are inactive during sleep. With ADNFLE mutations, Ca cannot activate α4β2, inhibition in brain is lost during a time of recurrent synchronizing firing by the thalamus and a seizure is generated (Fig. 4) (37).

INHIBITORY ION CHANNEL EPILEPSY GENES

Potassium channel mutations

The principal role of K channels is stabilization of the cell membrane potential including termination of intense activity, dampening of repetitive firing and lowering the effectiveness of excitatory inputs onto the cell. Among ion channels, K channel gene diversity is particularly striking, with 24 major classes and more than 80 different subunit genes (41). To date, three of these genes, *KCNQ2* (42,43), *KCNQ3* (44) and *KCNA1* (45,46), have been implicated in epilepsy.

KCNQ2 and KCNQ3 proteins combine in a heteromer to form the M type K current, which slowly activates in the voltage range of action potential initiation, repolarizing the membrane and suppressing repetitive firing (47). Mutations of *KCNQ2* and *KCNQ3* result in benign familial neonatal convulsions, where seizures occur essentially only in the first month of life and are inducible by provoked or natural arousal from sleep (48,49). Forty-eight mutations have been reported, most in *KCNQ2* (50–54) including three *de novo* mutations in non-inherited cases (55) (Fig. 3C).

Mutations in *KCNA1* were first identified in families with episodic ataxia type 1 (Fig. 3D). In two families, missense mutation in *KCNA1* was associated with focal-onset epilepsy(45,46). *KCNA1* is a rapidly activating, delayed-rectifier K channel ($K_v1.1$) that is primarily involved in the recovery phase of action potentials (41,56). Mutations in *KCNA1* associated with epilepsy dramatically reduce K currents *in vitro* (45,46), and knockout mice exhibit spontaneous focal-onset seizures (57).

Chloride channel mutations: the $GABA_A$ receptors

$GABA_A$ receptors are ligand (GABA)-gated Cl channels, which mediate fast inhibition. Their molecular structure comprises a heteropentameric protein complex assembled from 17 different classes of subunits (α1–6, β1–4, γ1–3, …δ, ϵ, π and θ). Thus far, epilepsy-causing mutations have been identified in *GABRG2, GABRA1*, and *GABRD*, encoding, respectively, the α1, γ2 and δ-subunits (58–63), and *in vitro* functional studies have revealed that the majority of these mutations result in a reduction of GABA-activated Cl currents (Fig. 5) (58,60,63,64).

In *GABRG2*, two mutations cause GEFS+ (58,62) and two others result in febrile seizures and CAE (59,61). In *GABRA1*, one mutation segregates with rare JME families (60,65), and in *GABRD*, two missense mutations are associated with GEFS+ (63). One of these *GABRD* mutations, E177A, like *GABRG2* and *GABRA1* mutations, results in decreased amplitude of GABA-evoked currents, the other, R220C, does not. Whether it is a rare neutral variant or is associated with more subtle effects on the $GABA_A$ receptor remains to be determined. In the same study, another variant, R220H, was detected in a JME family, but it was also present in the general population with a frequency of 4.2%. Nonetheless, this polymorphism reduced GABA-evoked currents, which is expected to increase neuronal excitability. This and similar functional polymorphisms represent candidates for the modifier gene–dose effects anticipated in common epilepsies with complex inheritance, including JME and CAE.

Chloride channel mutations: the voltage-gated chloride channels

Five epilepsy mutations have been identified in the *CLCN2* gene (encoding the ClC-2 voltage-gated chloride channel) (66,67), three of which have been subject to functional studies. The M200fsX231 and del74–117 mutations completely abolish the ClC-2 current. In contrast, the G715E mutation appears to act through a different mechanism. It alters ClC-2 gating, resulting in an outward (reverse) chloride current expected to severely affect membrane potential stability and responses to polarity changes (66).

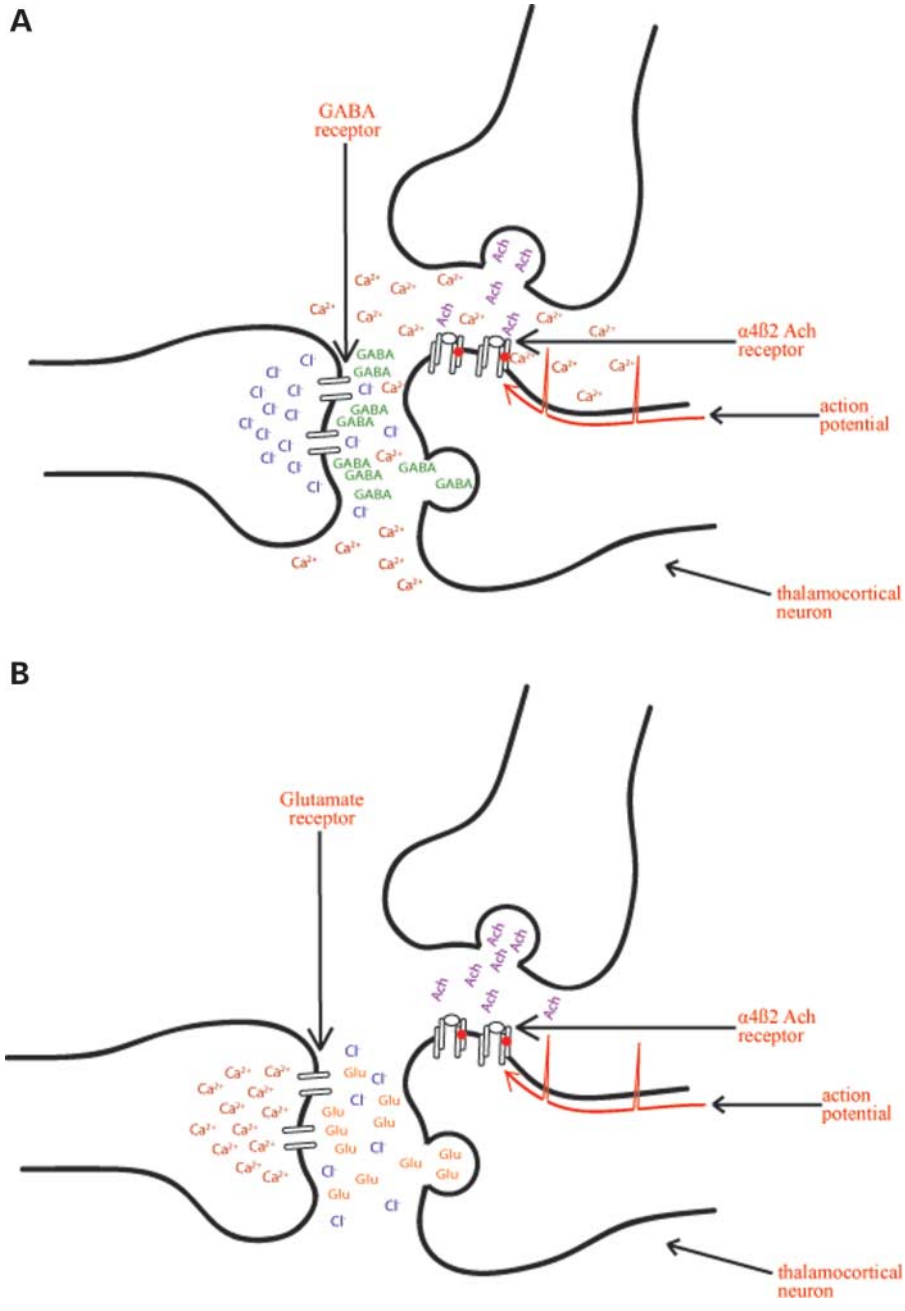

Figure 4. Model of sleep-related seizures due to mutations in the α4β2 nicotinic acetylcholine receptor (37,40). (**A**) At GABAergic synapses (inhibitory), Ca can no longer contribute to the activation of the acetylcholine receptor cation channel, because of mutation of its allosteric binding site on the channel (red dot). Decreased conduction through this cation channel results in decreased presynaptic amplification of the sleep-related trains of thalamocortical action potentials, and therefore, decreased synaptic transmission. (**B**) At glutamate synapses (excitatory), because synaptic Ca is quickly depleted into postsynaptic dendrites through glutamate receptors during repeated thalamocortical firing, it does not normally contribute to acetylcholine receptor activation. In sum, GABAergic synapses, but not glutamate synapses, are affected by the mutation during sleep, resulting in decreased inhibitory neurotransmission and seizure.

The phenotypic outcomes of the aforementioned mutations were remarkably varied. M200fsX231 was associated primarily with JME, del74–117 with generalized seizures upon awakening and G715E with juvenile absence epilepsy (a juvenile form of CAE) (66). These three epilepsies have primarily generalized seizures in common, but each has long been categorized as a separate clinical syndrome (65,68). Therefore, the *CLCN2* mutations in this study raise the possibility that variations in the same ion channel can underlie major syndrome-defining differences. Alternatively, *CLCN2* mutations merely predispose to generalized seizures, and modifier genes, different in each family, account for the phenotypic differences.

It is abundantly evident that epilepsy due to ion channel mutations is characterized by wide clinical and genetic heterogeneity. All the mutations reviewed earlier account for a mere

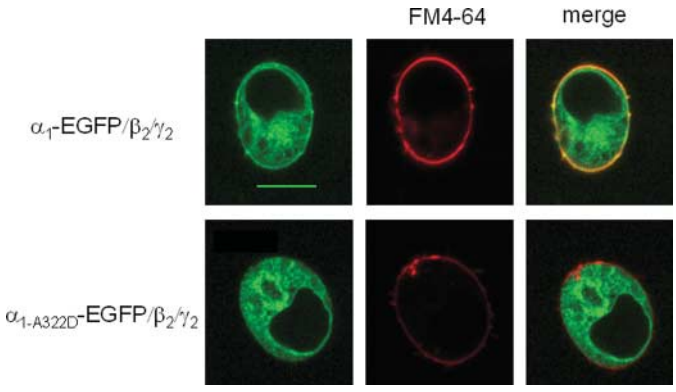

Figure 5. The A322D *GABRA1* mutation appears to reduce $GABA_A$ Cl currents through reduced surface expression of the mutated protein. HEK 293 cells were co-transfected with α1-EGFP/β2/γ2, α1-A322D-EGFP/β2/γ2, or EGFP alone and visualized using laser-scanning microscopy. Membrane specific labeling was performed by adding FM4-64 to the medium used for live confocal imaging. The overlay shows a clear localization in the surface membrane for wild-type, but not for mutant $GABA_A$ receptors (95). EGFP, enhanced green fluorescent protein.

fraction of the genetic contribution to epilepsy, and it is likely that many more ion channel mutations, singly or in groups, or mutations in proteins affecting ion channel functions will be found, tweaking the brain towards synchronized firings and seizures. However, epilepsy is also expected to result from miswirings in sections of the neural network, and perhaps some of the mutations discussed in the next section act in this fashion.

NON-ION CHANNEL EPILEPSY GENES

LGI1

Originally identified in glioma studies (69), the leucine-rich glioma-inactivated (*LGI1*) gene is currently considered not to play any important role in brain tumors (70). Instead, its mutations result in a focal-onset epilepsy with onset in or near the auditory center in the temporal lobe of the brain, resulting in auditory seizures with or without generalization to convulsion and unconsciousness (71–76).

Little is known about the *LGI1* protein function (named LGI1 and epitempin). It consists of an N-terminal leucine-rich repeat region and a C-terminal EAR (epilepsy-associated repeat) region (77), and it is a secreted protein (78,79). The EAR region is a common feature with the *Mass1* gene product mutated in the Frings mouse model of audiogenic epilepsy (77). Introduction of epilepsy-associated mutations results in unstable protein, suggesting that the mutations act through a loss of function mechanism (79). Finally, LGI1 appears to play a major role in suppressing the production of MMP1/3 through the phosphatidylinositol 3-kinase/ERK pathway. How LGI1 mutations result in seizure generation remains completely unknown, and why the temporal cortex is affected is equally mysterious. It is possible that LGI1 affects ion channels with particular relevance to auditory cortex or that it influences proper auditory cortex neuronal network establishment.

EFHC1

EFHC1 is yet another gene mutated in some families with JME. Its protein product, EFHC1 or myoclonin 1, localizes in the soma and dendrites of neurons in multiple brain regions. EFHC1 interacts with the R-type voltage-dependent Ca channel ($Ca_v2.3$) and leads to a specific increase of this current when expressed in tissue culture. Introduction of JME mutations greatly reduces the activating effect of EFHC1 on the channel (80).

EFHC1 may therefore cause JME through neuronal membrane electrical destabilization, as is the case in JME due to ion channel mutations. However, further studies raise an alternate or additional possibility. EFHC1 is pro-apoptotic, and the apoptosis it induces is reduced by *EFHC1* JME mutations. EFHC1-induced apoptosis is also specifically suppressed by a $Ca_v2.3$ antagonist, suggesting that it is driven by the Ca influx through this channel (80). During normal brain development, neuronal numbers and processes overshoot and are then trimmed as the final structure is established (81,82). The few JME brains that have been studied pathologically (83), or with detailed magnetic resonance imaging (84), reveal mildly thickened cerebral cortex and dystopic neurons. It is therefore possible that *EFHC1* mutations result in insufficient apoptotic shedding of unnecessary neurons during development and produce an imperfect, overpopulated and epileptogenic, cerebral network (80).

BRD2 and ME2

Finally, highly significant associations have been reported between non-coding SNPs in the *BRD2* gene and JME (85) and in the *ME2* gene and primarily generalized epilepsies including JME (86). BRD2 is a putative developmental transcription regulator expressed in brain and may be involved in the JME cortical microdysgenesis as mentioned earlier (85). *ME2* encodes malic enzyme 2, a mitochondrial enzyme involved in the synthesis of GABA, the ubiquitous inhibitory neuromediator (86).

The difficulty with the intriguing *BRD2* and *ME2* observations is in finding ways of establishing animal models to confirm the roles of these genes and as models for pathogenetic studies. This difficulty is shared with the increasing number of other common genetic diseases found segregating with SNPs. In most such instances, it is problematical to identify the effect of the SNP on its associated gene and find ways to replicate that effect in a mouse. Furthermore, most of these diseases are complex in inheritance, and one would need to identify and recreate several if not many participating polymorphisms. Perhaps, the solution will come not so much from engineered mice, but through detailed clinical and genetic studies in domesticated animals. A first canine epilepsy gene has already been discovered, albeit in the monogenic Lafora progressive myoclonus epilepsy (87). Epilepsy in dogs is five to 10 times more common than that in man (88). If, for example, naturally occurring JME could be characterized in dog, then one could attempt to replicate the genetic associations with *BRD2, ME2* and other JME genes in dog families, confirming the associations in a different organism and, at the same time, establishing an animal model.

Many more epilepsy genes than the ones reviewed in this article remain to be discovered. Epilepsy mutations affect proteins that regulate action potentials and synaptic function, both of which underlie neuronal communication. They also appear to affect proteins involved in proper cortical network establishment. Identifying epilepsy proteins and understanding their functions are clearly critical to better care for the tens of millions of patients afflicted with seizures (and with the devastating unpredictability of seizures). They are also of great value to the understanding of neuronal network formation and communication, i.e. ultimately, to the understanding of the human brain by the human brain.

Conflict of Interest statement. None declared.

REFERENCES

1. Riggs, A.J. and Riggs, J.E. (2005) Epilepsy's role in the historical differentiation of religion, magic, and science. *Epilepsia*, **46**, 452–453.
2. Mesulam, M.M. (1998) From sensation to cognition. *Brain*, **121** (Pt 6), 1013–1052.
3. Annegers, J.F., Rocca, W.A. and Hauser, W.A. (1996) Causes of epilepsy: contributions of the Rochester epidemiology project. *Mayo Clin. Proc.*, **71**, 570–575.
4. Steriade, M., McCormick, D.A. and Sejnowski, T.J. (1993) Thalamocortical oscillations in the sleeping and aroused brain. *Science*, **262**, 679–685.
5. Fisher, R.S., van Emde Boas, W., Blume, W., Elger, C., Genton, P., Lee, P. and Engel, J., Jr. (2005) Epileptic seizures and epilepsy: definitions proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE). *Epilepsia*, **46**, 470–472.
6. Escayg, A., MacDonald, B.T., Meisler, M.H., Baulac, S., Huberfeld, G., An-Gourfinkel, I., Brice, A., LeGuern, E., Moulard, B., Chaigne, D. *et al.* (2000) Mutations of SCN1A, encoding a neuronal sodium channel, in two families with GEFS+2. *Nat. Genet.*, **24**, 343–345.
7. Spampanato, J., Escayg, A., Meisler, M.H. and Goldin, A.L. (2001) Functional effects of two voltage-gated sodium channel mutations that cause generalized epilepsy with febrile seizures plus type 2. *J. Neurosci.*, **21**, 7481–7490.
8. Lossin, C., Wang, D.W., Rhodes, T.H., Vanoye, C.G. and George, A.L., Jr. (2002) Molecular basis of an inherited epilepsy. *Neuron*, **34**, 877–884.
9. Spampanato, J., Escayg, A., Meisler, M.H. and Goldin, A.L. (2003) Generalized epilepsy with febrile seizures plus type 2 mutation W1204R alters voltage-dependent gating of Na(v)1.1 sodium channels. *Neuroscience*, **116**, 37–48.
10. Lossin, C., Rhodes, T.H., Desai, R.R., Vanoye, C.G., Wang, D., Carniciu, S., Devinsky, O. and George, A.L., Jr. (2003) Epilepsy-associated dysfunction in the voltage-gated neuronal sodium channel SCN1A. *J. Neurosci.*, **23**, 11289–11295.
11. Spampanato, J., Kearney, J.A., de Haan, G., McEwen, D.P., Escayg, A., Aradi, I., MacDonald, B.T., Levin, S.I., Soltesz, I., Benna, P. *et al.* (2004) A novel epilepsy mutation in the sodium channel SCN1A identifies a cytoplasmic domain for beta subunit interaction. *J. Neurosci.*, **24**, 10022–10034.
12. Claes, L., Del-Favero, J., Ceulemans, B., Lagae, L., van Broeckhoven, C. and de Jonghe, P. (2001) *De novo* mutations in the sodium-channel gene SCN1A cause severe myoclonic epilepsy of infancy. *Am. J. Hum. Genet.*, **68**, 1327–1332.
13. Meisler, M.H. and Kearney, J.A. (2005) Sodium channel mutations in epilepsy and other neurological disorders. *J. Clin. Invest.*, **115**, 2010–2017.
14. Rhodes, T.H., Lossin, C., Vanoye, C.G., Wang, D.W. and George, A.L., Jr. (2004) Noninactivating voltage-gated sodium channels in severe myoclonic epilepsy of infancy. *Proc. Natl Acad. Sci. USA*, **101**, 11147–11152.
15. Sugawara, T., Tsurubuchi, Y., Agarwala, K.L., Ito, M., Fukuma, G., Mazaki-Miyazaki, E., Nagafuji, H., Noda, M., Imoto, K., Wada, K. *et al.* (2001) A missense mutation of the Na+ channel alpha II subunit gene Na(v)1.2 in a patient with febrile and afebrile seizures causes channel dysfunction. *Proc. Natl Acad. Sci. USA*, **98**, 6384–6389.
16. Heron, S.E., Crossland, K.M., Andermann, E., Phillips, H.A., Hall, A.J., Bleasel, A., Shevell, M., Mercho, S., Seni, M.H., Guiot, M.C. *et al.* (2002) Sodium-channel defects in benign familial neonatal–infantile seizures. *Lancet*, **360**, 851–852.
17. Berkovic, S.F., Heron, S.E., Giordano, L., Marini, C., Guerrini, R., Kaplan, R.E., Gambardella, A., Steinlein, O.K., Grinton, B.E., Dean, J.T. *et al.* (2004) Benign familial neonatal–infantile seizures: characterization of a new sodium channelopathy. *Ann. Neurol.*, **55**, 550–557.
18. Isom, L.L. (2001) Sodium channel beta subunits: anything but auxiliary. *Neuroscientist*, **7**, 42–54.
19. Wallace, R.H., Wang, D.W., Singh, R., Scheffer, I.E., George, A.L., Jr, Phillips, H.A., Saar, K., Reis, A., Johnson, E.W., Sutherland, G.R. *et al.* (1998) Febrile seizures and generalized epilepsy associated with a mutation in the Na+-channel beta1 subunit gene SCN1B. *Nat. Genet.*, **19**, 366–370.
20. Audenaert, D., Claes, L., Ceulemans, B., Lofgren, A., van Broeckhoven, C. and de Jonghe, P. (2003) A deletion in SCN1B is associated with febrile seizures and early-onset absence epilepsy. *Neurology*, **61**, 854–856.
21. Chen, Y., Lu, J., Pan, H., Zhang, Y., Wu, H., Xu, K., Liu, X., Jiang, Y., Bao, X., Yao, Z. *et al.* (2003) Association between genetic variation of CACNA1H and childhood absence epilepsy. *Ann. Neurol.*, **54**, 239–243.
22. Heron, S.E., Phillips, H.A., Mulley, J.C., Mazarib, A., Neufeld, M.Y., Berkovic, S.F. and Scheffer, I.E. (2004) Genetic variation of CACNA1H in idiopathic generalized epilepsy. *Ann. Neurol.*, **55**, 595–596.
23. Vitko, I., Chen, Y., Arias, J.M., Shen, Y., Wu, X.R. and Perez-Reyes, E. (2005) Functional characterization and neuronal modeling of the effects of childhood absence epilepsy variants of CACNA1H, a T-type calcium channel. *J. Neurosci.*, **25**, 4844–4855.
24. Suzuki, S. and Rogawski, M.A. (1989) T-type calcium channels mediate the transition between tonic and phasic firing in thalamic neurons. *Proc. Natl Acad. Sci. USA*, **86**, 7228–7232.
25. Coulter, D.A., Huguenard, J.R. and Prince, D.A. (1989) Characterization of ethosuximide reduction of low-threshold calcium current in thalamic neurons. *Ann. Neurol.*, **25**, 582–593.
26. Khosravani, H., Altier, C., Simms, B., Hamming, K.S., Snutch, T.P., Mezeyova, J., McRory, J.E. and Zamponi, G.W. (2004) Gating effects of mutations in the Cav3.2 T-type calcium channel associated with childhood absence epilepsy. *J. Biol. Chem.*, **279**, 9681–9684.
27. Khosravani, H., Bladen, C., Parker, D.B., Snutch, T.P., McRory, J.E. and Zamponi, G.W. (2005) Effects of Ca(v)3.2 channel mutations linked to idiopathic generalized epilepsy. *Ann. Neurol.*, **57**, 745–749.
28. Escayg, A., de Waard, M., Lee, D.D., Bichet, D., Wolf, P., Mayer, T., Johnston, J., Baloh, R., Sander, T. and Meisler, M.H. (2000) Coding and noncoding variation of the human calcium-channel beta4-subunit gene CACNB4 in patients with idiopathic generalized epilepsy and episodic ataxia. *Am. J. Hum. Genet.*, **66**, 1531–1539.
29. Barrett, C.F., Cao, Y.Q. and Tsien, R.W. (2005) Gating deficiency in a familial hemiplegic migraine type 1 mutant P/Q-type calcium channel. *J. Biol. Chem.*, **280**, 24064–24071.
30. Jodice, C., Mantuano, E., Veneziano, L., Trettel, F., Sabbadini, G., Calandriello, L., Francia, A., Spadaro, M., Pierelli, F., Salvi, F. *et al.* (1997) Episodic ataxia type 2 (EA2) and spinocerebellar ataxia type 6 (SCA6) due to CAG repeat expansion in the CACNA1A gene on chromosome 19p. *Hum. Mol. Genet.*, **6**, 1973–1978.
31. Jouvenceau, A., Eunson, L.H., Spauschus, A., Ramesh, V., Zuberi, S.M., Kullmann, D.M. and Hanna, M.G. (2001) Human epilepsy associated with dysfunction of the brain P/Q-type calcium channel. *Lancet*, **358**, 801–807.
32. Holtmann, M., Opp, J., Tokarzewski, M. and Korn-Merker, E. (2002) Human epilepsy, episodic ataxia type 2, and migraine. *Lancet*, **359**, 170–171.
33. Chioza, B., Wilkie, H., Nashef, L., Blower, J., McCormick, D., Sham, P., Asherson, P. and Makoff, A.J. (2001) Association between the alpha(1a) calcium channel gene CACNA1A and idiopathic generalized epilepsy. *Neurology*, **56**, 1245–1246.
34. Dajas-Bailador, F. and Wonnacott, S. (2004) Nicotinic acetylcholine receptors and the regulation of neuronal signalling. *Trends Pharmacol. Sci.*, **25**, 317–324.
35. Combi, R., Dalpra, L., Tenchini, M.L. and Ferini-Strambi, L. (2004) Autosomal dominant nocturnal frontal lobe epilepsy—a critical overview. *J. Neurol.*, **251**, 923–934.

36. Steinlein, O.K., Mulley, J.C., Propping, P., Wallace, R.H., Phillips, H.A., Sutherland, G.R., Scheffer, I.E. and Berkovic, S.F. (1995) A missense mutation in the neuronal nicotinic acetylcholine receptor alpha 4 subunit is associated with autosomal dominant nocturnal frontal lobe epilepsy. *Nat. Genet.*, **11**, 201–203.
37. Rodrigues-Pinguet, N., Jia, L., Li, M., Figl, A., Klaassen, A., Truong, A., Lester, H.A. and Cohen, B.N. (2003) Five ADNFLE mutations reduce the Ca2+ dependence of the mammalian alpha4beta2 acetylcholine response. *J. Physiol.*, **550**, 11–26.
38. Wonnacott, S. (1997) Presynaptic nicotinic ACh receptors. *Trends Neurosci.*, **20**, 92–98.
39. Galzi, J.L., Bertrand, S., Corringer, P.J., Changeux, J.P. and Bertrand, D. (1996) Identification of calcium binding sites that regulate potentiation of a neuronal nicotinic acetylcholine receptor. *EMBO J.*, **15**, 5824–5832.
40. Rodrigues-Pinguet, N.O., Pinguet, T.J., Figl, A., Lester, H.A. and Cohen, B.N. (2005) Mutations linked to autosomal dominant nocturnal frontal lobe epilepsy affect allosteric ca2+ activation of the {alpha}4{beta}2 nicotinic acetylcholine receptor. *Mol. Pharmacol.*, **68**, 487–501.
41. Hille, B. (2001) *Ion Channels of Excitable Membranes*, 3rd edn. Sinauer, Sunderland, MA.
42. Biervert, C., Schroeder, B.C., Kubisch, C., Berkovic, S.F., Propping, P., Jentsch, T.J. and Steinlein, O.K. (1998) A potassium channel mutation in neonatal human epilepsy. *Science*, **279**, 403–406.
43. Singh, N.A., Charlier, C., Stauffer, D., DuPont, B.R., Leach, R.J., Melis, R., Ronen, G.M., Bjerre, I., Quattlebaum, T., Murphy, J.V. *et al.* (1998) A novel potassium channel gene, KCNQ2, is mutated in an inherited epilepsy of newborns. *Nat. Genet.*, **18**, 25–29.
44. Charlier, C., Singh, N.A., Ryan, S.G., Lewis, T.B., Reus, B.E., Leach, R.J. and Leppert, M. (1998) A pore mutation in a novel KQT-like potassium channel gene in an idiopathic epilepsy family. *Nat. Genet.*, **18**, 53–55.
45. Zuberi, S.M., Eunson, L.H., Spauschus, A., de Silva, R., Tolmie, J., Wood, N.W., McWilliam, R.C., Stephenson, J.P., Kullmann, D.M. and Hanna, M.G. (1999) A novel mutation in the human voltage-gated potassium channel gene (Kv1.1) associates with episodic ataxia type 1 and sometimes with partial epilepsy. *Brain*, **122** (Pt 5), 817–825.
46. Eunson, L.H., Rea, R., Zuberi, S.M., Youroukos, S., Panayiotopoulos, C.P., Liguori, R., Avoni, P., McWilliam, R.C., Stephenson, J.B., Hanna, M.G. *et al.* (2000) Clinical, genetic, and expression studies of mutations in the potassium channel gene KCNA1 reveal new phenotypic variability. *Ann. Neurol.*, **48**, 647–656.
47. Rogawski, M.A. (2000) KCNQ2/KCNQ3 K+ channels and the molecular pathogenesis of epilepsy: implications for therapy. *Trends Neurosci.*, **23**, 393–398.
48. Rett, A. and Teubel, R. (1964) Neugeborenenkrämpfe im Rhamen einer epileptisch belasten Familie. *Wien. Klein. Wochenschr.*, **76**, 609–612.
49. Plouin, P. and Anderson, V.E. (2002) *Epileptic Syndromes in Infancy, Childhood and Adolescence.* John Libbey, London.
50. Richards, M.C., Heron, S.E., Spendlove, H.E., Scheffer, I.E., Grinton, B., Berkovic, S.F., Mulley, J.C. and Davy, A. (2004) Novel mutations in the KCNQ2 gene link epilepsy to a dysfunction of the KCNQ2-calmodulin interaction. *J. Med. Genet.*, **41**, e35.
51. Singh, N.A., Westenskow, P., Charlier, C., Pappas, C., Leslie, J., Dillon, J., Anderson, V.E., Sanguinetti, M.C. and Leppert, M.F. (2003) KCNQ2 and KCNQ3 potassium channel genes in benign familial neonatal convulsions: expansion of the functional and mutation spectrum. *Brain*, **126**, 2726–2737.
52. Borgatti, R., Zucca, C., Cavallini, A., Ferrario, M., Panzeri, C., Castaldo, P., Soldovieri, M.V., Baschirotto, C., Bresolin, N., Dalla Bernardina, B. *et al.* (2004) A novel mutation in KCNQ2 associated with BFNC, drug resistant epilepsy, and mental retardation. *Neurology*, **63**, 57–65.
53. Tang, B., Li, H., Xia, K., Jiang, H., Pan, Q., Shen, L., Long, Z., Zhao, G. and Cai, F. (2004) A novel mutation in KCNQ2 gene causes benign familial neonatal convulsions in a Chinese family. *J. Neurol. Sci.*, **221**, 31–34.
54. Pereira, S., Roll, P., Krizova, J., Genton, P., Brazdil, M., Kuba, R., Cau, P., Rektor, I. and Szepetowski, P. (2004) Complete loss of the cytoplasmic carboxyl terminus of the KCNQ2 potassium channel: a novel mutation in a large Czech pedigree with benign neonatal convulsions or other epileptic phenotypes. *Epilepsia*, **45**, 384–390.
55. Claes, L.R., Ceulemans, B., Audenaert, D., Deprez, L., Jansen, A., Hasaerts, D., Weckx, S., Claeys, K.G., Del-Favero, J., van Broeckhoven, C. *et al.* (2004) *De novo* KCNQ2 mutations in patients with benign neonatal seizures. *Neurology*, **63**, 2155–2158.
56. Meisler, M.H., Kearney, J., Ottman, R. and Escayg, A. (2001) Identification of epilepsy genes in human and mouse. *Annu. Rev. Genet.*, **35**, 567–588.
57. Smart, S.L., Lopantsev, V., Zhang, C.L., Robbins, C.A., Wang, H., Chiu, S.Y., Schwartzkroin, P.A., Messing, A. and Tempel, B.L. (1998) Deletion of the K(V)1.1 potassium channel causes epilepsy in mice. *Neuron*, **20**, 809–819.
58. Baulac, S., Huberfeld, G., Gourfinkel-An, I., Mitropoulou, G., Beranger, A., Prud'homme, J.F., Baulac, M., Brice, A., Bruzzone, R. and LeGuern, E. (2001) First genetic evidence of GABA(A) receptor dysfunction in epilepsy: a mutation in the gamma2-subunit gene. *Nat. Genet.*, **28**, 46–48.
59. Wallace, R.H., Marini, C., Petrou, S., Harkin, L.A., Bowser, D.N., Panchal, R.G., Williams, D.A., Sutherland, G.R., Mulley, J.C., Scheffer, I.E. *et al.* (2001) Mutant GABA(A) receptor gamma2-subunit in childhood absence epilepsy and febrile seizures. *Nat. Genet.*, **28**, 49–52.
60. Cossette, P., Liu, L., Brisebois, K., Dong, H., Lortie, A., Vanasse, M., Saint-Hilaire, J.M., Carmant, L., Verner, A., Lu, W.Y. *et al.* (2002) Mutation of GABRA1 in an autosomal dominant form of juvenile myoclonic epilepsy. *Nat. Genet.*, **31**, 184–189.
61. Kananura, C., Haug, K., Sander, T., Runge, U., Gu, W., Hallmann, K., Rebstock, J., Heils, A. and Steinlein, O.K. (2002) A splice-site mutation in GABRG2 associated with childhood absence epilepsy and febrile convulsions. *Arch. Neurol.*, **59**, 1137–1141.
62. Harkin, L.A., Bowser, D.N., Dibbens, L.M., Singh, R., Phillips, F., Wallace, R.H., Richards, M.C., Williams, D.A., Mulley, J.C., Berkovic, S.F. *et al.* (2002) Truncation of the GABA(A)-receptor gamma2 subunit in a family with generalized epilepsy with febrile seizures plus. *Am. J. Hum. Genet.*, **70**, 530–536.
63. Dibbens, L.M., Feng, H.J., Richards, M.C., Harkin, L.A., Hodgson, B.L., Scott, D., Jenkins, M., Petrou, S., Sutherland, G.R., Scheffer, I.E. *et al.* (2004) GABRD encoding a protein for extra- or peri-synaptic GABAA receptors is a susceptibility locus for generalized epilepsies. *Hum. Mol. Genet.*, **13**, 1315–1319.
64. McDonald, A.J., Mascagni, F. and Muller, J.F. (2004) Immunocytochemical localization of GABABR1 receptor subunits in the basolateral amygdala. *Brain Res.*, **1018**, 147–158.
65. (1989) Proposal for revised classification of epilepsies and epileptic syndromes. Commission on Classification and Terminology of the International League Against Epilepsy. *Epilepsia*, **30**, 389–399.
66. Haug, K., Warnstedt, M., Alekov, A.K., Sander, T., Ramirez, A., Poser, B., Maljevic, S., Hebeisen, S., Kubisch, C., Rebstock, J. *et al.* (2003) Mutations in CLCN2 encoding a voltage-gated chloride channel are associated with idiopathic generalized epilepsies. *Nat. Genet.*, **33**, 527–532.
67. D'Agostino, D., Bertelli, M., Gallo, S., Cecchin, S., Albiero, E., Garofalo, P.G., Gambardella, A., St Hilaire, J.M., Kwiecinski, H., Andermann, E. *et al.* (2004) Mutations and polymorphisms of the CLCN2 gene in idiopathic epilepsy. *Neurology*, **63**, 1500–1502.
68. Roger, J., Bureau, M., Dravet, C., Genton, P., Tassinari, C.A. and Wolf, P. (2002) *Epileptic Syndromes in Infancy, Childhood and Adolescence.* John Libbey, London.
69. Chernova, O.B., Somerville, R.P. and Cowell, J.K. (1998) A novel gene, LGI1, from 10q24 is rearranged and downregulated in malignant brain tumors. *Oncogene*, **17**, 2873–2881.
70. Gu, W., Brodtkorb, E., Piepoli, T., Finocchiaro, G. and Steinlein, O.K. (2005) LGI1: a gene involved in epileptogenesis and glioma progression? *Neurogenetics*, **6**, 59–66.
71. Kalachikov, S., Evgrafov, O., Ross, B., Winawer, M., Barker-Cummings, C., Martinelli Boneschi, F., Choi, C., Morozov, P., Das, K., Teplitskaya, E. *et al.* (2002) Mutations in LGI1 cause autosomal-dominant partial epilepsy with auditory features. *Nat. Genet.*, **30**, 335–341.
72. Morante-Redolat, J.M., Gorostidi-Pagola, A., Piquer-Sirerol, S., Saenz, A., Poza, J.J., Galan, J., Gesk, S., Sarafidou, T., Mautner, V.F., Binelli, S. *et al.* (2002) Mutations in the LGI1/epitempin gene on 10q24 cause autosomal dominant lateral temporal epilepsy. *Hum. Mol. Genet.*, **11**, 1119–1128.
73. Pizzuti, A., Flex, E., Di Bonaventura, C., Dottorini, T., Egeo, G., Manfredi, M., Dallapiccola, B. and Giallonardo, A.T. (2003) Epilepsy with auditory features: a LGI1 gene mutation suggests a loss-of-function mechanism. *Ann. Neurol.*, **53**, 396–399.

74. Michelucci, R., Poza, J.J., Sofia, V., de Feo, M.R., Binelli, S., Bisulli, F., Scudellaro, E., Simionati, B., Zimbello, R., D'Orsi, G. *et al.* (2003) Autosomal dominant lateral temporal epilepsy: clinical spectrum, new epitempin mutations, and genetic heterogeneity in seven European families. *Epilepsia*, **44**, 1289–1297.
75. Hedera, P., Abou-Khalil, B., Crunk, A.E., Taylor, K.A., Haines, J.L. and Sutcliffe, J.S. (2004) Autosomal dominant lateral temporal epilepsy: two families with novel mutations in the LGI1 gene. *Epilepsia*, **45**, 218–222.
76. Ottman, R., Winawer, M.R., Kalachikov, S., Barker-Cummings, C., Gilliam, T.C., Pedley, T.A. and Hauser, W.A. (2004) LGI1 mutations in autosomal dominant partial epilepsy with auditory features. *Neurology*, **62**, 1120–1126.
77. Scheel, H., Tomiuk, S. and Hofmann, K. (2002) A common protein interaction domain links two recently identified epilepsy genes. *Hum. Mol. Genet.*, **11**, 1757–1762.
78. Staub, E., Perez-Tur, J., Siebert, R., Nobile, C., Moschonas, N.K., Deloukas, P. and Hinzmann, B. (2002) The novel EPTP repeat defines a superfamily of proteins implicated in epileptic disorders. *Trends Biochem. Sci.*, **27**, 441–444.
79. Senechal, K.R., Thaller, C. and Noebels, J.L. (2005) ADPEAF mutations reduce levels of secreted LGI1, a putative tumor suppressor protein linked to epilepsy. *Hum. Mol. Genet.*
80. Suzuki, T., Delgado-Escueta, A.V., Aguan, K., Alonso, M.E., Shi, J., Hara, Y., Nishida, M., Numata, T., Medina, M.T., Takeuchi, T. *et al.* (2004) Mutations in EFHC1 cause juvenile myoclonic epilepsy. *Nat. Genet.*, **36**, 842–849.
81. Hua, J.Y., Smear, M.C., Baier, H. and Smith, S.J. (2005) Regulation of axon growth *in vivo* by activity-based competition. *Nature*, **434**, 1022–1026.
82. Ottersen, O.P. (2005) Neurobiology: sculpted by competition. *Nature*, **434**, 969.
83. Meencke, H.J. and Veith, G. (1999) *The Relevance of Slight Migrational Disturbances (Microdysgenesis) to the Etiology of the Epilepsies.* Lippincott Williams and Wilkins, Philadelphia.
84. Woermann, F.G., Sisodiya, S.M., Free, S.L. and Duncan, J.S. (1998) Quantitative MRI in patients with idiopathic generalized epilepsy. Evidence of widespread cerebral structural changes. *Brain*, **121** (Pt 9), 1661–1667.
85. Pal, D.K., Evgrafov, O.V., Tabares, P., Zhang, F., Durner, M. and Greenberg, D.A. (2003) BRD2 (RING3) is a probable major susceptibility gene for common juvenile myoclonic epilepsy. *Am. J. Hum. Genet.*, **73**, 261–270.
86. Greenberg, D.A., Cayanis, E., Strug, L., Marathe, S., Durner, M., Pal, D.K., Alvin, G.B., Klotz, I., Dicker, E., Shinnar, S. *et al.* (2005) Malic enzyme 2 may underlie susceptibility to adolescent-onset idiopathic generalized epilepsy. *Am. J. Hum. Genet.*, **76**, 139–146.
87. Lohi, H., Young, E.J., Fitzmaurice, S.N., Rusbridge, C., Chan, E.M., Vervoort, M., Turnbull, J., Zhao, X.C., Ianzano, L., Paterson, A.D. *et al.* (2005) Expanded repeat in canine epilepsy. *Science*, **307**, 81.
88. Licht, B.G., Licht, M.H., Harper, K.M., Lin, S., Curtin, J.J., Hyson, L.L. and Willard, K. (2002) Clinical presentations of naturally occurring canine seizures: similarities to human seizures. *Epilepsy Behav.*, **3**, 460–470.
89. Ophoff, R.A., Terwindt, G.M., Vergouwe, M.N., van Eijk, R., Oefner, P.J., Hoffman, S.M., Lamerdin, J.E., Mohrenweiser, H.W., Bulman, D.E., Ferrari, M. *et al.* (1996) Familial hemiplegic migraine and episodic ataxia type-2 are caused by mutations in the Ca2+ channel gene CACNL1A4. *Cell*, **87**, 543–552.
90. de Fusco, M., Becchetti, A., Patrignani, A., Annesi, G., Gambardella, A., Quattrone, A., Ballabio, A., Wanke, E. and Casari, G. (2000) The nicotinic receptor beta 2 subunit is mutant in nocturnal frontal lobe epilepsy. *Nat. Genet.*, **26**, 275–276.
91. Phillips, H.A., Favre, I., Kirkpatrick, M., Zuberi, S.M., Goudie, D., Heron, S.E., Scheffer, I.E., Sutherland, G.R., Berkovic, S.F., Bertrand, D. *et al.* (2001) CHRNB2 is the second acetylcholine receptor subunit associated with autosomal dominant nocturnal frontal lobe epilepsy. *Am. J. Hum. Genet.*, **68**, 225–231.
92. Dedek, K., Kunath, B., Kananura, C., Reuner, U., Jentsch, T.J. and Steinlein, O.K. (2001) Myokymia and neonatal epilepsy caused by a mutation in the voltage sensor of the KCNQ2 K+ channel. *Proc. Natl Acad. Sci. USA*, **98**, 12272–12277.
93. Browne, D.L., Gancher, S.T., Nutt, J.G., Brunt, E.R., Smith, E.A., Kramer, P. and Litt, M. (1994) Episodic ataxia/myokymia syndrome is associated with point mutations in the human potassium channel gene, KCNA1. *Nat. Genet.*, **8**, 136–140.
94. Gu, W., Brodtkorb, E. and Steinlein, O.K. (2002) LGI1 is mutated in familial temporal lobe epilepsy characterized by aphasic seizures. *Ann. Neurol.*, **52**, 364–367.
95. Krampfl, K., Maljevic, S., Cossette, P., Ziegler, E., Rouleav, G.A. Lerche, H., Bufler, J. (2005) Molecular analysis of the A322D mutation in the GABA receptor alpha-subnit causing juvenile myoclonic epilepsy. *Eur. J. Neurosci.*, **22**, 10–20.