Acta Medica Okayama

Volume 56, *Issue* 2 2002 *Article* 1

APRIL 2002

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Abstract

Genetic and molecular biological methodologies are being applied to the study of patients with epilepsy at an ever-increasing pace. Accurate classification of epilepsy within large families has allowed identification of genes through linkage analysis and then isolation of gene products. Mutations causing ion channel abnormalities coupled with clinical patterns of focal epilepsy syndromes are beginning to change our thinking about the etiology of recurrent seizures in all patients. Molecular methodology is beginning to have impact on understanding of the mechanisms of actions of drugs used to treat epilepsy and will have an impact on how future treatments are designed.

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*PMID: 12002619 [PubMed - indexed for MEDLINE]

Acta Med. Okayama, 2002
Vol. 56, No. 2, pp. 57-68

Acta Medica Okayama
http://www.lib.okayama-u.ac.jp/www/acta/

Review

Molecular Biology and Genetics of Epilepsy

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Genetic and molecular biological methodologies are being applied to the study of patients with epilepsy at an ever-increasing pace. Accurate classification of epilepsy within large families has allowed identification of genes through linkage analysis and then isolation of gene products. Mutations causing ion channel abnormalities coupled with clinical patterns of focal epilepsy syndromes are beginning to change our thinking about the etiology of recurrent seizures in all patients. Molecular methodology is beginning to have impact on understanding of the mechanisms of actions of drugs used to treat epilepsy and will have an impact on how future treatments are designed.

Key words: molecular, genetic, epilepsy, glutamate, transporter

While seizures are known to complicate structural and metabolic illnesses, epilepsy results from alternations in fundamental mechanisms of brain and membrane function that result in recurrent seizures without cause other than changes in the nervous system. Epilepsy is a rubric that collects a diverse yet common group of disorders that have all manner of etiologic mechanisms and clinical outcomes.

Defining the genes causing epilepsy requires a clear definition of seizure behaviors that are stable, an unremitting clinical course, and abundant clinical material. Therein lie the challenges for understanding the molecular biology of epilepsy. Accurate nosological observations followed by firm classification based upon all aspects of a patient's clinical dilemma are critical to the task of defining the genetics of epilepsy. While understanding the mode of inheritance and the etiology of genetic epilepsy syndromes forms the basis for genetic counseling, knowing the basic mechanism of epilepsy should lead to development of specific therapies.

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Genetic methodology

Patterns of molecular and genetic change that result in epilepsy vary from mutations to triplet repeat disorders, and include altered mitochondrial function. While the specific protein effect of altered gene function commonly is unknown, some genetic abnormalities can result in channel dysfunction, change in receptor efficiency, altered production of transporter proteins, or neocortical structural changes such as migrational abnormalities. As with most genetic diseases, single-gene disorders causing epilepsy are difficult to locate. DNA polymorphism with two or more alleles in close proximity provides a strategy of use of genetic markers for linkage analysis [1]. If the polymorphism is located near the gene of interest then they will be linked during crossovers that occur in meiosis; they co-segregate. During analysis, the probability the observed associations are caused by linkage is calculated and the probability that the observation was by chance is estimated. A ratio of these two probabilities is expressed at $\log_{10}$ or a LOD score. A score of >3

means the odds are 1,000 to 1 of linkage is accepted as proof. A LOD of −2 is proof that linkage does not exist. Genetic linkage identifies the chromosome and thence the location of the defective gene [1].

Techniques of molecular biological research have been applied to discern chromosomal locations of altered genes associated with several specific epilepsy syndromes. These disorders commonly are organized based upon the international classification of seizures and the epilepsies [2, 3]. Some syndromes appear to have simple mendelian inheritance, while others must result from complex gene interaction. For example genomic scanning of 91 families with idiopathic generalized epilepsy suggested a common locus for that form of epilepsy on chromosome 18 [4]. Loci associated with Juvenile Myoclonic Epilepsy (JME) were localized on chromosome 6 while non-JME types of generalized epilepsy were associated with chromosome 8. Durner *et al*. [4] suggest that a susceptibility locus on 18 may be associated with seizure expression with associated genomic effects that are required from other loci. Further, this scanning strategy is of great interest because of the potential for genetic classification of the idiopathic generalized epilepsies [4].

Molecular Biology of Epileptogenesis

Clinical phenotypes have been critical to early genetic studies and will continue to be critical to developments in the molecular biology of epilepsy. However, laboratory studies are beginning to suggest that regulation of endogenous seizure abatement systems that are under genomic control may be operate in the development of epilepsy. For example, the molecular regulation of glutamate appears to be important in the process of epileptogenesis. Three types of cDNAs, encoding high-affinity sodium-, potassium-dependent glutamate transporters have been cloned, their distribution estimated and their roles proposed [5]. Most glutamate is cleared from the extrasynaptic space by the action of high affinity glial transporters GLAST and GLT-1 [6]. More than 60% of glutamate transport is provided by these glial proteins. Preparation of knockdown and knockouts of glutamate transporter in mice suggest these proteins are important [6–8]. Amygdaloid kindling causes diminished production of glial transporter within the piriform cortex and amygdala of rats [9]. Kainic acid-induced seizures cause modest increase in the expression of glutamate transporters [10].

Neuronal GABA transporter provides glutamate for GABA synthesis [11] rather than having a protective function [12]. GABA synthesis depends on uptake of glutamate as a metabolic precursor with subsequent decarboxylation by glutamic acid decarboxylase [11]. Various models of focal epilepsy have shown collapse of production of glial glutamate transporter proteins [13]. In addition, GABA transporter proteins are up-regulated in seizing animals in the same regions [14]. GABA uptake by high-affinity transporters is mediated by Na^+ dependent subclasses of proteins located on neurons and glia that are [15, 16] highly selective and localized to pre- and postsynaptic neurons and to glial cells.

Idiopathic Generalized Epilepsy (Table 1)

Benign Familial Neonatal Convulsions. Benign familial neonatal convulsions (EBN1) is an autosomal dominant neonatal disorder that typically affects a child with seizures beginning on day 2 or 3 of life. Most seizures resolve completely by 6 months of age, but the pattern is not completely benign, with 10–14%, developing later epilepsy [17, 18]. Leppert *et al*. [19] linked Benign Familial Neonatal Convulsions (BFNC) to CMM6 and RMR6 regions on chromosome 20q. Linkage analysis from a multiplexed family containing 19 people with BFNC showed localization at two DNA regions on 20q [19, 20] but a locus on 8q was found in one family [21]. These markers are variable tandem repeats using a 9-base-pair core sequence of GNNGTGGG. Investigators observed a four-generation pedigree of 50 members and 19 affected individuals. LOD score was 5.77 with pooled French data.

Positional cloning studies of BFNC have shown that genes for novel voltage-gated potassium channels, called KCNQ2 and KCNQ3 correspond to 20q and 8q respectively [22, 23]. Positional cloning showed EBN1 on 20q [24, 25] with encoding gene KCNQ2 for this voltage-gated delayed rectifying potassium channel. Specific dysfunction associated by mutations of potassium channels suggests an effect on thresholds of excitability of neurons [26]. Voltage dependent potassium channels are instrumental in repolarization that follows membrane depolarization by Na^+ and Ca^{2+}. Channelopathy from mutation in KCNQ1 is known to cause cardiac conduction abnormalities [27, 28].

KCNQ3 also encodes a protein characteristic of a voltage-gated potassium channel; there is about 50%

Table 1 Idiopathic generalized epilepsy

Syndrome	Locus	Gene	Function
Benign familial neonatal convulsions [19]			Altered voltage-gated potassium channels [22]
(EBN1)	20q13.3	KCNQ2	
(EBN2) [21]	8q24	KCNQ3	
Childhood absence epilepsy [46]	8q24		
Juvenile absence epilepsy [51]	21q22.1	GRIK1	GluR5-kainate receptor
Juvenile myoclonic epilepsy [57, 59]	6p21.2-p11	–	α7 subunit of nicotinic acetylcholine receptor
	15q14	CHRNA7	
Generalized epilepsy with febrile seizures plus	2q [139]		
	19q13.1 [26]		
Febrile seizures [97]			Sodium channel β subunit
FEB 1	8q13-21	–	
FEB 2	19p13.3	SCN1B	
FEB 3	2q24	–	
Idiopathic generalized epilepsy [4]	8q24; 18		
Familial adult myoclonic epilepsy	8q24 [66]		

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homology with KCNQ2 [22, 29]. A Ser248Phe mutation appears to alter gating properties [30–32]. Proteins coded by KCNQ2 and 3 are coexpressed in many brain regions [24, 25] and result in altered function of the channels [29].

Benign Epilepsy in Infants. Benign epilepsy in infants occurs in 3 patterns [33]. Fukuyama (cited by Vigevano *et al.* [33]) reported a benign outcome of infants with partial seizures. These infants had bland developmental history and then had onset of partial seizures from 3 months to 20 months of age [34]. Seizures tend to have a duration of 30–200 sec and are characterized by arrest of motion and altered responsiveness with a blank stare and some mild convulsive movements. Motor patterns include eye deviation, head rotation and mild clonic movements in the context of occasional oral movements. Ictal EEG shows low voltage patterns with theta or delta frequencies in temporal regions [33]. Duration of treatment varies from 1 to 3 years with follow up of 3–10 years and most patients are seizure free and with normal development [33]. Benign epilepsies of infancy may be generalized in pattern and be associated with myoclonus as well [33, 35].

Benign infantile familial convulsions are difficult to define [35], but the pattern of inheritance appears to be autosomal dominant. Seizures begin between 3 and 7 months of life. Ictal behavior typically begins with arrested motion and is followed by a slow deviation of the head and eyes to one side. Body tone increases, the patient becomes cyanotic and there is limb myoclonus. Seizures generally are brief but cluster at 8–10 per day. EEG interictally is normal, but during the seizures slow waves and spikes in the occipital-temporal areas are observed. Almost all of these patients continue to develop normally. Pyridoxine dependence or deficiency must be excluded. Since the benign nature requires observation over time to be discerned, most patients are treated with antiepileptic medication. Linkages to 20q13.2 and to 19p have been reported [36]. As with BFNC, altered potassium channels have been identified [33, 35]. One group of families did not have an allelic form of the EBN1 gene [37].

Childhood Absence Epilepsy. Childhood Absence Epilepsy (CAE) is known to be a benign, age-dependent and age-limited form of epilepsy [38]. Clinical characteristics are an abrupt onset of severe impairment of consciousness with no verbal or other type of response to commands [39]. Patients do not recall events that occurred during the seizure. Clinical onset is within 3 sec of EEG discharge onset. Mean duration is 12 sec and many occur each day, from tens to hundreds per day. EEG shows 3 per sec regular spike and slow wave discharges that are generalized. Forced over breath-

ing provokes seizures. Although somewhat circular, including a patient in this syndrome requires a strict definition for inclusion. Patients with early onset (4–12 years old, mean of 6 years) have the best prognosis. Occurrence of mental retardation or altered EEG background does not fit this syndrome. Patients typically undergo complete remission 2–6 years after onset.

Absence seizures are likely to continue if myoclonus occurs during seizures or there is an atonic component. Photosensitive response on the EEG may be a marker for poor treatment response. Poor response to treatment, or development of intractable absence seizures is likely to occur if generalized tonic-clonic sesizures (GTCS) occur with the onset or before the onset of absence seizure manifestation. Patients with the pure syndrome have GTCS only in 3% of cases [40]. In one series only 65% remitted. Of those without remission, 42% evolved to typical JME [40]. Prediction was aided by the occurrence of myoclonus or by GTCS. One series of 53 patients older than 20 years that fit the pure definition when seizures began had about 10% persistence of absence seizures while 26% had mostly isolated GTCS [40].

Early workers recognized a pattern within families of probands with CAE that suggested complex autosomal dominant inheritance [41, 42]. Indeed, not only is CAE common in families of probands, with 15–44% of patients having a positive family history for epilepsy, but monozygotic twins [43] have a 75% concordance [44, 45].

Linkage at 8q24 [46] is suggested if the proband has CAE with tonic clonic seizures and the less specific EEG pattern of multispike and slow wave patterns with 3.4 Hz spike wave patterns. While typically defined CAE tends to abate in late adolescence, persistence of seizures with evolution to juvenile myoclinic epilepsy has been suggested to link to 1p [47].

Juvenile Absence Epilepsy. Juvenile absence epilepsy has a later onset, in the teenage years. This form of absence epilepsy has a less well-defined EEG pattern when compared to the regular 3 Hz of CAE. A greater percentage of these patients experience tonic clonic seizures, reaching 80% [48–50]. Allelic association has been reported with GRIK1, a GluR5 kainate receptor gene suggesting localization on 21q22.1 [51].

Juvenile Myoclonic Epilepsy. Juvenile myoclonic epilepsy has patterns of clinical seizures and EEG alternations within the families of probands that have suggested various patterns of genetic transmission, including complex inheritance with underlying autosomal dominant, autosomal recessive or multiple loci [52–56]. One group found support for linkage to 6p with comigration linked to BF (properdin factor)-HLA loci [57]. More specific localization to 6q21.2q11 [58] was suggested using DNA polymorphic markers. Further support to 6p has been reported [59–61] but some have derived exclusion of the HLA region [62] and exclusion of chromosome 6 as well. Of interest, a candidate gene strategy applied to thirty-four JEM families revealed linkage with heterogeneity in 15q14 region that encodes the alpha 7 subunit of the neuronal acetylcholine receptor (nAChR-CHRNA7) [63]. Linkage to 8q24 has been suggested [64] but not confirmed [65]. This pattern of observation followed by lack of replication may be related to the varied phenotypes within families and use of variation in criteria for either inclusion or exclusion into multiplexed families.

Familial Adult Myoclonic Epilepsy. Familial adult myoclonic epilepsy is a benign epilepsy that occurs in Japanese; it has a pattern of autosomal dominant with later age of onset that JME. Patients experience limb myoclonus but not upon awakening and with rare tonic clonic seizures. Neurological examination is normal and EEG patterns show generalized spike or polyspike and slow-wave discharges. Four families have shows mapping to 8q24 [62, 64, 66].

Localization-Related Partial Epilepsies (Table 2)

Autosomal Dominant Nocturnal Frontal Lobe Epilepsy. Autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE) patients have brief nocturnal motor seizures and may have secondarily generalization. Onset typically is 10–20 years of age. ADNFLE has mapped to 20q13.2-q13.3 [67]. Mutations alter function in CHRNA4, a gene encoding the alpha 4 subunit of the neuronal nicotinic acetylcholine receptor (nAChR) [68, 69]. These receptors are found in all layers of frontal cortex [70] and are thought to be presynaptic in location and function to modulate neurotransmitter release; they are hetero-pentameric ligand-gated ion channels. Two mutations in the M2 transmembrane domain reduce the efficacy of the channel by reducing Ca^{2+} permeability [71, 72]. An additional family with ADNFLE has mapped to 15q24 [73], a

Table 2 Idiopathic partial-onset epilepsy

Syndrome	Locus	Gene	Function
Autosomal dominant nocturnal frontal lobe epilepsy [67]	20q13.2-13.3 15q24 [73]	CHRNA4 CHRNA3/5/7 and CHRNB4	α4 subunit of nicotinic acetylcholine receptor
Benign infantile familial convulsions	9q11-13		
Familial temporal lobe epilepsy	10q [86]		
Partial epilepsy with variable foci [89]	2		
Partial epilepsy with auditory symptoms [88]	10q22-q24		
Benign epilepsy with centro-temporal spikes	15q14 [83]	CHRNA7 (possible)	Neuronal nicotinic acetylcholine receptor

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region located near the CHRNA3–5 and CHRNB4.

This partial epilepsy syndrome was defined in 6 families from 3 different regions of the world [74–76]. One particularly large multiplexed Australian family showed autosomal dominant inheritance with 75% penetrance [67]. Linkage analysis with a LOD score of 9.29 suggested 20q13.2. Positional candidate gene work produced isolation of the genetic defect to CHRNA4 that codes for the alpha 4 subunit of the neuronal nicotinic acetylcholine receptor. This missense mutation has serine replacing phenylalanine at codon 248 [77]. The altered nicotinic AchR [78] results in restricted calcium permeability with that is said to cause enhanced desensitization sensitivity of the alpha 4 beta 2 receptor. Another locus on 15q24 is near control for alpha 3 alpha 5 and beta 4 subunits for the same nAchR [73].

Benign Epilepsy with Central Temporal Spikes. Benign epilepsy with central temporal spikes (BECTS) syndrome has onset between 3–16 years, considered a window of childhood-older than infancy and before puberty. Patients experience unilateral motor or sensory seizures during sleep. Seizures are brief, infrequent and rarely generalized. Patients are most commonly neurologically normal and do not experience any altered cognitive function. Remission occurs in the second decade of life [79]. Genetic effects are suggested given the occurrence of various types of epilepsy in families of patients. Clinical patterns include perioral paresthesias with ipsilateral facial myoclonus. Loss of consciousness may occur, with patients uttering guttural noises. On occasion patients may experience a GTCS. Although 10–13% of patients have just one seizure about 20% become intractable, having several seizures each day or even with clusters of seizures. Seizures are typically 30–120 sec in duration. About 75% of patients have seizures only during sleep [79]. Accurate diagnosis is possible with a careful clinical history and an EEG obtained while the patient is sleeping since about 30% display the typical polyphasic dipole that is tangential to the perirolandic regions [80, 81]. Familial patterns of inheritance [82] suggested assessment with linkage suggested for 15q14, in the region coding for the neuronal acetylcholine receptor [83] and for some families with JME [63]. BECTS maps to CHRNA7 region of nAChR gene [83]. A kindred with rolandic epilepsy has been described, with speech dyspraxia added and showing anticipation typical for triplet repeat disorders [84].

Familial Temporal Lobe Epilepsy. Familial temporal lobe epilepsy was identified in twin studies [85] with simple partial seizures, occasional complex partial seizures and only infrequent generalization. Onset is in late adolescence. Pattern of inheritance appears to be autosomal dominant with partial penetrance. Linkage suggested to 10q in one family with auditory complaints in addition to temporal lobe epilepsy patterns [86].

Autosomal Dominant Partial Epilepsy with Auditory Features. Autosomal dominant partial epilepsy with auditory features have seizures that are complex partial in pattern and may secondarily generalize [87]. These patients are distinguished by auditory auras [86]. Kindreds with markers linking to chromosome 10q22–24 have been reported but a gene product has not been defined [87, 88].

Familial Partial Epilepsy with Variable

Foci. Familial partial epilepsy with variable foci is associated with a pattern of nocturnal or diurnal partial seizures that may be complex and of temporal, frontal, central or parietal origin. Linkage to chromosome 2 has been reported [89].

Febrile Seizures. Febrile seizures occur between 6 months and 48 months of life [90]. Fever appears to precipitate tonic or tonic-clonic seizures in otherwise normal patients. Some patients with febrile seizures have recurrent episodes during childhood [90, 91], but subsequent epilepsy is infrequent unless the events are complex in pattern [92]. Although causation has spawned speculation, a genetic component has been recognized because of patterns that occur in families [93, 94] and in greater concordance among monozygotic twins when compared to dizygotic cohorts [43, 95]. Speculation about the mode of inherence, probably complex in pattern, is supported by reporting of several loci. One family has shown autosomal dominant transmission and linkage on 8q13–21 (FEB1). Another US family with many generations available for study suggested linkage to 19p13.3 (FEB2). No consistent pattern has been found, but some other families link to 19p while others do not link to 8q [96]. One family has linked to 2p23–24 (FEB3) [97].

Generalized Epilepsy with Febrile Seizures Plus. Generalized epilepsy with febrile seizures plus (GEFS+) was identified in a four-generation Australian family [98] Patients have many febrile seizures during infancy and then have afebrile seizures that have an absence, myoclonic, or atonic pattern until abatement in adolescence. Linkage to 19p13.1 has been reported [26]. One family with GEFS+ appears to show a locus on 2q21–33 [99], and heterogeneity has been reported as well [100]. A point mutation has been identified in the regulatory beta 1 subunit of the voltage-gated sodium channel (SCN1B) [101, 102]. This changes a highly conserved cysteine to a tryptophan that is thought to disrupt a disulfide bridge critical for maintaining a fold in the extracellular domain of a protein. Change in a beta subunit of the sodium channel could alter the gating properties of the channel [103, 104]. Xenopus oocyte studies show the mutated gene reduces sodium channel expression with slowed inactivation and slowed recovery from inactivation [26]. Genes coding for several isoforms of the alpha-subunit of voltage-gated sodium channels are located in this region, making it of interest in FEB3 as well [105, 106]. Such changes that reduce sodium channel expression would result in slower inactivation, and slowed recovery from inactivation [107, 108]. Dysfunctional sodium channels could cause altered transmembrane potential tending toward lowering threshold for depolarization [23]. Why the clinical problem of fever triggers seizures remains unknown.

Neuronal migration disorders (Table 3)

Lissencephaly. Lissencephaly is associated with children who are mentally retarded and have facial dysmorphic changes along with epilepsy. Clinical patterns of seizures include myoclonic, tonic, and tonic clonic seizures, with infantile spasms occurring commonly.

Table 3 Symptomatic epilepsy

Syndrome	Locus	Gene	Function
Periventricular nodular heterotopia	Xq28	Filamin I [118]	Actin-binding phosphoprotein
Subcortical band heterotopia-double cortex	Xq21-24	Doublecortin [113]	
Isolated lissencephaly [109]	17p13.3	PAF	Platlet activiating factor acetylhydrolase
Progressive myoclonic epilepsy			
Unverricht-Lundborg [121]	21q22.3	CSTB-Cystatin B	–
Lafora Body myoclonus [126]	6q24	EPM2A-Laforin	Protein tyrosine phosphatase
Myoclonic epilepsy with ragged red fibers	Mitochondria: tRNA (lys) [131]	A to G-8344 tRNA (lys)	Respiratory chain enzyme deficiencies

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Arrest of neuronal migration between 9 and 13 weeks causes reduction in the number of gyri and the phenotype of a region of smooth surface. Cortex is thickened with enlarged ventricles and hypoplasia of the corpus callosum. Cortical layers are poorly organized, displaying 4 cortical layers and the presence of diffuse neuronal heterotopia [109]. The Miller-Dieker syndrome and isolated Lissencephaly sequence has a mutation in the LIS1 gene encoding a non-catalytic subunit of platelet activating factor (PAF) acetylhydrolase, a heterotrimeric enzyme that inactivates PAF [110, 111]. How this altered enzyme causes altered neuronal migration is unknown.

X-linked Lissencephaly and double cortex. X-linked Lissencephaly and double cortex, classical Lissencephaly, occurs in hemizygous males with milder effects in heterozygotic females where some neurons migrate abnormally to subcortical white matter causing a subcortical band heterotopia [112]. The mutated gene codes for DCX or doublecortin [113, 114]. Analysis of mutations of DCX have shown missense mutations, frameshift mutations and splice site mutation [110, 114, 115]. DCX is expressed in frontal lobes in adults but widely expressed in fetal brain [110, 114, 115]. Function of DCX is unknown at this time.

Periventricular heterotopia are formed of neurons in regions that fail to migrate and are found as nodules along the walls of ventricles. This X-linked dominant disorder is lethal to males while females have seizures and other systemic signs but with normal IQ [116, 117]. Locus is mapped to Xq28 with a regional gene FLN1 that encodes an actin-binding protein filamin1 [118]. Patients have shown point mutation and a frameshift mutation with resultant truncation of the FLN1 protein.

Progressive Myoclonus Epilepsies

This heterogeneous group of debilitating, sometimes fatal epileptic encephalopathies cause segmental arrhythmic myoclonus, massive myoclonus, GTCS or clonic seizures with or without absence, dementia, and progressive neurological deficits especially of cerebellar origin.

Unverricht-Lundborg (Baltic-Mediterranean PME). This disorder has been described worldwide, not just in the Baltic regions [119]. Clinical patterns tend to be uniform, with debilitating, slowly progressive, stimulus sensitive myoclonus. Onset is between 6–18 years. Generalized clonic and GTC seizures may appear on awakening. Valproic acid delays progression. Mild ataxia is present, and mild intellectual deterioration and dementia occur late in disease with patients becoming incapacitated in about 5 years [120]. Inheritance is autosomal-recessive with variable progression; 21q22.3 linkage in 12 Finnish families with 68 members and 26 affected. LOD was 10.08 [121].

Mapping located several highly polymorphic microsatellite markers with a critical region of ~175 Kb. Several cDNA fragments were isolated that encode cystatin B, a cysteine protease inhibitor. Southern blots revealed an unstable region of DNA in the noncoding region upstream of the transcription start site of the cystatin B. This region contains an expansion of a polymorphic dodecamer (5"cccgccccgcg-3'). This expansion of a dodecamer is the first example of instability of a repeat unit other than trinucleotides and accounts for about 92% of patients. Range of the expansion varies from 30 copies up to 75 copies [96, 122–125].

Lafora's Disease. This fatal progressive myoclonic syndrome has a pattern of autosomal recessive inheritance, with seizures beginning in early adolescence but they may start as late as 18 years. Patients commonly die within 5–10 years after first symptoms. Symptoms begin with GTCS, absence or drop attacks with subtle irregular or asymmetric myoclonus. With progression the myoclonus becomes almost constant. Photic induced high-voltage, spike waves and polyspikes interrupt the slow background of the EEG. Dementia, dyspraxis, and visual loss lead to vegetative state. Cytoplasmic inclusions in brain, muscle, liver, and skin are periodic acid-Schiff positive and contain polyglycosans. In 38 families with 16 containing consanguinity, localization was found to 6q24 [126] where the gene EPM2A codes for a protein tyrosine phosphatase called Laforin [127–129].

Mitochondrial Disorders. Mitochondrial disorders commonly present with seizures [130]. Mitochondrial encephalopathy is associated with segmental or generalized myoclonus. MERRF syndrome (Myoclonic epilepsy and ragged red fiber syndrome) has a clinical constellation of myopathy, ataxia, deafness and dementia with progressive myoclonic epilepsy [126]. Most common pathogenic mutation is A to G transition at position 8344 in tRNA-lys [131]. This heteroplasmic mutation has varied proportion of mutated DNA in families. This mutation results in premature termination of translation of mitrochondrial mRNAs with resultant reduced polypeptide synthesis [132–134].

Molecular Neuropharmacology

Knowledge of fundamentals of the molecular biology of epilepsy should lead to another level of drug development. For example, valproate reduces excitatory synaptic transmission responsible for synchronization of cell firing that leads to epileptic bursting [135–137]. Valproate interferes with excitatory synaptic processes and suppresses depolarization induced by NMDA. However, VPA has a molecular effect as well with resulting up-regulation of glutamate transporter protein production resulting in the inactivation of the effect of glutamate by termination of action following enhanced transport from the synaptic cleft [138]. In addition, Ueda *et al.* [138] demonstrated that valproate down-regulates the production of GABA transporter proteins, an effect that should result in prolongation of the inhibitory effect on intrasynaptic GABA. Future work should raise questions about the details of ion channelopathy that may be specific to epilepsy and how drugs can be designed to affect highly specified seizure disorders.

Reference

1. Watson JD, Tooze J and Kurtz DT: Recombinant DNA: A short course. Scientific American Books, New York (1983).
2. Commission on Classification and terminology of the International League Against Epilepsy: Proposal for classification of epilepsies and epileptic syndromes. Epilepsia (1985) **26**, 268–278.
3. Commission on Classification and terminology of the International League Against Epilepsy: Proposal for revised clinical and electroencephalographic classification of epileptic seizures. Epilepsia (1981) **22**, 489–501.
4. Durner M, Keddache MA, Tomasini L, Shinnar S, Resor SR, Cohen J, Harden C, Moshe SL, Rosenbaum D, Kang H, Ballaban-Gil K, Hertz S, Labar DR, Luciano D, Wallace S, Yohani D, Klotz I, Dicker E and Greenberg DA: Genome scan of idiopathic generalized epilepsy: Evidence for major susceptibility gene and modifying genes influencing the seizure type. Ann Neurol (2001) **49**, 328–335.
5. Kanai Y, Smith CP and Hediger MA: The elusive transporters with a high affinity for glutamate. Trends Neurosci (1993) **16**, 365–370.
6. Rothstein JD, Dykes-Hoberg M, Pardo CA, Bristol LA, Jin L, Kuncl RW, Kanai Y, Hediger MA, Wang Y, Schielke JP and Welty DF: Knockout of glutamate transporters reveals a major role for astroglial transport in excitotoxicity and clearance of glutamate. Neuron (1996) **16**, 675–686.
7. Tanaka K, Watase K, Manabe T, Yamada K, Watanabe M, Takahashi K, Iwama H, Nishikawa T, Ichihara N, Kikuchi T, Okuyama S, Kawashima N, Hori S, Takimoto M and Wada K: Epilepsy and exacerbation of brain injury in mice lacking the glutamate transporter GLT-1. Science (1997) **276**, 1699–1702.
8. Peghini P, Janzen J and Stoffel W: Glutamate transporter EAAC-1-deficient mice develop dicarboxylic aminoaciduria and behavioral abnormalities but no neurodegeneration. EMBO J (1997) **16**, 3822–3832.
9. Miller HP, Levey AI, Rothstein JD, Tzingounis AV and Conn PJ: Alterations in glutamate transporter protein levels in kindling-induced epilepsy. J Neurochem (1997) **68**, 1564–1570.
10. Simantov R, Crispino M, Hoe W, Broutman G, Tocco G, Rothstein JD and Baudry M: Changes in expression of neuronal and glial glutamate transporters in rat hippocampus following kainate-induced seizure activity. Mol Brain Res (1999) **65**, 112–123.
11. Eccles CU, Dykes-Hoberg M and Rothstein JD: Inhibition of synthesis of EAAC-1 glutamate transporter alters gamma-amonobutyric acid levels in discrete brain regions. Soc Neurosci (Abst) (1996) **22**, 1570.
12. Kanai Y: Family of neural and acidic amino acid transporters: Molecular biology, physiology and medical implications. Curr Opin Cell Biol (1997) **9**, 565–572.
13. Ueda Y, Doi T, Tokumaru J, Yokoyama H, Nakajima A, Mitsuyama U, Ohya-Nishiguchi H, Kamada H and Willmore LJ: Collapse of extracellular glutamate regulation during epileptogenesis: Down-regulation and functional failure of glutamate transporter function in rats with chronic seizures induced by kainic acid. J Neurochem (2001) **76**, 892–900.
14. Ueda Y and Willmore LJ: Sequential changes in glutamate transporter protein levels during Fe^{+++} induced epileptogenesis. Epilepsy Res (2000) **39**, 201–219.
15. Guastella J, Nelson N, Nelson H, Czyzyk L, Keynan S, Miedel MC, Davidson N, Lester HA and Kanner BI: Cloning and expression of a rat brain GABA transporter. Science (1990) **249**, 1303–1306.
16. Radian R, Bendahan A and Kanner BI: Purification and identification of the functional sodium- and chloride-coupled gamma-aminobutyric acid transport glycoprotein from rat brain. J Biol Chem (1986) **261**, 15437–15441.
17. Shevell MI, Sinclair DB and Metrakos K: Benign familial neonatal seizures: Clinical and electroencephalographic characteristics. Pediatr Neurol (2001) **2**, 272–275.
18. Zonana J, Silvey K and Strimling B: Familial neonatal and infantile seizures: An autosomal-dominant disorder. Am J Med Genet (1984) **18**, 455–459.
19. Leppert M, Anderson VE, Quattlebaum T, Stauffer D, O'connell P, Nakamura Y, Lalouel JM and White R: Benign familial neonatal convulsions linked to genetic markers on chromosome 20. Nature (1989) **337**, 647–648.
20. Berkovic SF, Kennerson ML, Howell RA, Scheffer IE, Hwang PA and Nicholson GA: Phenotypic expression of benign familial neonatal convulsions linked to chromosome 20. Arch Neurol (1994) **51**, 1125–1128.
21. Lewis TB, Leach RJ, Ward K, O'Connell P and Ryan SG: Genetic heterogeneity in benign familial neonatal convulsions: Identification of a new locus on chromosome 8q. Am J Hum Genet (1993) **53**, 670–675.
22. Charlier C, Singh NA, Ryan SG, Lewis TB, Reus BE, Leach RJ and Leppert M: A pore mutation in a novel KQT-like potassium channel gene in an idiopathic epilepsy family. Nature Genet (1998) **18**, 53–55.
23. Lerche H, Jurkat-Rott K and Lehmann-Horn F: Ion channels and epilepsy. Am J Med Genet (2001) **106**, 146–159.
24. Biervert C, Schroeder BC, Kubisch C, Berkovic SF, Propping P, Jentsch TJ and Steinlein OK: A potassium channel mutation in neonatal human epilepsy. Science (1998) **279**, 403–406.
25. Singh NA, Charlier C, Stauffer D, DuPont BR, Leach RJ, Melis R, Ronen GM, Bjerre I, Quattlebaum T, Murphy JV, McHarg ML, Gagnon D, Rosales TO, Peiffer A, Anderson VE and Leppert M: A novel potassium channel gene, KCNQ2, is mutated in an inherited epilepsy of newborns. Nature Genet (1998) **18**, 25–29.

26. Wallace RH, Wang DW, Singh R, Scheffer IE, George AL Jr, Phillips HA, Saar K, Reis A, Johnson EW, Sutherland GR, Berkovic SF and Mulley JC: Febrile seizures and generalized epilepsy associated with a mutation in the Na^+-channel beta1 subunit gene SCN1B. Nat Genet (1998) **19**, 366–370.
27. Wang Q, Curran ME, Splawski I, Burn TC, Millholland JM, VanRaay TJ, Shen J, Timothy KW, Vincent GM, de Jager T, Schwartz PJ, Toubin JA, Moss AJ, Atkinson DL, Landes GM, Connors TD and Keating MT: Postitional cloning of a novel potassium channel gene: KVLQT1 mutations cause cardiac arrhythmias: Nat Genet (1996) **12**, 17–23.
28. Neyroud N, Tesson F, Denjoy I, Leibovici M, Donger C, Barhanin J, Faure S, Gary F, Coumel P, Petit C, Schwartz K and Guicheney P: A novel mutation in the potassium channel gene KVLQT1 causes the Jervell and Lange-Nielsen cardioauditory syndrome. Nat Genet (1997) **15**, 186–189.
29. Schroeder BC, Kubisch C, Stein V and Jentsch TJ: Moderate loss of function of cyclic-AMP-modulated KCNQ2/KCNQ3 K^+ channels causes epilepsy. Nature (1998) **396**, 687–690.
30. Molina A, Ortega-Saenz P and Lopez-Barneo J: Pore mutations alter closing and opening kinetics in Shaker K^+ channels. J Physiol (1998) **509**, 327–337.
31. Dreyer I, Becker D, Bregante M, Gambale F, Lehnen M, Palme K and Hedrich R: Single mutations strongly alter the K^+-selective pore of the K (in) channel KAT1. FEBS Lett (1998) **430**, 370–376.
32. Guo L and Kubo Y: Comparison of the open-close kinetics of the cloned inward rectifier K^+ channel IRK1 and its point mutant (Q140E) in the pore region. Receptors Channels (1998) **5**, 273–289.
33. Vigevano F, Cusmai R, Ricci S and Watanabe K: Benign epilepsies of infancy; in Epilepsy: A Comprehensive Textbook, Engel J Jr and Pedley TA eds, Lippincott-Raven, Philadelphia (1997) pp 2269–2276.
34. Watanabe K, Yamamoto N, Negoro T, Takahashi I, Aso K and Maehara M: Benign infantile epilepsy with complex partial seizures. J Clin Neurophysiol (1990) **7**, 409–416.
35. Vigevano F, Fusco L, Di Capula M, Ricci S, Sebastianelli R and Lucchini P: Benign infantile familial convulsions. Eur J Pediatr (1992) **151**, 608–612.
36. Guipponi M, Rivier F, Vigevano F, Beck C, Crespel A, Echenne B, Lucchini P, Sebastianelli R, Baldy-Moulinier M and Malafosse A: Linkage mapping of benign familial infantile convulsions (BFIC) to chromosome 19q. Hum Mol Genet (1997) **6**, 473–477.
37. Malafosse A, Beck C, Bellet H, Di Capua M, Dulac O, Echenne B, Fusco L, Lucchini P, Ricci S and Sebastianelli R: Benign infantile familial convulsions are not an allelic form of the benign familial neonatal convulsions gene. Ann Neurol (2001) **35**, 479–482.
38. Dreifuss FE: Pediatric epilepsy syndromes: An overview. Cleve Clin J Med (1989) **56**, 166–171.
39. Gastaut H, Zifkin BG, Mariani E and Puig JS: The long-term course of primary generalized epilepsy with persisting absences. Neurology (1986) **36**, 1021–1028.
40. Wirrell EC, Camfield CS, Camfield PR, Gordon KE and Dooley JM: Long-term prognosis of typical childhood absence epilepsy: Remission or progression to juvenile myoclonic epilepsy. Neurology (1996) **47**, 912–918.
41. Metrakos K and Metrakos JDE: Genetics of convulsive disoders I: introduction problems methods and baselines. Neurology (1960) **10**, 228–240.
42. Metrakos K and Metrakos JDE: Genetics of convulsive disorders II: genetics and electroencephalographic studies in centrencephalic epilepsy. Neurology (1961) **11**, 474–483.
43. Berkovic SF, Howell RA, Hay DA and Hopper JL: Epilepsies in twins: Genetics of the major epilepsy syndromes. Ann Neurol (1998) **43**, 435–445.
44. Degen R, Degen HE and Roth C: Some genetic aspects of idiopathic and symptomatic absence seizures: Waking and sleep EEGs in siblings: Epilepsia (1990) **31**, 784–794.
45. Serratosa JM: Idiopathic epilepsies with a complex mode of inheritance. Epilepsia (1999) **40** (Suppl 3), 12–16.
46. Fong GC, Shah PU, Gee MN, Serratosa JM, Castroviejo IP, Khan S, Ravat SH, Mani J, Huang Y, Zhao HZ, Medina MT, Treiman LJ, Pineda G and Delgado-Escueta AV: Childhood absence epilepsy wtih tonic-clonic seizures and electroencephalogram 3–4-Hz spike and multispike-slow wave complexes: Linkage to chromosome 8q24. Am J Hum Genet (1998) **63**, 1117–1129.
47. Delgado-Escueta AV, Medina MT, Serratosa JM, Castroviejo IP, Gee MN, Weissbecker K, Westling BW, Fong CY, Alonso ME, Cordova S, Shah P, Khan S, Sainz J, Rubio-Donnadieu F and Sparkes RS: Mapping and positional cloning of common idiopathic generalized epilepsies: Juvenile myoclonus epilepsy and childhood absence epilepsy. Adv Neurol (1999) **79**, 351–374.
48. Loiseau P, Duche B and Pedespan JM: Absence epilepsies. Epilepsia (1995) **36**, 1182–1186.
49. Roger J, Bureau M, Dravet C, Dreifuss FE and Perret A and Wolf P: Epileptic syndromes in infancy childhood and adolescence. John Libbey, London (1992).
50. Wolf P and Inoue Y: Therapeutic response of absence seizures in patients of an epilepsy clinic for adolescents and adults. J Neurol (1984) **231**, 225–229.
51. Sander T, Hildmann T, Kretz R, Furst R, Sailer U, Bauer G, Schmitz B, Beck-Mannagetta G, Wienker TF and Janz D: Allelic associatoin of juvenile absence epilepsy with a GluR5 kainate receptor gene (GRIK1) polymorphism. Am J Med Genet (1997) **74**, 416–421.
52. Panayiotopoulos CP and Obeid T: Juvenile myoclonic epilepsy: An autosomal recessive disease. Ann Neurol (1989) **25**, 440–443.
53. Tsuboi T and Christian W: On the genetics of the primary generalized epilepsy with sporadic myoclonias of impulsive petit may type: A clinical and electroencephalographic study of 399 probands. Humangenetik (1973) **19**, 155–182.
54. Andermann E: Multifactorial inheritance of generalized and focal epilepsy; in Genetic Basis of the Epilepsies, Anderson VE, Hauser WA, Penry JK and Sing CF eds, Raven Press, New York (1982) pp 355–374.
55. Greenberg DA, Delgado-Escueta AV, Maldonaldo HM and Widelitz H: Segregation analysis of juvenile myoclonic epilepsy; in Genetics of the Epilepsies, Beck-Mannagetta G, Anderson VE, Doose H and Janz D eds, Springer, Berlin (1989) pp 53–61.
56. Greenberg DA, Durner M and Delgado-Escueta AV: Evidence for multiple gene loci in the expression of the common generalized epilepsies. Neurology (1992) **42** (Suppl 5), 56–62.
57. Greenberg DA, Delgado-Escueta AV, Widelitz H, Sparkes RS, Treiman L, Maldonaldo HM, Park MS and Terasaki PI: Juvenile myoclonic epilepsy (JME) may be linked to the BF and HLA loci on human chromosome 6. Am J Med Genet (1988) **31**, 185–192.
58. Liu AW, Delgado-Escueta AV, Serratosa JM, Alonso ME, Medina MT, Gee MN, Cordova S, Zhao HS, Spellman JM and Peek JR: Juvenile myoclonic epilepsy locus in chromosome 6p21.2-p11: Linkage to convulsions and electroencephalography trait. Am J Hum Genet (1995) **57**, 368–381.
59. Weissbecker KA, Durner M, Janz D, Scaramelli A, Sparkes RS and Spence MA: Confirmation of linkage between juvenile myoclonic epilepsy locus and the HLA region of chromosome 6. Am J Med Genet (1991) **38**, 32–36.

60. Sander T, Bockenkamp B, Hildmann T, Blasczyk R, Kretz R, Wienker TF, Volz A, Schmitz B, Beck-Mannagetta G, Riess O, Epplen JT, Janz D and Ziegler A: Refined mapping of the epilepsy susceptibility locus EJM1 on chromosome 6. Neurology (1997) **49**, 842–847.
61. Durner M, Sander T, Greenberg DA, Johnson K, Beck-Mannagetta G and Janz D: Localization of idiopathic generalized epilepsy on chromosome 6p in families of juvenile myoclonic epilepsy patients. Neurology (1991) **41**, 1651–1655.
62. Whitehouse WP, Rees M, Curtis D, Sundqvist A, Parker K, Chung E, Baralle D and Gardiner RM: Linkage analysis of idiopathic generalized epilepsy (IGE) and marker loci on chromosome 6p in families of patients with juvenile myoclonic epilepsy: No evidence for an epilepsy locus in the HLA region. Am J Hum Genet (1993) **53**, 652–662.
63. Elmslie FV, Rees M, Williamson MP, Kerr M, Kjeldsen MJ, Pang KA, Sundqvist A, Friis ML, Chadwick D, Richens A, Covanis A, Santos M, Arzimanoglou A, Panayiotopoulos CP, Curtis D, Whitehouse WP and Gardiner RM: Genetic mapping of a major susceptibility locus for juvenile myoclonic epilepsy on chromosome 15q. Hum Mol Genet (1997) **6**, 1329–1334.
64. Zara F, Bianchi A, Avanzini G, Di Donato S, Castellotti B, Patel PI and Pandolfo M: Mapping of genes predisposing to idiopathic generalized epilepsy. Hum Mol Genet (1995) **4**, 1201–1207.
65. Sander T, Kretz R, Schulz H, Sailer U, Bauer G, Scaramelli A, Epplen JT, Riess O and Janz D: Replication analysis of a putative susceptibility locus (EGI) for idoiopathic generalized epilepsy on chromosome 8q24. Epilepsia (1998) **39**, 715–720.
66. Plaster NM, Uyama E, Uchino M, Ikeda T, Flanigan KM, Kondo I and Ptacek LJ: Genetic localization of the familial adult myoclonic epilepsy (FAME) gene to chromosome 8q24. Neurology (1999) **53**, 1180–1183.
67. Phillips HA, Scheffer IE, Berkovic SF, Hollway GE, Sutherland GR and Mulley JC: Localization of a gene for autosomal dominant nocturnal frontal lobe epilepsy to chromosome 20q13.2. Nat Genet (1995) **10**, 117–118.
68. Steinlein OK, Mulley JC, Propping P, Wallace RH, Phillips HA, Sutherland GR, Scheffer IE and Berkovic SF: A missense mutation in the neuronal nicotinic acetylcholine receptor alpha 4 subunit is associated with autosoaml dominant nocturnal frontal lobe epilepsy. Nat Genet (1995) **11**, 201–203.
69. Steinlein O, Magnusson A, Stoodt J, Bertrand S, Weiland S, Berkovic SF, Nakken KO, Propping P and Bertrand D: An insertion mutation of the CHRNA4 gene in a family with autosomal dominant nocturnal frontal lobe epilepsy. Hum Mol Genet (1997) **6**, 943–947.
70. Wevers A, Jeske A, Lobron C, Birtsch C, Heinemann S, Maelicke A, Schroder R and Schroder H: Cellular distribution of nicotinic acetylcholine receptor subunit mRNAs in the human cerebral cortex as revealed by non-isotopic *in situ* hybridization. Mol Brain Res (1994) **25**, 122–128.
71. Weiland S, Witzemann V, Villarroel A, Propping P and Steinlein O: An amino acid exchange in the second transmembrane segment of a neuronal nicotinic receptor causes partial epilepsy by altering its desensitization kinetics. FEBS Lett (1996) **398**, 91–96.
72. Kuryatov A, Gerzanich V, Nelson M, Olale F and Lindstrom J: Mutation causing autosomal dominant nocturnal frontal lobe epilepsy alters Ca^{2+} permeability, conductance, and gating of human alpha4betra2 nicotinic acetylcholine receptors. J Neurosci (1997) **17**, 9035–9047.
73. Phillips HA, Scheffer IE, Crossland KM, Bhatia KP, Fish DR, Marsden CD, Howell SJ, Stephenson JB, Tolmie J, Plazzi G, Eeg-Olofsson O, Singh R, Lopes-Cendes I, Andermann E, Andermann F, Berkovic SF and Mulley JC: Autosomal dominant nocturnal frontal-lobe epilepsy: Genetic heterogeneity and evidence for a second locus at 15q24. Am J Hum Genet (1998) **63**, 1108–1116.
74. Berkovic SF and Scheffer IE: Epilepsies with single gene inheritance. Brain Dev (1997) **19**, 13–18.
75. Scheffer IE, Bhatia KP, Lopes-Cendes I, Fish DR, Marsden CD, Andermann F, Andermann E, Desbiens R, Cendes F, Manson JI and Berkovic SF: Autosomal dominant frontal epilepsy misdiagnosed as sleep disorder. Lancet (1994) **343**, 515–517.
76. Scheffer IE, Bhatia KP, Lopes-Cendes I, Fish DR, Marsden CD, Andermann E, Andermann F, Desbiens R, Keene D and Cendes F: Autosomal dominant nocturnal frontal lobe epilepsy: A distinctive clinical disorder. Brain (1995) **118**, 61–73.
77. Steinlein O, Smigrodzki R, Lindstrom J, Anand R, Kohler M, Tocharoentanaphol C and Vogel F: Refinement of the localization of the gene for neuronal nicotinic acetylcholine receptor alpha 4 subunit (CHRNA4) to human chromosome 20q13.2–13.3. Genomics (1994) **22**, 493–495.
78. Perucca E and Bialer M: The clinical pharmacokinetics of the newer antiepileptic drugs. Focus on topiramate, zonisamide and tiagabine. Clin Pharmacokinet (1996) **1**, 29–46.
79. Loiseau P, Duche B, Cordova S, Dartigues JF and Cohadon S: Prognosis of benign childhood epilepsy with centrotemporal spikes: A follow-up study of 168 patients. Epilepsia (1988) **29**, 229–235.
80. Frost JD Jr, Hrachovy RA and Glaze DG: Spike morphology in childhood focal epilepsy: Relationship to syndromic classification. Epilepsia (1992) **33**, 531–536.
81. Gutierrez AR, Brick JF and Bodensteiner J: Dipole reversal: An ictal feature of benign partial epilepsy with centrotemporal spikes. Epilepsia (1990) **31**, 544–548.
82. Bray FP and Wiser WC: Evidence for a genetic aetiology of temporal central abnormalities in focal epilepsy. N Eng J Med (1964) **271**, 926–933.
83. Neubauer BA, Fiedler B, Himmelein B, Kampfer F, Lassker U, Schwabe G, Spanier I, Tams D, Bretscher C, Moldenhauer K, Kurlemann G, Weise S, Tedroff K, Eeg-Olofsson O, Wadelius C and Stephani U: Centrotemporal spikes in families with rolandic epilepsy: Linkage to chromosome 15q14. Neurology (1998) **51**, 1608–1612.
84. Scheffer IE, Jones L, Pozzebon M, Howell RA, Saling MM and Berkovic SF: Autosomal dominant rolandic epilepsy and speech dyspraxia: A new syndrome with anticipation. Ann Neurol (1995) **38**, 633–642.
85. Berkovic SF, McIntosh A, Howell RA, Mitchell A, Sheffield LJ and Hopper JL: Familial temporal lobe epilepsy: A common disorder identified in twins. Ann Neurol (1996) **40**, 227–235.
86. Ottman R, Risch N, Hauser WA, Pedley TA, Lee JH, Barker-Cummings C, Lustenberger A, Nagle KJ, Lee KS and Scheuer ML: Localization of a gene for partial epilepsy to chromosome 10q. Nat Genet (1995) **10**, 56–60.
87. Winawer MR, Ottman R, Hauser WA and Pedley TA: Autosomal dominant paritial epilepsy with auditory features: Defining the phenotype. Neurology (2000) **54**, 2173–2176.
88. Michelucci R, Passarelli D, Pitzalis S, Dal Corso G, Tassinari CA and Nobile C: Autosomal dominant partial epilepsy with auditory features: Description of a new family. Epilepsia (2000) **41**, 967–970.
89. Scheffer IE, Phillips HA, O'Brien CE, Saling MM, Wrennall JA, Wallace RH, Mulley JC and Berkovic SF: Familial partial epilepsy with variable foci: A new partial epilepsy syndrome with suggestion of linkage to chromosome 2. Ann Neurol (1998) **44**, 890–899.
90. Verity CM, Butler NR and Golding J: Febrile convulsions in a national cohort followed up from birth I: Prevalence and recurrence in the first five years of life. Br Med J (1985) **290**, 1307–1310.
91. Nelson KB and Ellenberg JH: Prognosis in children with febrile sei-

zures. Pediatrics (1978) **61**, 720–727.
92. MacDonald BK, Johnson AL, Sander JW and Shorvon SD: Febrile convulsions in 220 children-neurological sequelae at 12 years follow-up. Eur Neurol (1999) **41**, 179–186.
93. Berg AT, Shinnar S, Shapiro ED, Salomon ME, Crain EF and Hauser WA: Risk factors for a first febrile seizure: A matched case-control study. Epilepsia (1995) **36**, 334–341.
94. Nelson KB and Ellenberg JH: Prenatal and perinatal antecedents of febrile seizures. Ann Neurol (1990) **27**, 127–131.
95. Corey LA, Berg K, Pellock JM, Solaas MH, Nance WE and DeLorenzo RJ: The occurrence of epilepsy and febrile seizures in Virginian and Norwegian twins. Neurology (1991) **41**, 1433–1436.
96. Kugler SL, Stenroos ES, Mandelbaum DE, Lehner T, McKoy VV, Prossick T, Sasvari J, Swannick K, Katz J and Johnson WG: Hereditary febrile seizures: Phenotype and evidence for a chromosome 19p locus. Am J Med Genet (1998) **79**, 354–361.
97. Peiffer A, Thompson J, Charlier C, Otterud B, Varvil T, Pappas C, Barnitz C, Gruenthal K, Kuhn R and Leppert M: A locus for febrile seizures (FEB3) maps to chromosome 2q23–24. Ann Neurol (1999) **46**, 671–678.
98. Scheffer IE and Berkovic SF: Generalized epilepsy with febrile seizures plus. A genetic disorder with heterogeneous clinical phenotypes. Brain (1997) **120**, 479–490.
99. Berkovic SF and Scheffer IE: Genetics of the epilepsies. Curr Opin Neurol (1999) **12**, 177–182.
100. Lerche H, Weber YG, Baier H, Jurkat-Roth K, Kraus de Camargo O, Ludolph AC, Bode H and Lehmann-Horn F: Generalized epilepsy with febrile seizures plus: Further heterogeneity in a large family. Neurology (2001) **57**, 1191–1198.
101. Makita N, Sloan-Brown K, Weghuis DO, Ropers HH and George AL Jr: Genomic organization and chromosomal assignments of the human voltage-gated Na^+ channel beta 1 subunit gene (SCN1B). Genomics (1994) **23**, 628–634.
102. Mohrenweiser HW, Tsujimoto S, Gordon L and Olsen AS: Regions of sex-specific hypo- and hyper-recombination identified through integration of 180 genetic markers into the metric physical map of human chromosome 19. Genomics (1998) **47**, 153–162.
103. Isom LL, De Jongh KS, Patton DE, Reber BF, Offord J, Charbonneau H, Walsh K, Goldin AL and Catterall WA: Primary structure and functional expression of the beta 1 subunit of the rat brain sodium channel. Science (1992) **256**, 839–842.
104. Makita N, Bennett PB Jr and George AL Jr: Voltage-gated Na^+ channel beta 1 subunit mRNA expressed in adult human skeletal muscle, heart, and brain is encoded by a single gene. J Biol Chem (1994) **269**, 7571–7578.
105. Moulard B, Guipponi M, Chaigne D, Mouthon D, Buresi C and Malafosse A: Identification of a new locus for generalized epilepsy with febrile seizures plus ($GEFS^+$) on chromosome 2q24-q33. Am J Hum Genet (1999) **65**, 1396–1400.
106. Wallace RH, Scheffer IE, Barnett S, Richards M, Dibbens L, Desai RR, Lerman-Sagie T, Lev D, Mazarib A, Brand N, Ben-Zeev B, Goikhman I, Singh R, Kremmidiotis G, Gardner A, Sutherland GR, George AL Jr, Mulley JC and Berkovic SF: Neuronal sodium-channel alpha1-subunit mutations in generalized epilepsy with febrile seizures plus. Am J Hum Genet (2001) **68**, 859–865.
107. Makita N, Bennett PB and George AL Jr: Molecular determinants of beta 1 subunit-induced gating modulation in voltage-dependent Na^+ channels. J Neurosci (1996) **16**, 7117–7127.
108. McCormick KA, Isom LL, Ragsdale D, Smith D, Scheuer T and Catterall WA: Molecular determinants of Na^+ channel function in the extracellular domain of the beta 1 subunit. J Biol Chem (1998) **273**, 3954–3962.
109. Dobyns WB and Truwit CL: Lissencephaly and other malformations of cortical development: 1995 update. Neuropediatrics (1995) **26**, 132–147.
110. Hattori M, Adachi H, Tsujimoto M, Arai H and Inoue K: Miller-Dieker lissencephaly gene encodes a subunit of brain platelet-activating factor acetylhydrolase. Nature (1994) **370**, 216–218.
111. Lo Nigro C, Chong CS, Smith AC, Dobyns WB, Carrozzo R and Ledbetter DH: Point mutations and an intragenic deletion in LIS1, the lissencephaly causative gene in isolated lissencephaly sequence and Miller-Dieker syndrom. Hum Mol Genet (1997) **6**, 157–164.
112. Dobyns WB, Andermann E, Andermann F, Czapansky-Beilman D, Dubeau F, Dulac O, Guerrini R, Hirsch B, Ledbetter DH, Lee NS, Motte J, Pinard JM, Radtke RA, Ross ME, Tampieri D, Walsh CA and Truwit CL: X-linked malformations of neuronal migration. Neurology (1996) **47**, 331–339.
113. des Portes V, Pinard JM, Billuart P, Vinet MC, Koulakoff A, Carrie A, Gelot A, Dupuis E, Motte J, Berwald-Netter Y, Catala M, Kahn A, Beldjord C and Chelly J: A novel CNS gene required for neuronal migration and involved in X-linked subcortical laminar heterotopia and lissencephaly syndrome. Cell (1998) **92**, 51–61.
114. Gleeson JG, Allen KM, Fox JW, Lamperti ED, Berkovic S, Scheffer I, Cooper EC, Dobyns WB, Minnerath SR, Ross ME and Walsh CA: Doublecortin, a brain-specific gene mutated in human X-linked lissencephaly and double cortex syndrome, encodes a putative signaling protein. Cell (1998) **92**, 63–72.
115. Sossey-Alaoui K, Hartung AJ, Guerrini R, Manchester DK, Posar A, Puche-Mira A, Andermann E, Dobyns WB and Srivastava AK: Human doublecortin (DCX) and the homologous gene in mouse encode a putative Ca^{2+}-dependent signaling protein which is mutated in human X-linked neuronal migration defects. Hum Mol Genet (1998) **7**, 1327–1332.
116. Huttenlocher PR, Taravath S and Mojtahedi S: Periventricular heterotopia and epilepsy. Neurology (1994) **44**, 51–55.
117. Eksioglu YZ, Scheffer IE, Cardenas P, Knoll J, DiMario F, Ramsby G, Berg M, Kamuro K, Berkovic SF, Duyk GM, Parisi J, Huttenlocher PR and Walsh CA: Periventricular heterotopia: An X-linked dominant epilepsy locus causing aberrant cerebral cortical development. Neuron (1996) **16**, 77–87.
118. Fox JW, Lamperti ED, Eksioglu YZ, Hong SE, Feng Y, Graham DA, Scheffer IE, Dobyns WB, Hirsch BA, Radtke RA, Berkovic SF, Huttenlocher PR and Walsh CA: Mutations in filamin 1 prevent migration of cerebral cortical neurons in human periventricular heterotopia. Neuron (1998) **21**, 1315–1325.
119. Berkovic SF, Cochius J, Andermann E and Andermann F: Progressive myoclonus epilepsies: Clinical and genetic aspects. Epilepsia (1993) **34** (Suppl 3), S19–S30.
120. Norio R and Koskiniemi M: Progressive myoclonus epilepsy: Genetic and nosological aspects with special reference to 107 Finnish patients. Clin Genet (1979) **15**, 382–398.
121. Lehesjoki A-E, Koskiniemi M, Sistonen P, Miao J, Hastbacka J, Norio R and de la Chapelle A: Localization of a gene for progressive myoclonus epilepsy to chromosome 21q22. Proc Natl Acad Sci USA (1991) **88**, 3696–3699.
122. Lehesjoki A-E, Koskiniemi M, Pandolfo M, Antonelli A, Kyllerman M, Wahlstrom J, Nergardh A, Burmeister M, Sistonen P and Norio R: Linkage studies in progressive myoclonus epilepsy: Unverricht-Lundborg and Lafora's diseases. Neurology (1992) **42**, 1545–1550.
123. Lalioti MD, Mirotsou M, Buresi C, Peitsch MC, Rossier C, Ouazzani R, Baldy-Moulinier M, Bottani A, Malafosse A and Antonarakis SE: Identification of mutations in cystatin B, the gene responsible for the

Unverricht-Lundborg type of progressive myoclonus epilepsy (EPM1). Am J Hum Genet (1997) **60**, 342–351.
124. Pennacchio LA, Lehesjoki A-E, Stone NE, Willour VL, Virtaneva K, Miao J, D'Amato E, Ramirez L, Faham M, Koskiniemi M, Warrington JA, Norio R, de la Chapelle A, Cox DR and Myers RM: Mutations in the gene encoding cystatin B in progressive myoclonus epilepsy (EPM1). Science (1996) **271**, 1731–1734.
125. Virtaneva K, D'Amato E, Miao J, Koskiniemi M, Norio R, Avanzini G, Franceschetti S, Michelucci R, Tassinari CA, Omer S, Pennacchio LA, Myers RM, Dieguez-Lucena JL, Krahe R, de la Chapelle A and Lehesjoki AE: Unstable minisatellite expansion causing recessively inherited myoclonus epilepsy EPM1: Nat Genet (1997) **15**, 393–396.
126. Wallace DC, Zheng XX, Lott MT, Shoffner JM, Hodge JA, Kelley RI, Epstein CM and Hopkins LC: Familial mitochondrial encephalomyopathy (MERRF): Genetic pathophysiological and biochemical characterization of a mitochondrial DNA disease. Cell (1988) **55**, 601–610.
127. Minassian BA, Lee JR, Herbrick JA, Huizenga J, Soder S, Mungall AJ, Dunham I, Gardner R, Fong CY, Carpenter S, Jardim L, Satishchandra P, Andermann E, Snead OC IIIrd, Lopes-Cendes I, Tsui LC, Delgado-Escueta AV, Rouleau GA and Scherer SW: Mutations in a gene encoding a novel protein tyrosine phosphatase cause progressive myoclonus epilepsy. Nat Genet (1998) **20**, 171–174.
128. Serratosa JM, Delgado-Escueta AV, Posada I, Shih S, Drury I, Berciano J, Zabala JA, Antunez MC and Sparkes RS: The gene for progressive myoclonus epilepsy of the Lafora type maps to chromosome 6q. Hum Mol Genet (1995) **4**, 1657–1663.
129. Serratosa JM, Gomez-Garre P, Gallardo ME, Anta B, de Bernabe DB, Lindhout D, Augustijn PB, Tassinari CA, Malafosse RM, Topcu M, Grid D, Dravet C, Berkovic SF and de Cordoba SR: A novel protein tyrosine phosphatase gene is mutated in progressive myoclonus epilepsy of the Lafora type (EPM2). Hum Mol Genet (1999) **8**, 345–352.
130. Canafoglia L, Franceschetti S, Antozzi C, Carrara F, Farina L, Granata T, Lamantea E, Savoiardo M, Uziel G, Villani F, Zeviani M and Avanzini G: Epileptic phenotypes associated with mitochondrial disorders. Neurology (2001) **56**, 1340–1346.
131. Shoffner JM, Lott MT, Lezza AM, Seibel P, Ballinger SW and Wallace DC: Myoclonic epilepsy and ragged-red fiber disease (MERRF) is associated with a mitochondrial DNA tRNA (Lys) mutation. Cell (1990) **61**, 931–937.
132. Silvestri G, Moraes CT, Shanske S, Oh SJ and DiMauro S: A new mtDNA mutation in the tRNA(Lys) gene associated with myoclonic epilepsy and ragged-red fibers (MERRF). Am J Hum Genet (1992) **51**, 1213–1217.
133. Montagna P, Gallassi R, Medori R, Govoni E, Zeviani M, Di Mauro S, Lugaresi E and Andermann F: MELAS syndrome: Characteristic migrainous and epileptic features and maternal transmission. Neurology (1988) **38**, 751–754.
134. DiMauro S, Bonilla E, Zeviani M, Nakagawa M and DeVivo DC: Mitochondrial myopathies. Ann Neurol (1985) **17**, 521–538.
135. Griffith WH and Taylor L: Sodium valproate decreases synaptic potentiation and epileptiform activity in hippocampus. Brain Res (1988) **474**, 155–164.
136. Gean P-W, Huang C-C, Hung C-R and Tsai J-J: Valproic acid suppresses the synaptic response mediated by the NMDA receptors in rat amygdalar slices. Brain Res Bull (1994) **33**, 333–336.
137. Zeise ML, Kasparow S and Zieglgansberger W: Valproate suppresses N-methyl-D-aspartate-evoked, transient depolarizations in the rat neocortex *in vitro*. Brain Res (1991) **544**, 345–348.
138. Ueda Y and Willmore LJ: Molecular regulation of glutamate and GABA transporter proteins by valproic acid in rat hippocampus during epileptogenesis. Exp Brain Res (2000) **133**, 334–339.
139. Baulac S, Gourfinkel-An I, Picard F, Rosenberg-Bourgin M, Prudhomme JF, Baulac M, Brice A and LeGuern E: A second locus for familial generalized epilepsy with febrile seizures plus maps to chromosome 2q21-q33. Am J Hum Genet (1999) **65**, 1078–1085.