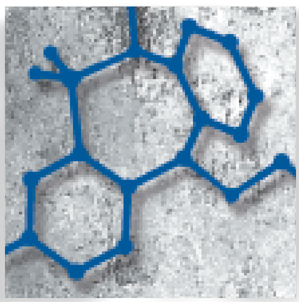
Genetics of inherited human epilepsies

Isabelle Gourfinkel-An, MD; Stéphanie Baulac, BS; Alexis Brice, MD; Eric Leguern, MD, PhD; Michel Baulac, MD



Major advances have recently been made in our understanding of the genetic basis of monogenic inherited epilepsies. Progress has been particularly spectacular with respect to idiopathic epilepsies, with the discovery that mutations in ion channel subunits are implicated. However, important advances have also been made in many inherited symptomatic epilepsies, for which direct molecular diagnosis is now possible, simplifying previously complex investigations. It is expected that identification of the genes implicated in familial forms of epilepsies will lead to a better understanding of the underlying pathophysiological mechanisms of these disorders and to the development of experimental models and new therapeutic strategies. In this article, we review the clinical and genetic data concerning most of the inherited human epilepsies.

Epilepsies are frequent heterogeneous disorders[1] and are caused by many factors.[2] The contribution of genetic and environmental factors varies among epileptic disorders. Genetic factors are generally thought to contribute to the etiology of 40% to 60% of human epilepsies.[2,3] Inherited epilepsies are usually classified according to whether the mode of inheritance is complex or monogenic. In epilepsies with a complex mode of inheritance, epilepsy results from the interaction between environmental factors and genetic susceptibility, whereas in monogenic epilepsies, the genetic component is prevalent, although environmental factors may contribute to phenotypic expression and could explain incomplete penetrance or variable clinical expression. Finally, in epilepsies caused by exogenous factors (the least genetically determined of the epilepsies), genetic susceptibility could explain why only some of the individuals exposed to the same factors later develop epilepsy.

Genetic studies in epilepsies are difficult to perform for several reasons. First, most epilepsies have a complex mode of inheritance and it is difficult to identify the genes involved. Nonparametric analyses in a large number of affected individuals (ie, hundreds) are necessary. However, difficulties are also encountered in genetic studies of monogenic epilepsies, particularly in the identification of large informative families with enough affected members to be useful for linkage analysis. Second, phenotype analysis can be problematic. The clinical status (ie, affected or not) of each member of the family must be determined. This involves a choice of more or less stringent electroclinical criteria to confirm the presence of the disease. The collection of reliable medical information may be difficult, especially in the first generation of affected families. Moreover, the presence of phenocopies (which are frequent for epilepsy and febrile convulsions) and possible intrafamilial phenotypic heterogeneity must be taken into account.

Despite these difficulties, major advances have been made in the genetics of epilepsy in the past 10 years. Nearly all concern epilepsies with a monogenic mode of inheritance, the least frequent of the inherited epilep-

Keywords: *channelopathies; complex mode of inheritance; familial epilepsy; idiopathic epilepsy; monogenic inheritance; neuronal migration; symptomatic epilepsy*

Author affiliations: Unité d'Epileptologie, Hôpital Pitié-Salpêtrière, Paris, France (Isabelle Gourfinkel-An, Michel Baulac); Service d'Electrophysiologie, Hôpital Pitié-Salpêtrière, Paris, France (Isabelle Gourfinkel-An); INSERM U 289, Hôpital Pitié-Salpêtrière, Paris, France (Stéphanie Baulac, Alexis Brice, Eric Leguern)

Address for correspondence: Prof Michel Baulac, Unité d'Epileptologie, Hôpital de la Pitié-Salpêtrière, 47, Bd de l'Hôpital, 75651 Paris Cedex 13, France (e-mail: michel.baulac@psl.ap-hop-paris.fr)

Selected abbreviations and acronyms

ADNFLE	*autosomal dominant nocturnal frontal lobe epilepsy*
BFNC	*benign familial neonatal convulsions*
GEFS+	*generalized epilepsy with febrile seizures–plus*
nAChR	*nicotinic acetylcholine receptor*
PME	*progressive myoclonus epilepsy*

sies. The progress in idiopathic epilepsies has been spectacular, with the discovery that some of them may involve mutations in ion channels, leading to the concept of "channelopathies." However, important advances have also been made in symptomatic epilepsies, with the discovery, for example, of genes implicated in neuronal migration and various metabolic pathways.

It is expected that elucidation of the genetic basis of monogenic epilepsy will also help us understand the genetic basis of epilepsies with complex inheritance.

In this article, we review recent advances in the genetics of epilepsy, focusing on the molecular and pathophysiological aspects of some inherited epilepsies.

Idiopathic epileptic syndromes

It has long been suspected that genetic factors are prevalent in the etiology of idiopathic epilepsies. Most are characterized by a complex inheritance—idiopathic epilepsies with monogenic inheritance are rare. Those in which a locus or genes have been identified are listed in *Table I*.[4-46] For some of these, voltage- or ligand-gated ion channels are implicated.

Idiopathic epileptic syndromes with monogenic inheritance: the new concept of channelopathies

To date, three familial idiopathic syndromes have been found to be mediated by mutations in voltage- or ligand-gated ion channels.

Autosomal dominant nocturnal frontal lobe epilepsy

The syndrome of autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE) was first described by Scheffer in 1994.[47,48] It is characterized clinically by the onset in infancy of frequent brief partial seizures occurring in clusters during sleep. Adult onset is less common. The motor component of seizures predominates (paroxysmal dystonic postures, thrashing, ambulation). Sometimes, the symptoms are limited to sudden awakening. Vocalizations or aura may precede the motor manifestations. Misdiagnoses are frequent, especially confusion with parasomnias (night terrors, somnambulism). Seizures usually persist in adults, but tend to be less frequent and respond to carbamazepine. Intrafamilial variations in severity are sometimes observed. Neuroimaging is normal. When ictal electroencephalography (EEG) recordings are interpretable, they show unilateral or bilateral frontal/temporal epileptic activity.

Familial studies of this rare new syndrome demonstrated autosomal dominant transmission with incomplete penetrance. One locus was found in the region 20q13.2 by linkage analysis in a large Australian pedigree.[4] The *CHRNA4* gene encoding for the alpha-4 subunit of the neuronal nicotinic acetylcholine receptor (nAChR), which has already been found in this genomic region, was a good candidate. Indeed, subsequent screening of the *CHRNA4* gene in the first ADNFLE Australian family described led to identification of a mutation in this gene.[5] Other mutations of the *CHRNA4* gene were subsequently detected in several families.[6-8]

nAChR receptors are heteropentameric ligand-gated ion channels. The genes for eight human nAChR subunits have been mapped. The alpha-4 subunit is expressed in all layers of the frontal cortex. The second transmembrane domain of the alpha-4 subunit is crucial to the permeability of the ion channel. Mutations of the alpha-4 subunit are thought to decrease the activity of nAChR by reducing its affinity for acetylcholine and permeability to calcium.[49,50] Neuronal nicotinic receptors are thought to be almost exclusively presynaptic, regulating the release of neurotransmitters such as glutamate. However, the mechanism by which hypoactive nAChRs cause this partial familial epilepsy is unknown.

Another ADNFLE locus has been found in the region 15q24 in one family.[9] Although this region is close to a cluster of genes encoding other nAChR subunits *(CHRNA3*, *CHRNA5*, and *CHRNB4)*, mutations have not been found in these subunits, and the causative gene remains to be identified.

A third locus was recently identified in the pericentromeric region of chromosome 1,[10] with the subsequent identification of mutations in the beta-2 subunit of nAChR *(CHRNB2)*.[11,12] However, most ADNFLE families are not linked to *CHRNB2* or *CHRNA4*.[51]

Disorder	Mode of inheritance	Chromosomal region, gene/protein
Partial idiopathic epilepsies		
• Autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE)	AD	• 20q, *CHRNA4*[4-8]
		15q, gene?[9]
		1 (pericentromeric region),
		CHRNB2[10-12]
• Familial lateral temporal epilepsy with auditory symptoms	AD	• 10q, gene?[13-15]
• Familial mesiotemporal epilepsy	AD	• Locus?[16,17]
• Autosomal dominant partial epilepsy with variable foci	AD	• 2qter, gene?[18]
		22q, gene?[19]
• Benign familial infantile convulsions (BFIC)	AD	• 19q, gene?[20]
		Other locus?
• Infantile convulsions with paroxysmal choreoathetosis (ICCA)	AD	• 16p, gene?[21,22]
• Familial rolandic epilepsy with paroxysmal	AR	• 16p, gene (only one family
exercise-induced dystonia and writer's cramp		published)[23]
• Familial rolandic epilepsy with speech dyspraxia	AD with anticipation	• Locus? Expansion of
and mental retardation		trinucleotidic repeat is suspected
		(only one family published)[24]
Generalized idiopathic epilepsies		
• Benign familial neonatal convulsions (BFNC)	AD	• 20q, *EBN1*, *KCNQ2*[25-29]
		8q, *EBN2*, *KCNQ3*[30,31]
		Third locus?
• Familial cortical tremor	AD	• 8q23.3-q24.1, gene?[32-34]
(or benign adult familial myoclonic epilepsy)		Other locus?
Familial febrile convulsions	Variable mode	• 8q13-q21, *FEB1*, gene?[35]
	of inheritance[a]	19p13.3, *FEB2*, gene?[36-38]
		11q, gene?[39]
		5q14-q15, *FEB4*, gene?[40]
Generalized epilepsy with febrile seizures–plus (GEFS+)	AD	• 19q13.1, *SCN1B*[41]
		2q21-q33, *SCN1A*[42-46]
		Third locus?

Table I. Genetics of idiopathic epilepsies with a monogenic mode of inheritance. AD, autosomal dominant; AR, autosomal recessive.
[a]Several modes of inheritance have been described for familial febrile convulsions: polygenic inheritance seems to be prevalent; however, autosomal dominant transmission with incomplete penetrance or autosomal recessive transmission have been described for some families.

Benign familial neonatal convulsions

The syndrome known as benign familial neonatal convulsions (BFNC) is characterized by the occurrence of unilateral or bilateral clonic, apneic, or even tonic seizures on the second or third day of life of a normal neonate. Interictal EEGs rarely show what is described as a "sharp alternating theta." The outcome is generally favorable, although some patients will develop febrile seizures or nonfebrile seizures later in life. This familial syndrome differs in several respects from the sporadic form (benign neonatal convulsions), in which tonic seizures are never observed, the typical interictal EEG feature of a "sharp alternating theta" is more frequent, and outcome is more favorable.

BFNC was the first idiopathic epilepsy in which genetic linkage was established,[25] first to the q arm of chromosome 20,[25,26] and then to the q arm of chromosome 8.[30] Mutations in novel voltage-gated potassium channel genes *KCNQ2* (region 20q)[27-29] and *KCNQ3* (region 8q)[31] were found in this familial syndrome, but the existence of one or more loci is suspected. Most families are linked to *KCNQ2*.[31] Only one *KCNQ3*-linked family has been published to date. *KCNQ2* and *KCNQ3* are heteromeric channels with highly homologous sequences. They are predominantly expressed in all regions of brain and are functionally associated, contributing to the M current that regulates excitability of many neurons.[28,52] As demonstrated by in vitro studies, the identified mutations cause a minor loss of function of the channels.[28,29,53] The age-dependence of this familial syndrome may result from difference in the cerebral expression of the potassium channel genes over time.[54] Interestingly, mutations in *KCNQ1*, a voltage-gated potassium channel gene that is expressed in the heart and ear and is homologous to *KCNQ2* and *KCNQ3*, cause two other familial syndromes: the long-QT syndrome and Jervell-Lange-Nielsen cardioauditory syndrome.[55,56]

Generalized epilepsy with febrile seizures–plus syndrome

Febrile seizures are frequent events, the genetic component of which is important. In some families, febrile seizures are associated with nonfebrile seizures, constituting the syndrome described in 1997 as generalized epilepsy with febrile seizures–plus (GEFS+).[57] In this heterogeneous familial phenotype, some affected members often have multiple febrile seizures that persist beyond the age of 6, whereas other family members have classic febrile seizures that disappear before the age of 6. Variable nonfebrile seizures are also observed. Initially, generalized seizures (tonic-clonic, myoclonic, atonic, and absence seizures) were described,[57] but hemiconvulsive, temporal, or frontal seizures were later observed in other families.[42-44,58] These afebrile seizures may begin in childhood in association with febrile seizures, after a seizure-free period, or later in life. Furthermore, not all affected members have febrile seizures. Several types of seizure can coexist in a given patient with electroclinical features that are more or less typical of generalized idiopathic epilepsies or myoclonic astatic epilepsy (Doose syndrome), but electroclinical patterns that do not correspond to the international classification of epilepsies are also observed.[59] Some patients are intellectually disabled.[42] Outcome and response to treatment are very variable within the same family. When available, neuroimaging is normal.

GEFS+ is transmitted as an autosomal dominant trait with incomplete penetrance, and is genetically heterogeneous. The first locus was found in the region 19q13.1, and a mutation in the *SCN1B* gene coding for the beta 1 subunit of the neuronal voltage-gated sodium channel was found in one family.[36] A second locus in region 2q21-q33 seems to be more frequently implicated, according to published reports in several families.[42-45] In two French families, two different mutations were identified in the *SCN1A* gene, which encodes for the alpha-1 subunit of the same voltage-gated sodium channel.[46] Functional studies in *Xenopus* oocytes have demonstrated that mutations in the beta-1 and alpha-1 subunits interfere with the functional properties of the sodium channel.

A third locus is suspected because some GEFS+ families are not linked to *SCN1A* or *SCN1B*.[36,46]

Idiopathic epilepsies with complex inheritance

Most idiopathic generalized epilepsies (including juvenile myoclonic epilepsy, juvenile absence epilepsy, childhood absence epilepsy, and epilepsy with tonic-clonic seizures on awakening) have a complex mode of inheritance. These diseases result from an interaction between genetic susceptibility (often mediated by several genes) and environmental factors. Linkage to the q arm of chromosome 8,[60,61] and the p arms of chromosomes 1[62] and 3[63] have been reported for generalized epilepsies. Because confirmatory reports in additional families have not been forthcoming, these results should be considered with caution.

Juvenile myoclonic epilepsy has been studied most extensively, with controversial findings concerning linkage to the regions 6p[64-69] and 15q14.[70]

Most febrile seizures and benign rolandic epilepsy are also thought to have complex modes of inheritance. Linkage to the q arm of chromosome 15 was suggested for benign rolandic epilepsy in one study.[71]

Inherited developmental cortical malformations (neuronal migration disorders)

These developmental disorders are an important cause of pharmacoresistant epilepsy, which is often associated with mental retardation.

Lissencephaly and double cortex syndrome

Lissencephaly is a rare disorder characterized by a reduced number of cerebral gyri due to an arrest of neuronal migration at 8 to 14 weeks of gestation.[72] The cortex is abnormally thick and the surface of the brain is smooth. Microscopically, the cortex is poorly organized with four to six primitive layers and diffuse neuronal heterotopia. Affected children have severe mental retardation, and often pharmacoresistant epilepsy and other neurological abnormalities. Various types of seizures (tonic-clonic, myoclonic, and tonic seizures, and infantile spasms) occur early in life. Lissencephaly can be isolated, as in isolated lissencephaly sequence or in hemizygous males affected with X-linked lissencephaly. However, in Miller-Dieker syndrome, lissencephaly is associated with facial dysmorphism.

In Miller-Dieker syndrome, and in around a third of patients with isolated lissencephaly sequence, a heterozygous deletion or mutation has been demonstrated in the *LIS1* gene, which is located in the region 17p13.3.[73-75] The *LIS1* gene is ubiquitously expressed and encodes a noncatalytic subunit of platelet activating factor (PAF) acetylhydrolase, an enzyme that inactivates PAF.

In males affected with X-linked lissencephaly, an X-linked dominant inherited disease, the gene involved is *DCX*, which encodes doublecortin and is located in the region Xq22.3-q23.[76,77] Interestingly, in females, the same mutations in the *DCX* gene lead to another phenotype, the double cortex syndrome, which is characterized by a laminar cerebral heterotopia.[76,77] Affected women have pharmacoresistant epilepsy, but are less mentally retarded than affected males.

More recently, rare cases of double cortex syndrome have been reported in men with mutations in the *LIS1* or *DCX* genes.[78,79] The *LIS1* and *DCX* gene products interact and interfere with dynamic properties of microtubules. The exact mechanism that underlies abnormal neuronal migration has not been elucidated.

Familial periventricular heterotopia

Periventricular heterotopia is characterized by the lining of the ventricular walls with nodules that consist of neurons that did not migrate to the cortex during brain development. X-linked periventricular heterotopia is lethal to males during the embryonic period. Affected females have epilepsy without mental retardation, associated with persistent ductus arteriosus, coagulopathies, and skeletal abnormalities. The causative gene is *FLN1*, which is located in the region Xq28[80] and encodes filamin 1, an actin-binding protein that interacts with other proteins of cytoskeleton.

Progressive myoclonus epilepsies

Progressive myoclonus epilepsies (PMEs) are rare disorders that have some clinical features in common, but different etiologies and variable outcomes. A specific diagnosis for some of these diseases has been possible for a long time, on the basis of characteristic stigmata detected by pathological investigation. Numerous advances in genetics now permit direct molecular diagnosis in most cases. We will focus here on the genetic bases of Unverricht-Lundborg disease and Lafora's disease. Other PMEs with their corresponding loci and genes are listed in *Table II*.[81-120]

Unverricht-Lundborg disease

Unverricht-Lundborg disease is an autosomal recessive PME classically with onset between 6 and 15 years of age, a slow progression, rare, late, and mild mental deterioration, and cerebellar ataxia.[121,122] However, more dramatic outcomes have been described, often precipitated by phenytoin prescription.[123] More recently, late-onset forms of the disease have been reported.[124] Both the Baltic and Mediterranean forms of the disease are caused by mutations in the cystatin B gene located in the region 21q22.3.[125,126] Rare point mutations and deletions in the coding region of the gene[81-84] lead to a loss of function of cystatin B. More frequently, expansion of a dodecamer (CCC CGC CCC GCG)$_n$ repeat in the 5′ untranslated region of the gene[85-88] decreases transcription. Normal alleles contain two to three copies of the dodecamer, whereas mutant alleles contain more than 30 repeats of the dodecamer. Preliminary studies have not provided evidence of a correlation between the size of the dodecamer expansion and age at onset of the disease.[88] There are probably premutation states, since intermediate size alleles with 12 to 17 dodecamer repeats have been detected in individuals with normal phenotype who were able to transmit pathologic alleles to their offspring.[86]

Disorder	Mode of inheritance	Locus, gene, protein
Unverricht-Lundborg disease	AR	● 21q, *EMP1*, cystatin B[81-88]
Lafora's disease	AR	● 6q, *EMP2A*, laforin[89,90] Other locus?
Neuronal ceroid lipofuscinoses		
● Early infantile form, late infantile form, and variant of juvenile form, all with cytoplasmic granular osmiophilic deposits	AR	● 1p32, *CLN1*, lysosomal palmitoyl-protein thioesterase I[91-95]
● Classic late infantile form	AR	● 11p15, *CLN2*, tripeptidyl peptidase I[96-98]
● Variant of late infantile form	AR	● 15q21-23, *CLN6*,[96] gene?
● Finnish late infantile form	AR	● 13q21-32, *CLN5*, new protein of unknown function[99]
● Turkish late infantile form[100]	AR	● Locus, *CLN7*? gene?
● Juvenile form	AR	● 16p12 (*CLN3*), novel protein involved in lysosomal pH regulation[101-103]
● Adult form (Kufs' disease)[104]	AD	● Locus (*CLN4*)? gene?
Myoclonus epilepsy and ragged-red fibers (MERRF) syndrome	Maternal transmission	● Mitochondrial genome 8344 $tRNA^{Lys}$ is the prevalent mutation[105-107]
Sialidoses	AR	● 6p, α-neuraminidase[108,109] 20q, stabilizing protein of the α-neuraminidase-β-galactosidase complex[110]
Juvenile form of Gaucher's disease	AR	● 1q, β-glucocerebrosidase[111,112]
Juvenile form of G_{M2} gangliosidosis	AR	● 15q23-24, β-hexosaminidase A α-subunit gene[113,114]
Dentatorubral-pallidoluysian atrophy[a]	AD	● 12p, atrophin[115]
Huntington's disease[a]	AD	● 4q, huntingtin[116,117]
Familial form of Alzheimer's disease[a]	AD	● 14q, presenilin 1[118,119]
Mutation in neuroserpin gene[a] (one family published)	AD	● 3q26, neuroserpin[120]

Table II. Inherited progressive myoclonus epilepsies. AD, autosomal dominant; AR, autosomal recessive.
[a]Progressive myoclonic epilepsy may be a clinical form of the disease.

The presence of these two types of mutations varies according to the geographic origin of affected families. The Baltic form of the disease is generally caused by a point mutation in one copy of the cystatin B gene and expansion of the dodecamer in the other copy or, more rarely, by point mutations in both copies of the gene. The Mediterranean form of the disease, characterized by frequent consanguinity, results from expansion of the dodecamer on both copies of the cystatin B gene. Cystatin B is a cystein-protease inhibitor that is thought to protect against apoptosis, but the mechanism leading to Unverricht-Lundborg disease remains to be elucidated.

Disorder	Mode of inheritance	Locus, gene, protein
Tuberous sclerosis	AD	● 9q34, *TSC1*, tuberin[133,134]
		16p13.3, *TSC2*, hamartin[133,135]
Type 1 neurofibromatosis	AD	● 17q11.2, *NF1*, neurofibromin[136]
Familial cerebral cavernomas	AD	● 7q, *KRIT1* gene[137-139]
		7p
		3q
Rett's syndrome	Dominant X-linked	● Xq28, *MECP2* gene[140]
Mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes (MELAS)	Maternal transmission	● Mitochondrial genome: 3243 tRNA^{Leu} is the prevalent mutation[106,141]
Fragile X syndrome	Dominant X-linked[a]	● Xq27.3, *FMR1* and *FMR2* genes[142-144]
Some types of gangliosidosis	AR	● Variable[145-147]

Table III. Principal inherited disorders with epilepsy as a part of phenotype. AD, autosomal dominant; AR, autosomal recessive.
[a]With unusual characteristics: the mutation can be passed through phenotypically normal males (normal male carriers) and their daughters are almost never affected. In contrast, 30% of carrier females are mentally retarded.

Lafora's disease

Lafora's disease is an autosomal recessive PME characterized by onset between age 10 and 18, rapid neurological and cognitive decline, and fatal outcome after about 10 years of progression. Focal occipital seizures are frequent.[127] Until recently, diagnosis was established by observation of intracellular polyglucosan inclusions (Lafora bodies) on skin biopsies.[128] Direct molecular diagnosis is now possible.
Linkage analysis and homozygosity mapping localized the gene in the region 6q23-25.[129,130] The gene, identified by positional cloning,[89,90] encodes a protein tyrosine phosphatase, laforin, which is a tyrosine kinase inhibitor. Laforin is thought to be involved in glycogen metabolism. Homozygous deletions and several homozygous point mutations in the coding part of the gene have been found in affected families.[89,90] At least one other locus is probably also responsible for Lafora disease.[131,132]

Inherited neurologic disorders and chromosomal disorders with epilepsy as a part of the phenotype

Epilepsy is observed among complex neurological or extraneurological symptoms in numerous chromosomal disorders and inherited disorders affecting the central nervous system. They cannot be described in detail in this review and most are listed in *Tables III* and *IV*.[106,133-147] The frequency of epilepsy in these complex syndromes is variable.

● Trisomy 21 (Down's syndrome)
● Angelman syndrome (partial monosomy 15q11)
● Trisomy 12p
● Wolf-Hirschhorn syndrome (partial monosomy 4p)
● Klinefelter's syndrome (XXY)
● Ring chromosome 20

Table IV. Principal chromosomal disorders associated with epilepsy.

Conclusion

Genetic studies of previously well-defined epileptic syndromes have led to the identification of causative genes in some cases, but also to the identification of new familial epileptic syndromes that are not yet included in the international classification of epilepsies and epileptic syndromes.[59] In the future, this classification will probably take into account these new familial epileptic disorders with their particular electroclinical features and prognoses.
The genetic heterogeneity of epilepsies is becoming more and more apparent. Different genes, which may or not be functionally linked, and different mutations may cause the same familial epileptic syndrome. At the same

time, significant intrafamilial phenotypic heterogeneity can often be observed. This is particularly clear in the GEFS+ syndrome. One hypothesis is that the expression of the mutated genes differs among family members, causing clinical heterogeneity. Alternatively, the gene may intervene in epileptogenesis at a very general level, affecting epileptic susceptibility or modulating the epileptogenic threshold, and other genetic or environmental factors may influence the electroclinical profile of the disease in each affected subject.

There are many pathophysiological mechanisms underlying inherited epilepsies. The functional or morphological consequences of the mutations that give rise to an epileptic process are extremely variable. The discovery of dysfunction of ion channels in several idiopathic epilepsies has led to the concept of channelopathies, but abnormal neuronal migration, premature neuronal death, metabolic disturbances, and other anomalies may also be involved.

Finally, progress in the genetics of human epilepsies has had important consequences for clinical practice. Specific molecular diagnosis is now possible in symptomatic individuals for several diseases, some of which have poor prognoses. Predictive diagnosis in presymptomatic individuals is also possible, although it does pose ethical problems. From a pharmacological point of view, these recent genetic discoveries should help understand the response (or resistance) of some epileptic syndromes to treatment and the adverse effects sometimes observed with antiepileptic drugs, and generate new antiepileptic drugs. ❑

We wish to thank Dr Merle Ruberg for critical reading of the manuscript.

Genética de las epilepsias humanas heredadas

Recientemente se han logrado importantes avances en la comprensión de las bases genéticas de las epilepsias monogénicas heredadas. El progreso ha sido particularmente espectacular en relación a las epilepsias idiopáticas, al descubrir que están involucradas las mutaciones en subunidades de los canales iónicos. Sin embargo, también se han obtenido importantes avances en muchas epilepsias sintomáticas heredadas, en las cuales el diagnóstico molecular directo ahora es posible, simplificando complejas investigaciones previas. Se espera que la identificación de genes involucrados en formas familiares de epilepsias conduzca a una mejor comprensión de los mecanismos fisiopatológicos subyacentes de estos trastornos y al desarrollo de modelos experimentales y nuevas estrategias terapéuticas. En este artículo se revisan datos clínicos y genéticos que se relacionan a la mayoría de las epilepsias humanas heredadas.

La génétique des épilepsies héréditaires

De grands progrès ont été récemment enregistrés dans la compréhension des bases génétiques des épilepsies héréditaires monogéniques. Ces progrès ont été particulièrement spectaculaires dans le domaine des épilepsies idiopathiques grâce à la découverte du rôle des mutations des sous-unités des canaux ioniques. Des avancées importantes ont par ailleurs également été réalisées en ce qui concerne de nombreuses épilepsies symptomatiques héréditaires puisque leur diagnostic moléculaire direct est maintenant possible, simplifiant ainsi les recherches complexes autrefois nécessaires. L'identification des gènes impliqués dans les formes familiales d'épilepsie devrait permettre une meilleure compréhension des mécanismes physiopathologiques sous-jacents à ces troubles ainsi que le développement de modèles expérimentaux et de nouvelles stratégies thérapeutiques. Dans cet article, nous passons en revue les données cliniques et génétiques concernant la plupart des épilepsies héréditaires humaines.

REFERENCES

1. Hauser WA, Annegers JF, Rocca WA. Descriptive epidemiology of epilepsy: contributions of population-based studies from Rochester, Minnesota. *Mayo Clin Proc.* 1996;71:576-586.
2. Annegers JF, Rocca WA, Hauser WA. Causes of epilepsy: contributions of the Rochester epidemiology project. *Mayo Clin Proc.* 1996;71:570-575.
3. Bird TD. Epilepsy. In: King RA, Rotter JI, Motulsky AG, eds. *The Genetic Basis of Common Diseases.* Oxford, UK: Oxford University Press; 1992:732-752.
4. Phillips HA, Scheffer IE, Berkovic SF, Hollway GE, Sutherland GR, Mulley JC. Localization for a gene for autosomal dominant nocturnal frontal lobe epilepsy to chromosome 20q13.2. *Nat Genet.* 1995;10:117-118.
5. Steinlein OK, Mulley JC, Propping P, et al. A missense mutation in the neuronal nicotinic acetylcholine receptor alpha 4 subunit is associated with autosomal dominant nocturnal frontal lobe epilepsy. *Nat Genet.* 1995;11:201-203.
6. Steinlein OK, Magnusson A, Stoodt J, et al. An insertion mutation of the *CHRNA4* gene in a family with autosomal dominant nocturnal frontal lobe epilepsy. *Hum Mol Genet.* 1997;6:943-947.
7. Hirose S, Iwata H, Akiyoshi H, et al. A novel mutation of *CHRNA4* responsible for autosomal dominant nocturnal frontal lobe epilepsy. *Neurology.* 1999;53:1749-1753.
8. Saenz A, Galan J, Caloustian C, et al. Autosomal dominant nocturnal frontal lobe epilepsy in a Spanish family with a Ser252Phe mutation in the *CHRNA4* gene. *Arch Neurol.* 1999;56:1004-1009.
9. Phillips HA, Scheffer IE, Crossland KM, et al. Autosomal dominant nocturnal frontal-lobe epilepsy: genetic heterogeneity and evidence for a second locus at 15q24. *Am J Hum Genet.* 1998;63:1108-1116.
10. Gambardella A, Annesi G, De Fusco M, et al. A new locus for autosomal dominant nocturnal frontal lobe epilepsy maps to chromosome 1. *Neurology.* 2000;55:1467-1471.
11. Fusco MD, Becchetti A, Patrignani A, et al. The nicotinic receptor beta2 subunit is mutant in nocturnal frontal lobe epilepsy. *Nat Genet.* 2000;26:275-276.
12. Phillips HA, Favre I, Kirkpatrick M, et al. CHRNB2 is the second acetylcholine receptor subunit associated with autosomal dominant nocturnal frontal lobe epilepsy. *Am J Hum Genet.* 2000;5:68.
13. Ottman R, Risch N, Hauser WA, et al. Localization of a gene for partial epilepsy to chromosome 10q. *Nat Genet.* 1995;10:56-60.
14. Poza JJ, Saenz A, Martinez-Gil A, et al. Autosomal dominant lateral temporal epilepsy: clinical and genetic study of a large Basque pedigree linked to chromosome 10q. *Ann Neurol.* 1999;45:182-188.
15. Mautner VF, Lindenau M, Gottesleben A, Goetze G, Kluwe L. Supporting evidence of a gene for partial epilepy on 10q. *Neurogenetics.* 2000;3:31-34.
16. Berkovic SF, McIntosh A, Howell RA, Mitchell A, Sheffield LJ, Hopper JL. Familial temporal lobe epilepsy: a common disorder identified in twins. *Ann Neurol.* 1996;40:227-235.
17. Gambardella A, Messina D, Le Piane E, et al. Familial temporal lobe epilepsy: autosomal dominant inheritance in a large pedigree from Southern Italy. *Epilepsy Res.* 2000;38:127-132.
18. Scheffer IE, Phillips HA, O'Brien CE, et al. Familial partial epilepsy with variable foci: a new partial epilepsy syndrome with suggestion of linkage to chromosome 2. *Ann Neurol.* 1998;44:890-899.
19. Xiong L, Labuda M, Li DS, et al. Mapping of a gene determining familial partial epilepsy with variable foci to chromosome 22q11-q12. *Am J Hum Genet.* 1999;65:1698-1710.
20. Guipponi M, Rivier F, Vigevano F, et al. Linkage mapping of benign familial infantile convulsions to chromosome 19q. *Hum Mol Genet.* 1997;6:473-477.
21. Szepetowski P, Rochette J, Berquin P, Piussan C, Lathrop GM, Monaco AP. Familial infantile convulsions and paroxysmal choreoathetosis: a new neurological syndrome linked to the pericentromeric region of human chromosome 16. *Am J Hum Genet.* 1997;61:889-898.
22. Lee WL, Tay A, Ong HT, Goh LM, Monaco AP, Szepetowski P. Association of infantile convulsions with paroxysmal dyskinesias (ICCA syndrome): confirmation of linkage to human chromosome 16p12-q12 in a Chinese family. *Hum Genet.* 1998;103:608-612.
23. Guerrini R, Bonanni P, Nardocci N, et al. Autosomal recessive rolandic epilepsy with paroxysmal exercise-induced dystonia and writer's cramp: delineation of the syndrome and gene mapping to chromosome 16p12-11.2. *Ann Neurol.* 1999;45:344-352.
24. Scheffer IE, Jones L, Pozzebon M, Howell RA, Saling MM, Berkovic SF. Autosomal dominant rolandic epilepsy and speech dyspraxia: a new syndrome with anticipation. *Ann Neurol.* 1995;38:633-642.
25. Leppert M, Anderson VE, Quattlebaum T, et al. Benign familial neonatal convulsions linked to genetic markers on chromosome 20. *Nature.* 1989;337:647-648.
26. Malafosse A, Leboyer M, Dulac O, et al. Confirmation of linkage of benign familial neonatal convulsions to *D20S19* and *D20S20*. *Hum Genet.* 1992;89:54-58.
27. Singh NA, Charlier C, Stauffer D, et al. A novel potassium channel gene, *KCNQ2*, is mutated in an inherited epilepsy of newborns. *Nat Genet.* 1998;18:25-29.
28. Biervert C, Schroeder BC, Kubisch C, et al. A potassium channel mutation in neonatal human epilepsy. *Science.* 1998;279:403-406.
29. Lerche H, Bievert C, Alekov AK, et al. A reduced K^+ current due to a novel mutation in *KCNQ2* causes neonatal convulsions. *Ann Neurol.* 1999;46:305-312.
30. Lewis TB, Leach RJ, Ward K, O'Connell P, 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.
31. Charlier C, Singh NA, Ryan SG, et al. A pore mutation in a novel KQT-like potassium channel gene in an idiopathic epilepsy family. *Nat Genet.* 1998;18:53-55.
32. Terada K, Ikeda A, Mima T, et al. Familial cortical myoclonic tremor as a unique form of cortical reflex myoclonus. *Mov Dis.* 1997;12:370-377.
33. Plaster NM, Uyama E, Uchino M, et al. Genetic localization of the familial adult myoclonic epilepsy (FAME) gene to chromosome 8q24. *Neurology.* 1999;53:1180-1183.
34. Mikami M, Yasuda T, Terao A, et al. Localization of a gene for benign adult familial myoclonic epilepsy to chromosome 8q23.3-q24.1. *Am J Hum Genet.* 1999;65:745-751.
35. Wallace RH, Berkovic SF, Howell RA, Sutherland GR, Mulley JC. Suggestion of a major gene for familial convulsions mapping to 8q13-21. *J Med Genet.* 1996;33:308-312.
36. Dubovsky J, Weber JL, Orr HT, et al. A second gene for familial febrile convulsions maps on chromosome 19p. *Am J Hum Genet.* 1996;59(suppl 1):A223.
37. Johnson EW, Dubovsky J, Rich SS, et al. Evidence for a novel gene for familial febrile convulsions, FEB2, linked to chromosome 19p in an extended family from the Midwest. *Hum Mol Genet.* 1998;7:63-67.
38. Kugler SL, Stenroos ES, Mandelbaum DE, et al. Hereditary febrile seizures: phenotype and evidence for a chromosome 19p locus. *Am J Med Genet.* 1998;79:354-361.
39. Anderson VE, Rich SS, Wilcox KJ, Ahrens MJ, Weber JL, Dubovsky J. Gene maping studies in febrile convulsions. *Epilepsia.* 1995;36(suppl 3):S215.
40. Nakayama J, Hamano K, Iwasaki N, et al. Significant evidence for linkage of febrile seizures to chromosome 5q14-q15. *Hum Mol Genet.* 2000;9:87-91.
41. Wallace RH, Wang DW, Singh R, et al. Febrile seizures and generalized epilepsy associated with a mutation in the Na^+-channel beta1 subunit gene *SCN1B*. *Nat Genet.* 1998;19:366-370.
42. Baulac S, Gourfinkel-An I, Picard F, et al. A second locus for familial generalized epilepsy with febrile seizures plus maps to chromosome 2q21-q23. *Am J Hum Genet.* 1999;65:1078-1085.
43. Moulard B, Guipponi M, Chaigne D, Mouthon D, Buresi C, 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.
44. Peiffer A, Thompson J, Charlier C, et al. A locus for febrile seizures (FEB3) maps to chromosome 2q23-24. *Ann Neurol.* 1999;46:671-678.
45. Lopes-Cendes I, Scheffer IE, Berkovic SF, Rousseau M, Andermann E, Rouleau GA. A new locus for generalized epilepsy with febrile seizures plus maps to chromosome 2. *Am J Hum Genet.* 2000;66:698-701.
46. Escayg A, MacDonald BT, Meisler MH, et al. Mutations of *SCN1A*, encoding a neuronal sodium channel, in two families with GEFS+2. *Nat Genet.* 2000;24:343-345.
47. Scheffer IE, Bhatia KP, Lopes-Cendes I, et al. Autosomal dominant frontal epilepsy misdiagnosed as sleep disorder. *Lancet.* 1994;343:515-517.
48. Scheffer IE, Bhatia KP, Lopes-Cendes I, et al. Autosomal dominant nocturnal frontal epilepsy. A distinctive clinical disorder. *Brain.* 1995;118:61-73.
49. Kuryatov A, Gerzanich V, Nelson M, Olale F, Lindstrom J. Mutation causing autosomal dominant nocturnal frontal lobe epilepsy alters Ca^{2+} permeability, conductance, and gating of human alpha4beta2 nicotinic acetylcholine receptors. *J Neurosci.* 1997;17:9035-9047.
50. Bertrand S, Weiland S, Berkovic SF, Steinlein OK, Bertrand D. Properties of neuronal nicotinic acetylcholine receptor mutants from humans suffering from autosomal dominant nocturnal frontal lobe epilepsy. *Br J Pharmacol.* 1998;125:751-760.
51. Picard F, Baulac S, Kahane P, et al. Dominant partial epilepsies. A clinical electrophysiological and genetic study of 19 European families. *Brain.* 2000;123:1247-1262.
52. Wang HS, Pan Z, Shi W, et al. *KCNQ2* and *KCNQ3* potassium channel subunits: molecular correlates of the M-channel. *Science.* 1998;282:1890-1893.

53. Schroeder BC, Kubisch C, Stein V, Jentsch TJ. Moderate loss of function of cyclic-AMP-modulated KCNQ2/KCNQ3 K^+ channels causes epilepsy. *Nature.* 1998;396:687-690.
54. Tinel N, Lauritzen I, Choabe C, Lazdunski M, Borsotto M. The KCNQ2 potassium channel: splice variants, functional and developmental expression. Brain localization and comparison with KCNQ3. *FEBS Lett.* 1998;438:171-176.
55. Wang Q, Curran ME, Splawski I, et al. Positional cloning of a novel potassium channel gene: *KVLQT1* mutations cause cardiac arrhythmias. *Nat Genet.* 1996;12:17-23.
56. Neyroud N, Tesson F, Denjoy I, et al. A novel mutation in the potassium channel gene *KVLQT1* causes the Jervell and Lange-Nielsen cardioauditory syndrome. *Nat Genet.* 1997;15:186-189.
57. Scheffer IE, Berkovic SF. Generalized epilepsy with febrile seizures plus: a genetic disorder with heterogeneous clinical phenotypes. *Brain.* 1997;120:479-490.
58. Singh R, Scheffer IE, Crossland K, Berkovic SF. Generalized epilepsy with febrile seizures plus: a common childhood-onset genetic epilepsy syndrome. *Ann Neurol.* 1999;45:75-81.
59. Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for revised classification of epilepsies and epileptic syndromes. *Epilepsia.* 1989;30:389-399.
60. Zara F, Bianchi A, Avanzini G, et al. Mapping of genes predisposing to idiopathic generalized epilepsy. *Hum Mol Genet.* 1995;4:1201-1207.
61. Fong CG, Shah PU, Gee MN, et al. Childhood absence epilepsy with 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.
62. Westling B, Weissbecker K, Serratosa JM, et al. Evidence for linkage of juvenile myoclonic epilepsy with absence to chromosome 1p. *Am J Hum Genet.* 1996;59:A241.
63. Zara F, Labuda M, Garofalo PG, et al. Unusual EEG pattern linked to chromosome 3p in a family with idiopathic generalized epilepsy. *Neurology.* 1998;51:493-498.
64. Greenberg DA, Delgado-Escueta AV, Widelitz H, et al. 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.
65. Weissbecker KA, Durner M, Janz D, Scaramelli, Sparkes RS, Spence VA. Confirmation of linkage between juvenile myoclonic epilepsy locus and the HLA region of chromosome 6. *Am J Med Genet.* 1991;38:32-36.
66. Greenberg DA, Durner M, Resor S, Rosenbaum D, Shinnar S. The genetics of idiopathic generalized epilepsies of adolescent onset: difference between juvenile myoclonic epilepsy and epilepsy with random grand mal and with awakening grand mal. *Neurology.* 1995;45:942-946.
67. Liu AW, Delgado-Escueta AV, Serratosa JM, et al. Juvenile myoclonic epilepsy locus in chromosome 6p21.2-p11: linkage to convulsions and electroencephalography trait. *Am J Hum Genet.* 1995;57:368-381.
68. Elmslie FV, Williamson MP, Rees M, et al. Linkage analysis of juvenile myoclonic epilepsy and microsatellite loci spanning 61 cM of human chromosome 6p in 19 nuclear pedigrees provides no evidence for a susceptibility locus in this region. *Am J Hum Genet.* 1996;59:653-663.
69. Sander T, Bockenkamp B, Hildmann T, et al. Refined mapping of the epilepsy susceptibility locus EJM1 on chromosome 6. *Neurology.* 1997;49:842-847.
70. Elmslie FV, Rees M, Williamson MP, et al. Genetic mapping of a major susceptibility locus for juvenile myoclonic epilepsy on chromosome 15q. *Hum Mol Genet.* 1997;6:1329-1334.
71. Neubauer BA, Fiedler B, Himmelein B, et al. Centrotemporal spikes in families with rolandic epilepsy: linkage to chromosome 15q14. *Neurology.* 1998;51:1608-1612.
72. Palmini A, Andermann F, de Grissac H, et al. Stages and patterns of centrifugal arrest of diffuse neuronal migration disorders. *Dev Med Child Neurol.* 1993;35:331-339.
73. Dobyns WB, Reiner O, Carrozzo R, Ledbetter DH. Lissencephaly. A humain brain malformation associated with deletion of the *LIS1* gene located at chromosome 17p13. *JAMA.* 1993;270:2838-2842.
74. Hattori M, Adachl H, Tsujlmoto M, Aral H, Inoue K. Miller-Dieker lissencephaly gene encodes a subunit of brain platelet-activating factor. *Nature.* 1994;370:216-218.
75. Lo Nigro C, Chong CS, Smith AC, Dobyns WB, Carrozzo R, Ledbetter DH. Point mutations and an intragenic deletion in *LIS1*, the lissencephaly causative gene in isolated lissencephaly sequence and Miller-Dieker syndrome. *Hum Mol Genet.* 1997;6:157-164.
76. des Portes V, Pinard JM, Billuart P, et al. A novel CNS gene required for neuronal migration and involved in X-linked subcortial laminar heterotopia and lissencephaly syndrome. *Cell.* 1998;92:51-61.
77. Gleeson JG, Allen KM, Fox JW, et al. 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.
78. Pilz DT, Kuc J, Matsumoto N, et al. Subcortical band heterotopia in rare affected males can be caused by missense mutations in *DCX (XLIS)* or *LIS1*. *Hum Mol Genet.* 1999;8:1757-1760.
79. Gleeson JG. Classical lissencephaly and double cortex (subcortical band heterotopia): LIS1 and doublecortin. *Curr Opin Neurol.* 2000;13:121-125.
80. Fox JW, Lamperti E, Eksioglu YZ, et al. Mutations in filamin 1 prevent migration of cerebral cortical neurons in human periventricular heterotopia. *Neuron.* 1998;21:1315-1325.
81. Pennacchio LA, Lehesjoki AE, Stone NE, et al. Mutations in the gene encoding cystatin B in progressive myoclonus epilepsy. *Science.* 1996;271:1731-1734.
82. Bespalova IN, Pranzatelli M, Burmeister M. G to C transversion at a splice acceptor site causes exon skipping in the cystatin B gene. *Mutat Res.* 1997;382:67-74.
83. Bespalova IN, Adkins S, Pranzarelli M, Burmeister M. Novel cystatin B mutation and diagnostic PCR assay in an Unverricht-Lundborg progressive myoclonus epilepsy patient. *Am J Med Genet.* 1997;74:467-471.
84. Lalioti MD, Mirotsou M, Buresi C, et al. 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.
85. Lafreniere RG, Rochefort DL, Chretien N, et al. Unstable insertion in the 5' flanking region of the cystatin B gene is the most common mutation in progressive myoclonus epilepsy type 1, EPM1. *Nat Genet.* 1997;15:298-302.
86. Lalioti MD, Scott HS, Buresi C, et al. Dodecamer repeat expansion in cystatin B gene in progressive myoclonus epilepsy. *Nature.* 1997;386:847-851.
87. Virtaneva K, D'Amato E, Miao J, et al. Unstable minisatellite expansion causing recessively inherited myoclonus epilepsy, EPM1. *Nat Genet.* 1997;15:393-396.
88. Lalioti MD, Scott HS, Genton P, et al. A PCR amplification method reveals instability of the dodecamer repeat in progressive myoclonus epilepsy (EPM1) and no correlation between the size of the repeat and age at onset. *Am J Hum Genet.* 1998;62:842-847.
89. Minassian BA, Lee JR, Herbrick JA, et al. Mutations in a gene encoding a novel protein tyrosine phosphatase cause progressive myoclonus epilepsy. *Nat Genet.* 1998;20:171-174.
90. Serratosa JM, Gomez-Garre P, Gallardo ME, et al. A novel protein tyrosine phosphatase gene is mutated in progressive myoclonus epilepsy of the Lafora type (EPM2). *Hum Mol Genet.* 1999;8:345-352.
91. Jarvela I, Schleutker J, Haataja L, et al. Infantile form of neuronal ceroid lipofuscinosis (CLN1) maps to the short arm of chromosome 1. *Genomics.* 1991;9:170-173.
92. Vesa J, Hellsten E, Verkruyse LA, et al. Mutations in the palmitoyl protein thioesterase gene causing infantile neuronal ceroid lipofuscinosis. *Nature.* 1995;376:584-587.
93. Das AK, Becerra CH, Yi W, et al. Molecular genetics of palmitoyl-protein thioesterase deficiency in the US. *J Clin Invest.* 1998;102:361-370.
94. O'Rawe A, Mitchison HM, Williams R, et al. Genetic linkage analysis of a variant of juvenile onset neuronal ceroid lipofuscinosis with granular osmiophilic deposits. *Neuropediatrics.* 1997;28:21-22.
95. Mitchison HM, Hofmann SL, Becerra CH, et al. Mutations in the palmitoyl-protein thioesterase gene (PPT; CLN1) causing juvenile neuronal ceroid lipofuscinosis with granular osmiophilic deposits. *Hum Mol Genet.* 1998;7:291-297.
96. Sharp JD, Wheeler RB, Lake BD, et al. Loci for classical and a variant late infantile neuronal ceroid lipofuscinosis is mapped to chromosomes 11p15 and 15q21-23. *Hum Mol Genet.* 1997;6:591-595.
97. Sleat DE, Donnelly RJ, Lackland H, et al. Association of mutations in a lysosomal protein with classical late-infantile neuronal ceroid lipofuscinosis. *Science.* 1997;277:1802-1805.
98. Ezaki J, Takeda-Ezaki M, Kominami E. Tripeptidyl peptidase I, the late infantile neuronal ceroid lipofuscinosis gene product, initiates the lysosomal degradation of subunit c of ATP synthase. *J Biochem.* 2000;128:509-516.
99. Savukoski M, Klockars T, Holmberg V, Santavuori P, Lander ES, Peltonen L. *CLN5*, a novel gene encoding a putative transmembrane protein mutated in Finnish variant late infantile neuronal ceroid lipofuscinosis. *Nat Genet.* 1998;19:286-288.
100. Wheeler RB, Sharp JD, Mitchell WA, et al. A new locus for variant late infantile neuronal ceroid lipofuscinosis-CLN7. *Mol Genet Metab.* 1999;66:337-338.
101. Mitchison HM, O'Rawe AM, Taschner PE, et al. Batten disease gene, *CLN3*: linkage disequilibrium mapping in the Finnish population, and analysis of European haplotypes. *Am J Hum Genet.* 1995;56:654-662.
102. Mitchison HM, Taschner PE, Kremmidiotis G, et al. Structure of the *CLN3* gene and predicted structure, location and function of CLN3 protein. *Neuropediatrics.* 1997;28:12-14.

103. Golabek AA, Kida E, Walus M, Kaczmarski W, Michalewski M, Wisniewski KE. CLN3 protein regulates lysosomal pH and alters intracellular processing of Alzheimer's amyloid-beta protein precursor and cathepsin D in human cells. *Mol Genet Metab.* 2000;70:203-213.
104. Berkovic SF, Carpenter S, Andermann F, Andermann E, Wolfe LS. Kuf's disease: a critical reappraisal. *Brain.* 1988;111:27-62.
105. Shoffner JM, Lott MT, Lezza AM, Seibel P, Ballinger SW, Wallace DC. Myoclonic epilepsy and ragged red fiber disease (MERRF) is associated with a mitchondrial DNA tRNA(Lys) mutation. *Cell.* 1990;61:931-937.
106. Nakamura M, Nakano S, Goto Y, et al. A novel point mutation in the tRNA (Ser(UCN)) gene detected in a family with MERRF/MELAS overlap syndrome. *Biochem Biophys Res Commun.* 1995;214:86-93.
107. Jaksch M, Klopstock T, Kurlemann G, et al. Progressive myoclonus epilepsy and mitochondrial myopathy associated with mutations in the tRNA Ser(UCN) gene. *Ann Neurol.* 1998;44:635-640.
108. Mueller OT, Henry WM, Haley LL, Byers MG, Eddy RL, Shows TB. Sialidosis and galactosialidosis: chromosomal assignment of two genes associated with neuraminidase-deficiency disorders. *Proc Natl Acad Sci U S A.* 1986;83:1817-1821.
109. Pshezhetsky AV, Richard C, Michaud L, et al. Cloning, expression and chromosomal mapping of human lysosomal sialidase and characterization of mutations in sialidosis. *Nat Genet.* 1997;15:316-320.
110. Sips HJ, de Wit-Verbeek HA, de Wit A, Westerveld A, Galjaard H. The chromosomal localization of human beta-galactosidase revisited: a locus for beta-galactosidase on human chromosome 3 and for its protective protein on human chromosome 20. *Hum Genet.* 1985;69:340-344.
111. King JO. Progressive myoclonic epilepsy due to Gaucher's disease in an adult. *J Neurol Neurosurg Psychiatry.* 1975;38:849-854.
112. Winkelman MD, Banker BQ, Victor M, Moser HW. Non-infantile neuronopathic Gaucher's disease: a clinicopathologic study. *Neurology.* 1983;33:994-1008.
113. Brett EM, Ellis RB, Haas L, et al. Late onset GM2-gangliosidosis: clinical, pathological and biochemical studies on eight patients. *Arch Dis Child.* 1973;48:775-785.
114. Eiris J, Chabas A, Coll MJ, Castro-Gago M. Late infantile and juvenile form of GM2-gangliosidosis variant B1. *Rev Neurol.* 1999;29:435-438.
115. Ilzuka R, Hirayama K, Maehara K. Dentato-rubro-pallido-luysian atrophy: a clinico-pathological study. *J Neurol Neurosurg Psychiatr*. 1984;47:1288-1298.
116. Garrel S, Joannard A, Feuerstein C, Serre F. Formes myocloniques de la chorée de Huntington. *Rev Electroencephalogr Neurophysiol Clin.* 1978;8:123-128.
117. Carella F, Scaioli V, Ciano C, et al. Adult onset myoclonic Huntington's disease. *Mov Disord.* 1993;8:210-215.
118. Campion D, Flaman JM, Brice A, et al. Mutations of the presenilin I gene in families with early-onset Alzheimer's disease. *Hum Mol Genet.* 1995;4:2373-2377.
119. Ezquerra M, Carnero C, Blesa R, Gelpi JL, Ballesta F, Oliva R. A presenilin 1 mutation (Ser169Pro) associated with early-onset AD and myoclonic seizures. *Neurology.* 1999;52:566-570.
120. Takao M, Benson MD, Murrell JR, et al. Neuroserpin mutation S52R causes neuroserpin accumulation in neurons associated with progressive myoclonus epilepsy. *J Neuropathol Exp Neurol.* 2000;59:1070-1086.
121. Norio R, Koskiniemi M. Progressive myoclonus epilepsy: genetic and nosological aspects with special reference to 107 Finnish patients. *Clin Genet.* 1979;15:382-398.
122. Genton P, Michelucci R, Tassinari CA, Roger J. The Ramsay Hunt syndrome revisited: Mediterranean myoclonus versus mitochondrial encephalomyopathy with ragged-red fibers and Baltic myoclonus. *Acta Neurol Scand.* 1990;81:8-15.
123. Eldridge R, Iivanainen M, Stern R, Koerber T, Wilder BJ. Baltic myoclonus epilepsy: hereditary disorder of childhood made worse by phenytoin. *Lancet.* 1983;2:838-842.
124. Gouider R, Ibrahim S, Fredj M, et al. Unverricht-Lundborg disease: clinical and electrophysiologic study of 19 Maghreb families. *Rev Neurol.* 1998;154:503-507.
125. Lehesjoki AE, Koskiniemi M, Sistonen P, et al. Localization of a gene for progressive myoclonus epilepsy to chromosome 21q22. *Proc Natl Acad Sci U S A.* 1991;88:3696-3699.
126. Pennacchio LA, Myers RM. Isolation and characterization of the mouse cystatin B gene. *Genome Res.* 1996;6:1103-1109.
127. Roger J, Genton P, Bureau M. Progressive myoclonus epilepsies. In: Dam M, Gram L, eds. *Comprehensive Epileptology.* New York, NY: Raven Press; 1990:215-231.
128. Carpenter S, Karpati G. Sweat gland duct cells in Lafora disease: diagnosis by skin biopsy. *Neurology.* 1981;31:1564-1568.
129. Serratosa JM, Delgado-Escueta AV, Posada I, et al. The gene for progressive myoclonus epilepsy of the Lafora type maps to chromosome 6q. *Hum Mol Genet.* 1995;4:1657-1663.
130. Sainz J, Minassian BA, Serratosa JM, et al. Lafora progressive myoclonus epilepsy: narrowing the chromosome 6q24 locus by recombinations and homozygosities. *Am J Hum Genet.* 1997;61:1205-1209.
131. Gomez-Garre P, Anta B, Castro-Gago M, et al. Reduction of the Lafora disease candidate gene region to a 2-cM interval in chromosome 6q24 and evidence for genetic heterogeneity. *Eur J Hum Genet.* 1998;6:152.
132. Minassian BA, Sainz J, Serratosa JM, et al. Genetic locus heterogeneity in Lafora's progressive myoclonus epilepsy. *Ann Neurol.* 1999;45:262-265.
133. Povey S, Burley MW, Attwood J, et al. Two loci for tuberous sclerosis: one on 9q34 and one on 16p13. *Ann Hum Genet.* 1994;58:107-127.
134. van Slegtenhorst M, de Hoogt R, Hermans C, et al. Identification of the tuberous sclerosis gene *TSC1* on chromosome 9q34. *Science.* 1997;277:805-808.
135. Consortium. TECTS. Identification and characterization of the tuberous sclerosis gene on chromosome 16. *Cell.* 1993;75:1305-1315.
136. Gutmann DH, Collins FS. The neurofibromatosis type 1 gene and its protein product, neurofibromin. *Neuron.* 1993;10:335-343.
137. Dubovsky J, Zabramski JM, Kurth J, et al. A gene responsible for cavernous malformations of the brain maps to chromosome 7. *Hum Mol Genet.* 1995;4:453-458.
138. Zhang J, Clatterbuck RE, Rigamonti D, Dietz HC. Mutations in *KRIT1* in familial cerebral cavernous malformations. *Neurosurgery.* 2000;46:1272-1277.
139. Sahoo T, Johnson EW, Thomas JW, et al. Mutations in the gene encoding KRIT1, a Krev-1/rap1A binding protein, cerebral cavernous malformations (CCM1). *Hum Mol Genet.* 1999;8:2325-2333.
140. Amir RE, van den Veyver IB, Wan M, Tran CQ, Francke U, Zoghbi HY. Rett syndrome is caused by mutations in X-linked MECP2, encoding methyl-CpG-binding protein 2. *Nat Genet.* 1999;23:185-188.
141. Goto YI, Matsuoka T, Horai S. A mutation in the tRNALeu(UUR) gene associated with the MELAS subgroup of mitochondrial encephalopathies. *Nature.* 1990;348:651-653.
142. Verkerk AJ, Pieretti M, Sutcliffe JS, et al. Identification of a gene (*FMR-1*) containing a CGG repeat coincident with a breakpoint cluster region exhibiting length variation in fragile X syndrome. *Cell.* 1991;65:905-914.
143. Gecz J, Gedeon AK, Sutherland GR, Mulley JC. Identification of the gene FMR2, associated with FRAXE mental retardation. *Nat Genet.* 1996;13:105-108.
144. Gu Y, Shen Y, Gibbs RA, Nelson DL. Identification of FMR2, a novel gene associated with the FRAXE CCG repeat and CpG island. *Nat Genet.* 1996;13:109-113.
145. Oshima A, Tsuji A, Nagao Y, Sakuraba H, Suzuki Y. Cloning, sequencing and expression of cDNA for human beta-galactosidase. *Biochem Biophys Res Commun.* 1988;157:238-244.
146. Proia RL. Gene encoding the human beta-hexoaminidase beta-chain: extensive homology of intro placement in the alpha and beta chain genes. *Proc Natl Acad Sci U S A.* 1988;85:1883-1887.
147. Proia RL, Soravia E. Organization of the gene encoding the human beta-hexosaminidase alpha-chain. *J Biol Chem.* 1987;262:5677-5681.