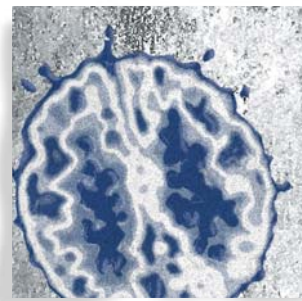# Basic research

Genetics and epilepsy
Ortrud K. Steinlein, MD, PhD

The term "epilepsy" describes a heterogeneous group of disorders, most of them caused by interactions between several or even many genes and environmental factors. Much rarer are the genetic epilepsies that are due to single-gene mutations or defined structural chromosomal aberrations, such as microdeletions. The discovery of several of the genes underlying these rare genetic epilepsies has already considerably contributed to our understanding of the basic mechanisms in epileptogenesis. The progress made in the last 15 years in the genetics of epilepsy is providing new possibilities for diagnosis and therapy. Here, different genetic epilepsies are reviewed as examples, to demonstrate the various pathways that can lead from genes to seizures.

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Epilepsy is one of the most common and heterogeneous neurological conditions, and the molecular pathomechanisms underlying the different seizure disorders have now been studied intensively for more than two decades.[1] There exists a large group of epilepsies that are often labeled as symptomatic, in order to distinguish them from the idiopathic epilepsies that are believed to be mainly of genetic origin. However, with the progress in genetic analysis, it has become more and more obvious that no clear division exists between the two groups of epilepsies. Findings such as *SCN1A* mutations underlying severe myoclonic epilepsy of infancy (SMEI), an epilepsy syndrome that was formerly labeled as symptomatic, as well as the failure to find major genes for common idiopathic epilepsies such as juvenile myoclonic epilepsy, raise questions about the usefulness of a strict classification that distinguishes between symptomatic and idiopathic cases. In the etiology of most epilepsies, a combination of acquired and genetic factors is involved, while predominantly genetic epilepsies constitute only a minority of all seizure disorders *(Figure 1)*.[2] The latter nevertheless serve as an important source for our increasing knowledge about the genes and gene families that can be involved in epileptogenesis, and help us gain insight into the pathomechanisms underlying the more common forms of epilepsy. In the following paragraphs, examples of seizure syndromes are described that are representative of the different genetic mechanisms in epileptogenesis known today. These include ion-channel disorders, examples of the different mechanisms underlying progressive myoclonus epilepsies, a group of neurogenetic disorders that can be due to either developmental abnormality, and defects in energy metabolism or metabolic disturbances, as well as neuronal migration disorders.

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Ion-channel mutations in epilepsy

Dysfunctions of mutated voltage- or ligand-gated ion channels have been shown to be a major cause of idiopathic epilepsies, at least in the rare genetic forms *(Table I)*. The detailed genetic and electrophysiological analyses of different ion channels have provided significant knowledge on the pathophysiological pathways leading from mutation to seizures.[3] Ion-channel mutations are a known cause of rare monogenic idiopathic epilepsies, but are also suspected to play a major role in more common epilepsies such as juvenile myoclonic epilepsy or childhood and juvenile absence epilepsies. In the following paragraphs, some monogenic epilepsies have been selected as examples, to illustrate the importance of ion channels in epileptogenesis.

Familial nocturnal frontal lobe epilepsy

The gene for autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE) was the first one described for an inherited form of idiopathic epilepsy. The mean age of onset in ADNFLE is during adolescence or young adulthood, with considerable intra- and interfamilial variance. Most mutations (with the exception of low penetrance mutation I312M) demonstrate a penetrance of 70% to 80%. The clusters of brief motor seizures that are typical of ADNFLE occur mostly out of nonREM (rapid eye movement) sleep. Patients often have recurrent parox-
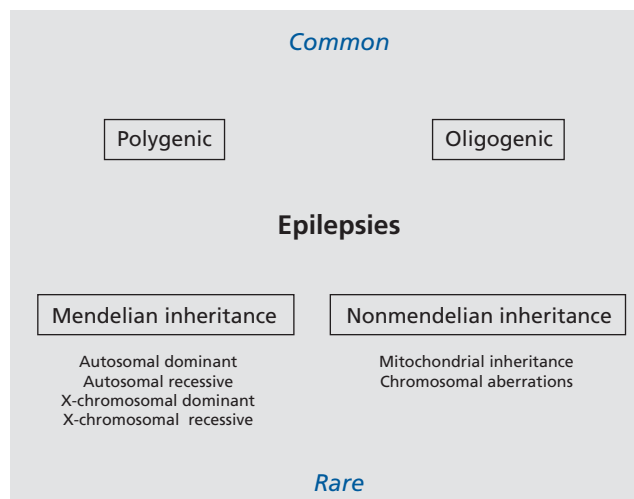
Figure 1. Schematic representation of genetic and nongenetic etiologies in epilepsy.

Abbreviation	Syndrome	Gene(s)	Chromosome	Mode of inheritance
ADNFLE	Autosomal dominant nocturnal frontal lobe epilepsy	*CHRNA4*	20q13.3	AD
		CHRNB2	1q21	
BFNC	Benign familial neonatal convulsions	*KCNQ2*	20q13.3	AD
		KCNQ3	8q24	
BFNIS	Benign familial neonatal-infantile seizures	*SCN2A*	2q24	AD
GEFS+	Generalized epilepsy with febrile seizures plus	*SCN1A*	2q24	AD, OG
		SCN2A	2q24	
		SCN2B	11q23	
		GABRG2	5q31.1-q33.1	
SMEI	Severe myoclonic epilepsy of infancy	*SCN1A*	2q24	AD, OG
JME	Autosomal dominant juvenile myoclonic epilepsy	*GABRA1*	5q34-q35	OG, (AD)
		CACNB4	2q22-q23	
		CLCN2	3q26	
EJM1	Juvenile myoclonic epilepsy type 1	*EFHC1*	6p12-p11	AD
ADPEAF	Autosomal dominant epilepsy with auditory features	*LGI1*	10q24	AD

Table I. Genes in idiopathic epilepsy. AD, autosomal dominant; OG, oligogen; (AD), rare families with monogenic inheritance have been described

ysmal awakenings associated with stereotyped movements. Most seizure episodes are of 2 to 20 s duration, but some of them might last considerably longer. In sleep-walking periods, patients might move around, speak unintelligibly, or scream for 3 min or more. Patients report aura phenomena including epigastric, sensory, or psychic symptoms that often precede the seizures. A typical seizure starts with gasps, grunts, or vocalizations followed by thrashing hyperkinetic activity or tonic stiffening of the limbs, and superimposed clonic jerking. Many patients are, at least initially, not aware of their seizures, or they underestimate their number of seizures per night. Typical complaints are tiredness during daytime and poor sleep quality. Treatment with antiepileptic drugs such as carbamazepine is effective with respect to seizure control or reduction in many, but not all, patients.[4]

In 1995 a first mutation was identified in the *CHRNA4* gene as the underlying cause in a large Australian ADNFLE family that previously helped to map the disorder to chromosome 20q13.3.[5] Since then, additional *CHRNA4* mutations, as well as mutations in two additional genes (*CHRNB2*, *CHRNA2*), have been found in sleep-related frontal lobe epilepsy.[6-8] *CHRNA4*, *CHRNA2*, and *CHRNB2* encode the α4- and β2-subunits of the neuronal nicotinic acetylcholine receptor (nAChR), respectively. The nAChRs are members of the large family of ligand-gated ion channels. They are characterized by five (identical or different) homologous subunits that assemble around a central axis and form a cation-selective ion channel. With the exception of *CHRNB2*-I312M the known ADNFLE mutations in either *CHRNA4* or *CHRNB2* are located within the second transmembrane domain. The second transmembrane (and in parts the third) domain mainly builds the walls of the ion channel; thus, it seems that ADNFLE mutations specifically target the channel's gating structure. Until now, four *CHRNA4* and three *CHRNB2* mutations have been described in ADNFLE families from different parts of the world. Most interesting are those mutations that have occurred independently in different families, because they offer the opportunity to study the effects genetic backgrounds might have on the clinical expression of the disorder.[9]

Not surprisingly in view of the important role of the cholinergic system in higher brain functions, there has been evidence presented that at least some ADNFLE mutations not only cause epilepsy but are also associated with other neurological disorders or cognitive deficits. A good example is presented by the Norwegian ADNFLE family carrying the *CHRNA4*-776ins3 mutation.[10,11] More than half of the 11 mutation carriers are affected by either schizophrenia, negative symptoms of schizophrenia, or severe apathy. Another ADNFLE mutation, *CHRNA4*-S252L, is associated with mental retardation and/or behavioral problems in two families of different geographic origin. In the latter families the differences in geographic origin strongly suggest that the cognitive deficits are caused by the mutation rather than by unrelated factors.[8] Most of the known ADNFLE mutations have already been studied in different expression systems. They typically display an increased sensitivity for the natural agonist acetylcholine, demonstrated by a shift of the agonist response curve to the left. Thus, the pathomechanism caused by these mutations seems to be based on a gain-of-function effect that is likely to increase ion flow through the channel pore. Furthermore, comparison between the mutations showed that they are characterized by different biopharmacological profiles. For example, reduced calcium permeability was observed for the mutants *CHRNA4*-S248F and *CHRNA4*-776ins3 but not for the *CHRNA4*-S252L mutation. It is tempting to speculate that the particular functional signatures of each mutant contribute to the abovementioned observations of associated neurological features or cognitive defects in ADNFLE, while the gain-of-function effect might be responsible for the epilepsy phenotype itself.[12]

It has been hypothized that in presynaptically located nAChRs the gain-of-function effect might activate inhibitory γ-aminobutyric acid (GABA)ergic interneurons. Such interneurons have an important role in controlling the activity of neuronal networks in brain structures such as neocortex and hippocampus by synchronizing the firing of the participating neurons. An enhanced GABA release would first inhibit a larger number of pyramidal cells than usual. After recovery from inhibition, the sudden enhancement in network synchrony could eventually cause the pathological hypersynchronization that might give rise to a seizure.

Benign familial neonatal convulsions

Benign familial neonatal convulsions (BFNC) is an autosomal dominantly inherited seizure disorder of the newborn. BFNC is characterized by an age of onset between the first day and, at latest, the fourth month of life. The seizures are mostly unprovoked, generalized, or multifocal, and of the tonic and/or clonic type. They are often

accompanied by dyspnea, ocular symptoms, or other autonomic signs. The course of the disorder is usually benign and self-limiting, and, with or without pharmacotherapy, in the majority of patients the seizures remit spontaneously within a few days or weeks. Most patients are seizure-free by the age of 6 months.[13] Later in life seizures can reoccur in about 10% to 15% of the patients, starting mostly at school age or in young adulthood. These late-onset seizures are often provoked, for example, by lack of sleep. Recently, it has become a point of discussion as to whether the term "benign" should be used to describe the course of the disorder, since several BFNC families have come to attention in which some or all of the patients had a less than benign outcome. These patients often show a higher frequency of seizures and are often not seizure-free after the age of 4 months. Two BFNC families have been described in which a mutation carrier developed drug-resistant seizures and/or epileptic encephalopathy shortly after birth, resulting in severe psychomotor retardation.[14,15] Follow-up studies showed that even patients that have formerly been believed to have a benign course of the disorder later often showed moderate delays of psychomotor development.

Mutations in the voltage gated potassium channel genes *KCNQ2* (chromosome 20q13.3) and (more rarely) *KCNQ3* (chromosome 8q24) have been described in different BFNC families.[16-18] Both genes encode channel subunits with identical structures including six transmembrane regions (TM), a voltage sensor in TM4, a loop between TM5 and TM6 that builds the ion channel pore, and a long C-terminal region that contains sequence motifs for subunit assembling. So far more than 40 mutations have been reported for *KCNQ2* and three for *KCNQ3*. The BFNC mutations are either missense mutations located in one of the TMs, truncating mutations (nonsense, insertion/deletions or splice site mutations), or large deletions. The majority of mutations are private, ie, they have not been found in other BFNC families.

The ion channel encoded by *KCNQ2* and *KCNQ3* provides one of the major physical equivalents of the so-called M-current, a potassium current which is known to be a powerful controller of neuronal firing. M-currents regulate the frequency with which action potentials are built by opposing sustained membrane depolarization. They have a pivotal role in the stabilization of membrane potentials, and are therefore in a powerful position to control excess neuronal excitability and prevent seizures.[19] Given this important role in brain excitability,

it is not surprising that BFNC mutations were shown to cause only modest reductions (20% to 30%) in potassium currents in reconstitution experiments. Even such slight alterations of M-channel activity are obviously sufficient to increase seizure susceptibility in affected newborns.[20] Only a few *KCNQ2* mutations have been identified that, at least in reconstitution experiments, had a dominant negative effect on channel function, ie, reduced the current by more than 50%. One of these mutations is the R207W amino acid exchange in *KCNQ2* that causes both BFNC and myokymia, a spontaneous and repetitive involuntary contraction of muscle fiber groups. In the BFNC/myokymia syndrome the occurrence of both central and peripheral neurological symptoms might be explained by the unusual electrophysiological profile of the underlying mutation. The magnitude in loss of current observed for R207W depends strongly on the pattern and time course of depolarization. It is therefore possible that the unusual dominant negative effect of R207W establishes itself only in the peripheral nervous system, causing symptoms like myokymia.[21]

Infantile convulsion syndromes

Benign familial infantile convulsions (BFIC) is an autosomal dominantly inherited partial epilepsy syndrome of early childhood.[22] Seizures usually start between months 4 and 6, with remission before the age of 3 years. The partial seizures occur in clusters and usually respond well to antiepileptic drug treatment. BFIC is genetically heterogeneous, and has been linked to loci on chromosomes 1q23, 2q24, 19q, and 16p12-q12 in various families. Interestingly, three other disorders with overlapping neurological features map to the candidate region on chromosome 16p12-q12, including the infantile convulsions and choreoathetosis syndrome (ICCA; OMIM 602066), paroxysmal kinesigenic choreoathetosis (PKC; OMIM 128200), and a syndrome comprising rolandic epilepsy, paroxysmal exercise-induced dystonia, and writer's cramp (EPRPDC; OMIM 608105). Another rare seizure disorder with an age of onset intermediate between BFNC and BFIC is benign familial neonatal/infantile convulsions (BFNIC). In BFNIC both neonatal and early infantile onsets of the seizures can be present in the same family. BFNIC has been shown to be caused by mutations in the voltage-gated sodium channel subunit gene *SCN2A*, a gene that is also discussed as a minor gene for generalized epilepsy with febrile seizures plus (GEFS+).[23]

Febrile seizures, generalized epilepsy with febrile seizures plus, and Dravet syndrome

Febrile seizures are the most common seizure type in humans; they affect 5% to 10% of children under the age of 6 years. In most patients an oligo- or polygenic background rather than a monogenic cause of the seizures is assumed. Rare families with an apparent autosomal dominant mode of inheritance have been identified, and several putative gene loci described. These tentative gene locations include FEB1 on chromosome 8q13-q21, FEB2 on 19p, FEB3 on 2q23-q24, FEB4 on 5q14-q15, FEB5 on 6q22-q24, and FEB6 on 18p11.2.

In some families febrile seizures may persist beyond the age of 6 years and/or may be associated with variable afebrile seizures (febrile seizures plus). This probably not so rare syndrome has been named generalized epilepsy with febrile seizures plus (GEFS+). Afebrile seizure types in GEFS+ individuals include generalized tonic-clonic seizures, myoclonic, absence, and atonic seizures, and in some patients also partial seizures.[24] The mode of inheritance underlying GEFS+ is still a matter of debate. Although in some families the trait is likely to be autosomal dominant, in others it is probably better described as oligogenic or as a major gene effect. A genetic concept involving more than one gene would also better fit to the observed clinical variability in GEFS+. Several different ion channel genes have been implicated in GEFS+—*SCN1B*, *SCN1A*, *SCN2A*, *GABRG2*—but in most families the underlying mutation(s) remain elusive. The first GEFS+ mutation was identified in the *SCN1B* gene on chromosome 19q13.1, a gene that encodes an accessory subunit of the voltage gated sodium channel.[25] Nevertheless, most of the mutations identified since then were found in the *SCN1A* gene, one of the genes coding for the major, pore-forming α-subunit of the voltage gated sodium channel.[2] These α-subunits are composed of four domains each containing six TM (TM1-TM6), and the SCN1A mutations are distributed over the whole length of this large gene.[26]

Mutations in the *SCN1A* gene have also been identified in patients with SMEI (also known as Dravet syndrome) and in the phenotypically overlapping syndromes of borderline SMEI (SMEB) or intractable childhood epilepsy with generalized tonic-clonic seizures (ICEGTC).[27] The clinical phenotype of SMEI is characterized by an initially normal psychomotor development, onset of febrile seizures within the first year of life, and subsequent manifestation of various afebrile seizure types including absence, myoclonic, and partial seizures. Pharmacoresistant seizures and developmental delay become manifest during the second year of life. Nearly all reported SMEI mutations are de novo, and they are often truncating and/or located in functionally critical parts of the gene, while GEFS+ mutations are mostly found in less highly conserved parts of *SCN1A*. It is therefore likely that SMEI and GEFS+ mutations differ with respect to their predicted impact on ion channel function, explaining the differences in clinical severity between both syndromes.

Expression experiments with different SMEI and GEFS+ mutations have shown, probably due to different experimental setups, a variety of biophysical aberrations, including complete loss-of-function, altered gating properties, or even gain-of-function effects. Thus, the exact functional effects of SMEI and GEFS+ mutations and their correlations to clinical phenotypes are still unclear.[28]

Non-ion channel genes in idiopathic epilepsy

Most of the epilepsy genes mentioned so far code for various ion channels, or for proteins that modulate ion-channel function (eg, accessory channel subunits). This has led to the assumption that idiopathic epilepsies are a group of channelopathies. However, in 2001 it was demonstrated that non-ion channel genes play at least a minor role in the etiology of idiopathic epilepsies. Mutations in the *LGI1* gene (leucine-rich glioma inactivated gene 1) have been shown to be a cause of autosomal dominant partial epilepsy with auditory features (AD-PEAF), also called autosomal dominant lateral temporal lobe epilepsy.[29] This rare syndrome is characterized by simple partial seizures with mainly acoustic and sometimes also visual hallucinations.[30] Some families have been described in which the seizures tend to start with a brief sensory aphasia without reduced consciousness.[31] The mutational spectrum known for the *LGI1* gene on chromosome 10q24 includes both missense mutations and truncating mutations. So far, not much is known about the function of the *LGI1* gene, which codes for a protein characterized by a leucine-rich repeat motif (LRR) in its N-terminal end and seven so-called epilepsy-associated repeats (EARs) in the C-terminal half. The LRR motif is found mostly in proteins that participate in some kind of protein-protein interaction or receptor function.[32,33] Two recently published articles have shed some light on the possible function of LGI1 protein

in human brain. They were able to show that two different isoforms of LGI1 protein are expressed in brain, with a long isoform that is secreted and a short isoform that is retained in the intracellular compartment. In the experimental setup the secreted isoform of LGI1 binds to differentiated PC12 cells, suggesting that a LGI1-specific receptor complex is present on these cells. A putative receptor for LGI1 has been identified in ADAM22, a trans-membrane protein anchored to the postsynaptic density-95 (PSD-95)-associated protein complex by stargazin.[34] Both ADAM22 and stargazin are genetically linked to epilepsy, at least in knockout animal models. The PSD-95 protein complex has a scaffolding function at excitatory synapses and is involved in both synaptogenesis and synaptic plasticity. It controls synaptic AMPA receptor surface expression, and the number of expressed receptors could be significantly increased by *LGI1* expression in cultured hippocampal neurons. Thus, ADPEAF mutations might cause epilepsy by interfering with the protein-protein interaction between LGI1 and ADAM22, causing a dysregulation of synaptic transmission.[34] Additional non-ion channel genes have been described in epilepsy families since LGI1 was first reported several years ago. Examples are the *EFHC1* gene and the *MASS1/VLGR1* gene, but so far the respective initial reports have not been confirmed in independent studies.[35]

Progressive myoclonus epilepsies

Numerous neurogenetic syndromes are known in which seizures are a predominant feature but are usually accompanied by other neurological or non-neurological symptoms. The genetic causes (and therefore the pathways leading to epilepsy) found in these disorders are more diverse than those described above for idiopathic epilepsies. Mutated genes might be involved in many different functions, such as metabolic disturbances, mitochondrial dysfunction, or aberrant neuronal (precursor) cell migration. The heterogeneous group of progressive myoclonus epilepsies that includes Unverricht-Lundborg disease (Baltic myoclonus), myoclonic epilepsy and ragged-red fiber disease (MERRF), neuronal ceroid lipofuscinosis (CLN), dentatorubropallidoluysian atrophy, Gaucher disease, Lafora disease, and sialidosis, is representative of the various mechanisms that might underlie different neurogenetic syndromes characterized predominantly by seizures and cognitive decline. Some of these syndromes are therefore discussed in more detail in the following sections.

Unverricht-Lundborg disease

Unverricht-Lundborg disease (EPM1, also known as Baltic or Mediterranean myoclonus epilepsy) is a typical example of a progressive myoclonus epilepsy characterized by generalized epileptic seizures, myoclonus (brief contraction of a muscle or a group of muscles), and progressive neurological deterioration including ataxia and dementia. EPM1, the most common form of progressive myoclonus epilepsy, is an autosomal recessive neurodegenerative disorder with an age of onset between 6 and 18 years. Severe stimulus-sensitive myoclonus and generalized tonic-clonic seizures are the main features; additionally, mental deterioration, intention tremor, dysarthria, and mild ataxia may develop in later stages of the disorder. So far a few point mutations in the *CSTB* gene (cystatin B, also stefin B) on chromosome 21q22.3 have been identified in different EPM1 patients *(Table II)*. However, in the majority of patients the disorder is caused by an unstable expansion of a dodecamer repeat located in the 5' flanking region of the *CSTB* gene.[36] Expansion of the repeat causes absence of, or greatly reduced, *CSTB* expression; thus, a loss-of-function effect is a key event in EPM1

Mutation	Predicted effects
Dodecamer repeat expansion	Disruption of promotor function, resulting in reduction of mRNA expression
426G>C	Amino acid exchange at codon 4, affects contact of cystatin B with papain
149G>A*	Amino acid exchange at codon 50
168+1_18del*	Intronic deletion affecting splicing
1925G>C	Abnormal splicing of pre-mRNA
2353A>G	Abnormal splicing of pre-mRNA
2388T>C	Stop codon mutation at codon 75, causing RNA decay or protein truncation
del2400TC	Frame shift leading to premature stop codon at codon 75, causing RNA decay or protein truncation

Table II. Cystatin B mutations in Unverricht-Lundborg disease. *different nucleotide numbering

pathogenesis. *CSTB* encodes the cystatin B protein, a widely expressed reversible inhibitor of cysteine protease that is thought to have lysosome-associated physiological functions. Cysteine protease inhibitors play an important role in controlling endogenous and exogenous protease activities, protecting organisms from protein degradation. Cystatin B is thought to be involved in the maintenance of normal neuronal structure, and loss of its expression in mouse models caused increased expression of genes involved in proteolysis, apoptosis, and glial activation. Thus neuronal loss by apoptosis and gliosis seems to be an important mechanism in the pathogenesis of EPM1.[37,38] There is also mounting evidence that Cystatin B might have an additional function in the cerebellum unrelated to its role in protease inhibition. Coprecipitation experiments showed that cystatin B interacts with different cerebellum-expressed proteins that are not functioning as proteases. What this additional role of cystatin B might be remains unknown so far.[39]

Myoclonic epilepsy and ragged-red fiber disease

Mitochondria are small intracellular organelles that possess their own circular DNA molecules (mtDNA). Mutations in mtDNA that interfere with or even abolish the ability of mitochondria to perform their role in aerobic respiration are known to cause a wide spectrum of different disorders. They all have in common a pattern of symptoms that predominantly affect tissues with a high dependence on oxidative metabolism, such as brain, muscle, and heart. The clinical manifestations of mitochondrial disorders are extremely heterogeneous; they range from lesions of single tissues to severe impairments including myopathies, encephalomyopathies, cardiomyopathies, or complex multisystem syndromes.[40,41] A typical example of such a mitochondrial disorder is MERRF, another member of the group of progressive myoclonus epilepsies. MERRF is characterized by myoclonus, generalized epileptic seizures, myopathy, and slowly progressive dementia. Additional symptoms can be hearing loss, ataxia, and lipomatosis. Histopathological analysis of muscle bioptic material typically shows ragged-red fibers and abnormal mitochondria with concentric cristae. Age of onset and clinical severity differ widely from patient to patient, even between siblings. This is mainly explained by heteroplasmy, ie, each patient inherits a different mixture of normal and mutated mitochon-

dria from his or her mother (there is no paternal inheritance of mitochondria since sperm mitochondria that enter the oocyte are "digested"). The most commonly found MERRF mutation is mt8344A>G that affects the tRNALysine gene within the mtDNA.[42] Due to the heteroplasmatic nature of the disorder the molecular diagnosis from blood not always reliably detects the underlying mutation. Skeletal muscle frequently has the highest percentage of mutated mtDNA molecules in MERRF patients, and this percentage correlates best with the clinical severity of the disorder.[43] Muscle biopsy is therefore the first choice to obtain material for diagnostic mutation analysis. Close to 150 pathogenic mutations in 21 of the 22 mitochondrial tRNA genes have been described up to now, and 50% of these mutations are located in either one of three tRNA genes, tRNA[Leu(UUR)], tRNA[LYS], or tRNA[Ile]. Mutations in tRNA genes might have different pathological effects, including structural perturbances of the three-dimensional tRNA structure, reduced or abolished binding capacity to translation factors such as the elongation factor EF-Tu, or impairment of tRNA maturation. All of these mutations affect the essential role tRNA genes have in the synthesis of proteins involved in energy metabolism, causing various neuromuscular and neurodegenerative disorders.

Neuronal ceroid lipofuscinoses

The different subtypes of neuronal ceroid lipofuscinoses (CLN, or NCL) are (with one exception) autosomal recessively inherited neurodegenerative disorders belonging to the group of lysosomal storage diseases.[44] The childhood forms of CLN are characterized by mental and motor deterioration, as well as progressive loss of vision, myoclonic, tonic-clonic, and atypical absence seizures, and premature death, while dementia presents as the main feature in the rare adult forms of CLN. The human CLNs are presently classified into eight main genetic forms (CLN1–8). The infantile subtype of CLN, Santavuori-Haltia-Hagberg disease (CLN1), occurs primarily in the Finish population. The classical late-infantile form of CLN, Jansky-Bielschowsky disease (CLN2), starts at age 2 to 4 years with myoclonus and seizures. There are at least three additional subtypes that are classified as variants of late infantile CLN. These include the Finnish variant (CLN5), the CLN6 variant of late infantile CLN, and the Turkish variant of CLN (CLN8). The *CLN8* gene also causes Northern epilepsy or progressive

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epilepsy with mental retardation, an autosomal recessive epilepsy of childhood onset that is only found in parts of northern Finland. Juvenile-onset CLN (Batten disease, Vogt-Spielmeyer disease) is the most common neurodegenerative disorder of childhood, with an age of onset at 5 to 10 years. Kufs disease or adult CLN (CLN4) is distinguished clinically from the infantile and juvenile subtypes by onset of progressive myoclonus epilepsy in adulthood and by the absence of ocular involvement. Additionally, a few rare forms exist that have not been genetically assigned yet, including congenital NCL and dominantly inherited adult onset NCL (Parry disease, *Table III*).[45-48]

Characteristic features of CLN are an accumulation of autofluorescent, periodic acid-Schiff- and Sudan black B-positive granules in the cytoplasm of most nerve cells, astrocytic proliferation and hypertrophy, and progressive and remarkably selective neuronal degeneration and loss.[49] The storage cytosomes characteristic for CLN mainly contain of two hydrophobic proteins, the sphingolipid activator proteins A and D (infantile form of CLN) or the subunit c of mitochondrial ATP synthase (late infantile and juvenile CLN).[50] The CLN1 and CLN2 genes code for the soluble lysosomal enzymes PPT1 and tripeptidyl peptidase 1 (TPP1), whereas CLN3, CLN6, CLN8 and, possibly, CLN5 are transmembrane proteins of largely unknown functions. It is still unclear how a group of genes as heterogeneous as the CLN genes can cause such a remarkably uniform morphological phenotype characterized by intraneuronal accumulation of hydrophobic proteins. Different mechanisms including both apoptotic and excitotoxic processes are discussed, but the exact nature of the pathophysiological pathways underlying the different CLN subtypes remain to be elucidated.[51]

Neuronal migration disorders

The migration and maturation of neurons, synapses, and cortical neuronal networks during embryonal and fetal development is a sequential process composed of different steps that are regulated by genetic and environmental factors.[52] The cortical neurons are formed in the neuroepithelium of the ventricular zone, and then migrate considerable distances to reach their final position in the cortex. In humans, neuronal migration in the cortex starts at approximately 7 weeks of gestation from the proliferative ventricular zone. The radially migrating neurons as well as the nonradially (tangential) migrating future interneurons are guided by glial fibers through an interaction of adhesion molecules, trophic factors, and guidance molecules. Any disturbances (genetic or environmental) of these complicated migration and matu-rating processes have the potential to cause severe neurological disorders with various symptoms, including mental retardation and epilepsy. Genetic neuronal migration disorders include different lissencephaly syndromes and subcortical band heterotopia, cobblestone dysplasia (a term describing the bumpy surface of the brain that is caused by ectopic neurons and gliovascular proliferation), and different gray matter heterotopia disorders (see also the article by Leventer et al in this issue, p 47).

Conclusion

Although the number of already known epilepsy genes is impressive, they probably represent only the tip of the proverbial iceberg. A roughly estimated 50% of all genes are, at least during fetal development, expressed in brain and might therefore be regarded as candidates for

CLN subtype	Eponym	Gene	Chromosome	Inheritance
CLN1	Haltia–Santavuori disease, INCL	*CLN1*	1p32	AR
CLN2	Janskˇ-Bielschowsky disease, LINCL	*CLN2*	11p15	AR
CLN3	Spielmeyer-Sjögren disease	*CLN3*	16p12	AR
CLN4a	Kufs disease, ANCL	NK	NK	AR
CLN5	vLINCL Finnish	*CLN5*	13q22	AR
CLN6	Lake-Cavanagh disease, vLINCL	*CLN6*	15q21–23	AR
CLN7	vLINCL Turkish	NK	NK	AR
CLN8	Northern epilepsy, progressive epilepsy with mental retardation	*CLN8*	8p32	AR
CLN10	Congenital CLN	*CTSD*	11p15.5	AR
CLN4b	Parry disease	NK	NK	AD

Table III. Ceroid lipofuscinosis subtypes in humans. AR, autosomal recessive; AD autosomal dominant; INCL, infantile CLN; LINCL, late infantile CLN; ANCL, adult NCL; vLINCL, variant late infantile CLN; NK, not known

seizure disorders. Furthermore, recent research has shown that alterations of genomic DNA copy number and gene regulatory elements are likely to be as important for human disorders as mutations that directly affect genes.[53] In the future, whole-genome screening methods such as array-based comparative genomic hybridization (aCGH) or genome-wide single nucleotide polymorphism (SNP) analysis will become important tools for the identification of genetic alterations with potential application to common forms of human epilepsy. ❑

Genética y epilepsia

El término "epilepsia" describe un grupo heterogéneo de trastornos, la mayoría de los cuales son causados por interacciones entre algunos o incluso muchos genes, y factores ambientales. Son bastante más raras las epilepsias genéticas que se deben a mutaciones de un gen único o aberraciones cromosómicas estructurales definidas, como las microdeleciones. El descubrimiento de algunos de los genes que están a la base de estas raras epilepsias genéticas ya ha contribuido considerablemente a la comprensión de los mecanismos básicos en la epileptogénesis. El progreso que se ha llevado a cabo en los últimos 15 años en la genética de la epilepsia está aportando nuevas posibilidades diagnósticas y terapéuticas. En este artículo se revisan, a modo de ejemplo, diferentes epilepsias genéticas para demostrar las diversas vías que pueden llevar desde los genes a las convulsiones.

Génétique et épilepsie

Le terme « épilepsie » décrit un groupe hétérogène de troubles dont la plupart sont dus à des interactions entre quelques, ou même de nombreux gènes et des facteurs environnementaux. Plus rares sont les épilepsies génétiques qui sont dues à des mutations d'un seul gène ou à des aberrations chromosomiques de structure définies comme les microdélétions. Notre compréhension des mécanismes de base de l'épileptogenèse a déjà été considérablement améliorée par la découverte de plusieurs de ces gènes impliqués dans ces épilepsies génétiques peu répandues. Les progrès effectués ces 15 dernières années dans la génétique de l'épilepsie ouvrent de nouvelles perspectives de diagnostic et de traitement. Dans cet article, nous passons en revue différentes épilepsies génétiques comme exemples illustrant les différentes voies qui mènent des gènes à l'apparition d'une crise comitiale.

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