Genetic epilepsies. Remarks on the proposed "Organization of the Epilepsies"*

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SUMMARY

Introduction. Genetic findings in several epilepsy syndromes provide insights into the pathophysiology of specific subtypes of epilepsy and into mechanisms of epileptogenesis, because the genes encoding ion channels, and proteins associated to the vesical synaptic cycle, or involved in energy metabolism, influence neuronal excitability.

Aim. The following aspects of genetic epilepsies will be discussed: new proposed "organization of the epilepsies", genetic and other etiologies, electroclinical syndromes and their genetics and genetic testing in the epilepsies.

Methods. The updated review is based on OMIM™ (Online Mendelian Inheritance in Man).

Review and remarks. Because of the vast genetic and phenotypic heterogeneity, bridging genotype and phenotype remains a major challenge in epilepsy genetics. The so-called "idiopathic" epilepsies are genetically determined. The new ILAE proposal on the "organization" of the epilepsies takes into account the genetic advances. However, despite proposed changes in the nomenclature, the concept of the electroclinical syndrome, i.e. seizure types, age-dependent onset, electroencephalographic criteria, and concomitant symptoms, such as movement disorders or developmental delay, remain important criteria to group the epilepsies. Although also the differentiation "generalized" versus "focal" is nowadays discussed critically, for practical reasons these categories remain valid. Similarly the categories "benign" syndromes of early childhood, epileptic encephalopathies, and fever-associated syndromes, have their utility.

Conclusions. The large number of genetic defects in the epilepsies complicates their analysis. However, it is anticipated that novel genetic methods, that are able to analyze all known genes at a reasonable price, will help identify novel diagnostic and therapeutic avenues, including prognostic and genetic counseling. Today it is already possible to include into genetic testing genes responsible for the side effects of AEDs. In addition, for some epilepsy phenotypes it has became possible to predict the most efficacious antiepileptic drugs for patients based on their genetic makeup. Thus, the development of individualized medicine is expected to greatly improve the management of epilepsy patients.

Key words: epilepsies • genetic etiology • "organization of epilepsies" • genetic testing in the epilepsies

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Review paper

INTRODUCTION

Knowledge base of human genes and genetic disorders

Due to the rapid progress of knowledge, the nomenclature describing the genetic causes of epilepsies is extremely complex, if not sometimes puzzling. In 2010 the state of knowledge has been masterly summarized in the Epilepsia Report of the ILAE Genetics Commission (Ottman et al., 2010).

AIM

The following aspects of genetic epilepsies will be discussed: new proposed "Organization of the epilepsies", genetic and other etiologies, electroclinical syndromes and their genetics and genetic testing in the epilepsies.

METHOD

A short article like this must by necessity rely on authoritative updated reviews from experts in the field. Many of these reviews have tried to summarize the most important gene findings in comprehensive tables (Huber et al., 2009; Nicita et al., 2012; Weber and Lerche, 2013). This approach is followed in this article. A permanently updated and thus the knowledge base of human genes and genetic disorders is OMIM™ (Online Mendelian Inheritance in Man). It was started by Dr. Victor A. McKusick. OMIM is distributed electronically by the National Center for Biotechnology Information, and integrated with the Entrez suite of databases. It is written and edited at Johns Hopkins University. Each OMIM entry has a full-text summary of a genetically determined phenotype and/or gene and has numerous links to other genetic databases such as DNA and protein sequence, PubMed references, general and locus-specific mutation databases, HUGO nomenclature, MapViewer, GeneTests, patient support groups and many others.

REVIEW AND REMARKS

New proposed "Organization of the Epilepsies"

The recently distributed "Report of the ILAE Commission on Classification and Terminology" (Scheffer et al., 2014) refers no longer on the "classification" but on the "Organization of the Epilepsies" with the following etiological categories:

1. Genetic
2. Structural
3. Metabolic
4. Immune
5. Infectious
6. Unknown

Furthermore, this report suggests that the term "benign" should be replaced by "self-limited" where possible to reflect that even the milder epilepsy syndromes may be associated with psychosocial and cognitive comorbidities. Whether this is realistic is questionable, simply because many electroclinical syndromes found their definitive place in the literature and a change in the nomenclature would create further confusion. Apart from some minor adjustments in the nomenclature, fortunately this 2014 report does not change the concept of the electroclinical syndrome. This is very important, because the electroclinical syndromes are distinctive clinical entities. They are defined by age of onset, seizure types, EEG patterns, imaging features and co-morbidities, such as intellectual impairment, and they carry treatment and prognostic implications.

In the new proposal "Organization of the Epilepsies" application of multiple etiologies to one patient is possible and indeed frequent, i.e., each etiology is not meant to be discrete. A good example is **glucose transporter 1 (GLUT1) deficiency** which has a metabolic-genetic etiology that has a wide range of clinical presentations, including:

- epilepsy with myoclonic-atonic seizures,
- early onset absence epilepsy (syn: absence epilepsies beginning from infancy to young adult life)
- focal epilepsies and
- genetic generalized epilepsies

As mentioned above, knowing the etiology is important for treatment (e.g. the ketogenic diet for GLUT1 deficiency).

Genetic Etiology

The discovery of epilepsy-causing gene mutations improved classification/organization of epilepsies and epileptic encephalopathies as well as knowledge on epileptogenic mechanisms and therapeutic options.

Genetic etiology means that genetic factors play a major role in the causation of the individual's epilepsy. Thus the concept of genetic implies that the epilepsy is the direct result of a known or presumed genetic defect and that seizures are the core symptom of

the disorder. In most cases, the underlying genes are not yet known. Determination to be genetic based is on clinical genetic studies, such as twin and familial aggregation studies. Up to 47% of all epilepsies are so-called "idiopathic epilepsies". Only 2–3% of the "idiopathic epilepsies" are **monogenic**. In a monogenic etiology, a single mutation is causative. In the majority of these monogenic epilepsies, the mutated genes encode ion channels (voltage-gated sodium and potassium channel subunits) that mediate neuronal excitability. In such a case the pathophysiology is fairly well understood. Epilepsy-causing gene defects coding for non-ion channel proteins are often less clear.

A good example for a monogenic etiology is **Dravet syndrome**. In Dravet syndrome 80% have an abnormality of SCN1A gene (encoding for the alpha-1 subunit of the sodium channel). A monogenic etiology may cause a spectrum of **mild** to **severe epilepsies**, such as *SCN1A mutations* which are associated with **Dravet syndrome** and **Genetic Epilepsy with Febrile Seizures Plus (GEFS+)**.

In the group of the "idiopathic generalized epilepsies" numerous family and twin studies support a genetic etiology. Therefore, in the new 2014 proposal, the name "idiopathic generalized epilepsies" is now referred to as the "genetic generalized epilepsies (GGE)" to reflect the knowledge that clinical genetic studies demonstrate a genetic basis. The GGE account for one third of all epilepsies. Often they have a complex inheritance, i.e. a **polygenic** basis. Environmental factors play a role.

Genetic variants are often **susceptibility variants**, i.e. they may be inherited, but alone are insufficient to cause epilepsy. In this setting, there is often no family history of seizures as other family members do not have enough epilepsy genetic variants to be affected. Susceptibility loci at 1q43, 2p16.1, 2q22.3 and 17q21.32 (EPICURE Consortium, 2012a) as well as 2q34 and 13q31.3 for GGE have been identified (EPICURE Consortium, 2012b).

Polygenic refers to a trait that is controlled by two or more genes. In some epilepsies the interaction of various genes seems to be important: A key gene may be decisive for the manifestation of the epilepsy and additional genes on other chromosomes are crucial for the phenotype.

Electroclinical syndromes may be associated with **heterogeneous etiologies.** An example is **West syndrome** which may occur in the setting of:

- hypoxic-ischemic encephalopathy,
- a malformation of cortical development,
- tuberous sclerosis complex,
- a genetic mutation in a range of genes such as ARX ("aristaless related homeobox", controlling the development of GABAergic interneurons), or STXBP1 ("syntaxin binding protein 1", which plays a role in release of neurotransmitters, and is associated with Ohtahara syndrome)
- or where the etiology is unknown.

It is important to emphasize that *"genetic" is not the same as "inherited". De novo mutations* are increasingly identified, especially in the severe epilepsies. Examples include the large subgroup of epileptic encephalopathies, e.g. Dravet syndrome. Recently many genes have been identified that cause epileptic encephalopathies due to de novo mutations (Carvill et al. 2013; EPI4K, 2013).

Other Etiologies

Because of the overlap, the other etiologies in the new ILAE proposal are briefly mentioned.

Structural. The underlying basis for a structural abnormality may be genetic or acquired or both. For example, **polymicrogyria** may be secondary to **mutations in genes such as GPR56** (G protein-coupled receptor 56 = a protein-coding gene, which regulates the migration of neural precursor cells), or acquired, secondary to intrauterine cytomegalovirus infection.

Metabolic. This category comprises well delineated metabolic defects with manifestations or biochemical changes throughout the body, such as porphyria, uremia, amino-acidopathies or pyridoxine dependent seizures.

Immune. A pathogenic role of immunity in epilepsies has long been suggested based on the efficacy of immune-modulating treatments and, more recently, by the finding of inflammation markers including auto antibodies in individuals with a number of epileptic disorders. Clinical and experimental data suggest that both innate and adaptive immunity may be involved in epilepsy. Innate immunity represents an immediate, non-specific host response against pathogens via activation of resident brain immune cells and inflammatory mediators. These are hypothesized to contribute to seizures and epileptogenesis. Adaptive immunity employs activation of antigen-specific B and T lymphocytes or antibodies in the context of viral infections and auto-

immune disorders. The most important immune epilepsies are **Limbic Encephalitis** (with its potential relationship to Ammon's Horn Sclerosis), and within this the (1) **anti-NMDA receptor encephalitis**, and (2) **anti-LGI1 encephalitis**. Although with much less evidence, some recent authoritative summaries also discuss **Rasmussen's Encephalitis, West Syndrome 1** (Infantile Spasms), **Landau-Kleffner Syndrome** and **Continuous Spike Waves during Sleep, Hemiconvulsion–Hemiplegia Syndrome**, and **Batten Disease** in the context of immune-mediated epilepsies (Granata et al., 2011).

Table 1. Examples of electroclinical syndromes and other epilepsies arranged according to age (modified from Berg et al., 2010. Please note that we did not change the term "benign" to "self-limited")

Neonatal period
- Benign neonatal seizures
- Benign familial neonatal epilepsy
- Early myoclonic encephalopathy (EME)
- Ohtahara syndrome

Infancy (onset under 2 years)
- Febrile seizures
- Febrile seizures plus
- Epilepsy of infancy with migrating focal seizures
- West syndrome
- Myoclonic epilepsy in infancy (MEI)
- Benign infantile epilepsy
- Benign familial infantile epilepsy
- Dravet syndrome
- Myoclonic encephalopathy in non-progressive disorders

Childhood
- Febrile seizures
- Febrile seizures plus (FS+)
- Early onset childhood occipital epilepsy (Panayiotopoulos type)
- Epilepsy with myoclonic atonic (previously astatic) seizures
- Benign epilepsy with centrotemporal spikes (BECTS)
- Autosomal-dominant nocturnal frontal lobe epilepsy (ADNFLE)
- Late onset childhood occipital epilepsy (Gastaut type)
- Childhood absence epilepsy (CAE)
- Epilepsy with myoclonic absences
- Lennox-Gastaut syndrome
- Epileptic encephalopathy with continuous spike-and-wave during sleep (CSWS)
- Landau-Kleffner syndrome (LKS)

Adolescence – Adult
- Juvenile absence epilepsy (JAE)
- Juvenile myoclonic epilepsy (JME)
- Epilepsy with generalized tonic–clonic seizures alone (GTCA)
- Autosomal dominant epilepsy with auditory features (ADEAF)
- Other familial temporal lobe epilepsies
- Familial epilepsy syndromes
- Familial focal epilepsy with variable foci (FFEVF)
- Genetic epilepsy with febrile seizures plus (GEFS+)

Infectious includes tuberculosis, HIV, cerebral malaria, neurocysticercosis, subacute sclerosing panencephalitis, and cerebral toxoplasmosis. These infections sometimes have a structural correlate.

Electroclinical Syndromes and their Genetics (Phenotype-Genotype Associations)

A still widely used age-related arrangement of electroclinical syndromes and other epilepsies is that of Berg et al., (2010) and Berg and Cross (2012). This is summarized in Table 1 to facilitate the understanding of data highlighted in the other Tables and for further discussion.

In the following section we shall discuss a few electroclinical syndromes and their genetics. Table 2 lists the most important genetic electroclinical syndromes and epilepsies. Table 3 shows the «Idiopathic» generalized epilepsy with their genetics and Table 4 shows Juvenile myoclonic epilepsy.

Various "idiopathic" or "genetic generalized epilepsy" (IGE, GGE) syndromes overlap. This is particularly the case for the more common IGE sub-syndromes. These consist of:

- Childhood Absence Epilepsy (CAE=ECA; Childhood absence epilepsy-1 ECA1),
- Juvenile Absence Epilepsy (JAE),
- Juvenile Myoclonic Epilepsy (JME= EJM; Syn: Impulsive petit mal; Janz syndrome),
- Epilepsy with Generalized Tonic-Clonic Seizures (EGTCS = IGE-GTC)

Patients with these classical IGE sub-syndromes usually have pharmacoresponsive epilepsies without other neurological features. Imaging studies in patients are normal. IGE-GTC, for example, is a relatively benign epilepsy syndrome with complete remission in 75% of patients. In the Nova Scotia Childhood Epilepsy Population-Based Cohort Study, 6% (40 pts.) had IGE-GTC. All were neurologically and intellectually normal with generalized spike-wave on EEG. Learning problems and unsatisfactory social outcome are unfortunately common (Camfield and Camfield, 2010).

Several *rare* IGE syndromes have been described. Many of which are associated with intellectual disability, and include:

- **Benign Myoclonic Epilepsy of Infancy (BMEI),**
- **Early Onset Absence Epilepsy,**

- **Myoclonic Astatic Epilepsy (MAE),**
- **Epilepsy with Myoclonic Absences (EMA)** Syn: Myoclonic absence epilepsy (MAE). EMA is a somewhat controversial entity. Myoclonic absences (MA) are typical absences associated with synchronous generalized spike and wave discharges on the EEG. Absences are characterized by axial hypertonia and jerks. During axial hypertonia subjects usually bend forward and slightly raise their shoulders and arms. The prognosis of EMA remains variable. Valproic acid and ethosuximide are usually effective. In a proportion of patients, seizures are resistant to drug treatment, and these patients may experience cognitive deterioration. Patients with myoclonic absences as the only seizure type have a good outcome. If myoclonic absences are associated with other seizures, especially generalized tonic-clonic seizures, outcome is less favourable (Genton and Bureau, 2006).

- **Eyelid Myoclonia with Absences and Absence Status Epilepsy.**

Clinically, **Dravet Syndrome** and the genetically related **Genetic (Generalized) Epilepsy with Febrile Seizures Plus (GEFS+)** spectrum are considered distinct from IGE. Dravet Syndrome (Severe Myoclonic Epilepsy of Infancy, SMEI; Early infantile epileptic encephalopathy-6, EIEE6) represents a severe epileptic encephalopathy of early childhood caused by mutations in SCN1A.

An interesting subtype is **Generalized epilepsy and**

Table 2. Compilation of the most important genetic electroclinical epilepsy syndromes and epilepsies (modified from Nicita et al., 2012)

Protein	Sub-unit	Gene	Gene locus	Phenotype
Neuronal nicotinic acetylcholinic receptor	α2-	CHRNA2	8p21	Autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE)
	α4-	CHRNA4	20q13	
	β2-	CHRNB2	1q21	
M-current protein channel	Kv7.2	KCNQ2	20q13	Benign familial newborn seizure (BFNS)
	Kv7.3	KCNQ3	8q24	
Voltage gated Sodium channel	α1	SCN1A	2q24	Generalised epilepsy with febrile seizures plus (GEFS+)
				Severe myoclonic epilepsy of infancy (=Dravet = SMEI)
				Idiopathic generalized epilepsy – generalized tonic clonic (IGE-GTC)
				Myoclonic absence epilepsy (MAE)
	α2	SCN2A	2q23-q24.3	Benign familiar newborn infantile seizures (BFNIS)
				Benign familiar infantile seizures (BFIS)
				Severe myoclonic epilepsy of infancy (=Dravet = SMEI)
	β2	SCN2B	19q13	Generalised epilepsy with febrile seizures plus (GEFS+)
				Early onset absence epilepsy + febrile seizures plus (EOAE +FS plus)
GABA receptor	α1	GABRA1	5q34-q35	Juvenile myoclonic epilepsy (JME) = Janz Syndrome
	γ2	GABRG2	5q34	Generalised epilepsy with febrile seizures plus (GEFS+)
				Childhood absence epilepsy (CAE)
Leucine rich glioma inactivated 1		LGI1	10q24	Autosomal dominant partial epilepsy with auditory features = Autosomal dominant lateral temporal lobe epilepsy ADPEAF/ADLTE
Glucose transporter type 1		SLC2A1	1p35-p31.3	Early onset absence epilepsy (EOAE)
EF hand motif containing 1		EFHC1	6p12-p11	Juvenile myoclonic epilepsy (JME)
Protochaderin		PCDH19	Xq22	Epilepsy in females with mental retardation (EFMR)
Cyclin-dependent kinase-like 5		CDKL5/STK9	Xq28	X-linked infantile spasms (ISSX) – Rett Syndrome (RTT)
Aristaless related homeobox		ARX	Xp22.13	Ohtahara Syndrome (OS)
Syntaxin binding protein 1		STXBP1 (MUNC18–1)	9q34.1	Ohtahara Syndrome (OS)
Solute carrier family 25 member 22		SLC25A22	11p15.5	Early myoclonic encephalopathy (EME)

Table 3. "Idiopathic" generalized epilepsy (IGE). As a group IGE are believed to have a strong underlying genetic basis. Patients with an IGE subtype are typically otherwise normal and have no structural brain abnormalities. Patients also often have a family history of epilepsy and a genetically predisposed risk of seizures

Benign myoclonic epilepsy in infancy	< 1% of cases; twice as prevalent in boys compared to girls. Age of seizure onset is between ½–5 years of age. Head drops & brief arm jerks.	Although believed to be due to a genetic basis, no genetic linkage has been shown.
Generalized epilepsy with febrile seizures plus (GEFS+)	Patients experience febrile seizures early in childhood and have other types of seizures later in life.	Known causative genes are the sodium channel α subunit genes SCN1A and SCN2A and the β subunit gene SCN1B. Mutations in the GABA$_A$ receptor γ subunit GABRG1 are also causative for this disorder.
Epilepsy with myoclonic absences	Rare; wide age range (from the first year of life through the early teens). Absence seizures concurrent with myoclonic jerks, typically occurring several times daily. Seizures from this disorder often cease within 5 years.	Genetics have not been delineated.
Epilepsy with myoclonic-astatic seizures (Doose syndrome)	~2% of childhood epilepsies. Brief (<100ms) myoclonic jerks followed by equally brief loss of muscle tone, -> falls. Some patients have longer lasting seizures of this type. Many patients also have absence seizures.	Believed to be a polygenic disorder.
Childhood absence epilepsy (CAE), Pyknolepsy	Represents up to 10% of all childhood epilepsies. It first manifests in childhood between the ages of 4 and 8 as brief periods of unconsciousness (absence).	Susceptibility for CAE: Mutations in the calcium channel α subunit encoding gene CACNA1H and GABA receptor γ subunit encoding gene GABRG2.
Juvenile absence epilepsy	Similar to CAE but onset between ages 9 and 13. Absence seizures are less frequent but longer compared with CAE	There are a number of possible genetic loci for this disorder, but no causative genes have been demonstrated.
Juvenile myoclonic epilepsy (JME), Janz Syndrome	Common: ~25% of cases of IGE. Many children with CAE develop JME. JME first presents between the ages of 12 and 18 with prominent myoclonic seizures, early in the morning. Also: generalized tonic-clonic and absence seizures	Linkage of this disorder has been shown to mutations in the genes GABRA1, CACNB4, CLCN2, GABRD2, EFHC1 and EFHC2 (Table 4).
Epilepsy with generalized tonic-clonic seizures only	At almost any age; Poorly characterized and loose definition	

Table 4. Genetics of Juvenile myoclonic epilepsy

Epilepsy Syndrome	OMIM Entry #	Location chromosome	Gene	Gene/Locus MIM #	Refs.
Juvenile myoclonic epilepsy (JME= EJM) Syn: Impulsive petit mal; Janz syndrome	EJM1 254770 (606904 moved to 253770)	6p12.2	EFHC1 ("EF-hand domain-containing 1 gene") interacts with calcium channel and stimulates apoptosis	608815	Janz, 1989; Suzuki et al., 2004; Katano et al., 2012
Linkage of this disorder has been shown also to mutations in the genes CLCN2 (chloride channel, voltage-sensitive 2), GABRD2, & EFHC2	608816	6p21	GABRA1-Gene (GABA$_A$ receptor, α1-subunit); CACNB4 (calcium channel, voltage-dependent, β4-subunit; BRD2-Gene (transcription regulation). ME2-Gene (malic enzyme 2, GABA-synthesis)	Genomic coordinates (GRCh37): 6:30,400, 000 - 46, 200, 000	Delgado-Escueta et al., 1989; Greenberg et al., 2000 Shi et al., 2010

A locus for juvenile JME linked to HLA on chromosome 6p21.3 was originally termed 'EJM1'. Since then, EJM1 has been used to refer to a different JME phenotype (254770) caused by a mutation in the EFHC1 gene (608815) on chromosome 6p12-p11. The locus at 6p21 is symbolized EJM3. Greenberg et al. (2000) found highly significant linkage disequilibrium between JME and a core haplotype of 5 SNP and microsatellite markers in this critical region, with linkage disequilibrium peaking in the BRD2 gene (601540). Significant evidence supports a major susceptibility locus located on **chromosome 15q14**, where the **gene connexin36 (CX36)** is also mapped. Since electrotonic communication between neurons connected by gap junctions is likely to be implicated in the generation and maintenance of neuronal synchrony, mutations in the CX36 gene may be associated with JME. Association of connexin36 gene with JME has been reported by Mas et al. (2004)

paroxysmal dyskinesia (GEPD). GEPD has the OMIM Entry # 609446. Location is on chromosome 10q22.3. Two genes encoding ion channels in the 8.4-cM region have been identified by linkage analysis: KCNMA1 (potassium large conductance calcium-activated channel, subfamily M, alpha member 1) and VDAC2 (encoding voltage-dependent anion channel 2) (Du et al., 2005; Guerrini et al., 2002).

Benign familial neonatal seizures (BFNS). BFNS occurs in approximately 1 in 100,000 newborns and is characterized by recurrent seizures. Seizures (generalized and focal) occur around day 3 of life to 1–4 months. Interictal EEG is often normal or may show *the theta pointu alternant pattern*. By age 2 years, most affected individuals who had EEG abnormalities have a normal EEG. Most individuals with BFNS develop normally, some may show intellectual disability that becomes noticeable in early childhood. In a small proportion BFNS may be associated with myokymia. About 15% of people with BFNS will experience recurrent seizures (epilepsy) later in life.

Mutations in two genes, KCNQ2 and KCNQ3, have been found to cause BFNS. Mutations in the KCNQ2 gene are a much more common. Mutations in the KCNQ2 or KCNQ3 gene result in a reduced or altered M-current, which leads to excessive excitability of neurons.

BFNS is inherited in an autosomal dominant pattern, which means one copy of the altered gene in each cell is sufficient to cause the disorder. In most cases, an affected person inherits the mutation from one affected parent. A few cases result from new mutations in the KCNQ2 gene. Zara et al (2013) showed that PRRT2 (Proline-rich transmembrane protein 2) mutations are clustered in families with benign familial neonatal-infantile seizures. The function of this PRRT2 is unknown, although it is thought to be involved in signaling in the brain. Other disorders caused by mutations of PRRT2 are familial hemiplegic migraine, familial paroxysmal kinesigenic dyskinesia and infantile convulsions and choreoathetosis. For further details see Table 5.

Autosomal dominant partial epilepsy with auditory features (*ADPEAF*) is a rare form of epilepsy. Its prevalence is unknown. ADPEAF is inherited in an autosomal dominant pattern, which means one copy of the altered leucine-rich, glioma-inactivated 1(LGI1) gene in each cell is sufficient to raise the risk of developing epilepsy. About two-thirds of people who inherit a mutation in this gene will develop seizures. In most cases, an affected person has one affected parent and other relatives with the condition. According to Nobile et al. (2009) ADPEAF is associated in about half of the families with mutations of LGI1 and de novo LGI1 mutations are found in about 2% of sporadic cases.

Seizures usually are characterized by sound-related (auditory) symptoms such as buzzing, humming, or ringing. More complex sounds during a seizure, such as specific voices or music, or changes in the volume of sounds, may be experienced. ADPEAF may be associated with receptive aphasia, less commonly with visual hallucinations, a disturbance in the sense of smell, a feeling of dizziness, vertigo, or other symptoms affecting the senses.

Seizures associated with ADPEAF usually begin in adolescence or young adulthood. In a small proportion they may be triggered by specific sounds, or speech. Seizures are infrequent and effectively controlled with medication. Seizures originate in the lateral temporal lobe. Consciousness is preserved, but secondarily generalized seizures may occur.

Table 5. Genetics of Benign familial infantile seizures

Epilepsy Syndrome	OMIM Entry #	Location chromosome	Gene	Gene/Locus MIM #	Refs.
Benign familial infantile seizures BFIS3: Syn: Benign familial infantile convulsions 3 (BFIC3); Benign familial neonatal-infantile seizures (BFNIS)	BFIS1 (601764)	19q	BFIS1, BFIC1		Deprez et al., 2009
	BFIS2 (605751)	16p11.2	mutation in the PRRT2 gene		
	BFIS3 (607745)	2q24.3	SCN2A	182390	Shevell et al 1986; Berkovic et al., 2004
Benign familial newborn convulsions (BFNC)	607745	8q24	KCNQ2 and KCNQ3 generate together M-potassium current.		Miraglia del Giudice et al., 2000
	BFIS4	1p36.12-p35.1		612627	

ADPEAF are caused by mutations in the LGI1 gene. This gene provides instructions for making a protein called leucine-rich, glioma inactivated 1 (LGI1) or epitempin, which is found primarily in neurons in the brain. Its precise role in the brain remains uncertain.

LGI1 mutations have been identified in about half of all families diagnosed with ADPEAF. At least 22 mutations in the LGI1 gene have been identified. Some LGI1 mutations change a single protein building block (amino acid) in the epitempin protein. Other mutations lead to the production of an abnormally short, nonfunctional version of the protein.

Epilepsy in females with mental retardation (EFMR, syn. Juberg-Hellman Syndrome). The first family was reported in 1971 in USA (Juberg and Hellman, 1971). EFMR occurs almost exclusively in girls, has been associated with febrile seizures or following immunization before three years old. In the University of Melbourne study on 4 families with 58 individuals, EFMR seizures occurred with a mean onset at 14 months and were of various types (tonic, tonic-clonic, myoclonus, absences and atonic seizures) and occurred in clusters. Many seizures of short duration occur over a period of several days. The EEG showed "generalized and focal epileptiform abnormalities" (Scheffer et al., 2008). Vaccines can trigger seizures, especially the vaccine for pertussis-diphtheria-tetanus (Specchio et al., 2011). Diagnosis can be made through genetic testing. Potential developmental delays or developmental regression and associated disorders (there appears to be a connection to depression, autism, obsessive and aggressive behaviors and other psychiatric disorders) eases diagnosis. 67% of the females have mild to profound intellectual disability or borderline intellectual functioning. Some of the patients also had a diagnosis of Angelman syndrome, sodium channelopathies, or forms of Rett syndrome.

EFMR is considered X-linked dominant with male carriers. Women and men with the affected gene can transmit the disease. Men express a normal phenotype. The disorder was shown to be linked to mutations via Xq22 microsatellite markers (Ryan et al., 1997). EFMR is thought to develop because of a deficiency of the *calcium-dependent cell-adhesion PCDH19* (*protocadherin 19*) gene. Although classified as a rare disease, 11 early studies indicate that 5–10% of children with febrile seizures could have the PCDH19 gene. Dibbens et al. (2011) reported instances where patients had PCDH19 mutation, but their parents did not. They found that "gonadal mosaicism" of a PCDH19 mutation in a par-

ent is an important molecular mechanism associated with the inheritance of EFMR.

Patients may respond well to treatment with levetiracetam. In cases of drug resistance, an alternative treatment is stiripentol. Galaxolona, a neurosteroid that is currently in Phase III clinical trials, may offer an alternative therapy.

Ohtahara syndrome, also known as Early Infantile Epileptic Encephalopathy with Burst-Suppression (EIEE), is a progressive epileptic encephalopathy. The syndrome is characterized by tonic spasms and partial seizures, and burst-suppression activity in the EEG. It is an extremely debilitating neurological disorder, involving intractable seizures and severe mental retardation. In many cases structural brain damage is present.

Although originally not considered to have a genetic connection, several genes have since been associated. Ohtahara syndrome can be associated with mutations in ARX (aristaless related homeobox) (Kato et al., 2007), CDKL5 (cyclin-dependent kinase-like 5), SLC25A22 (solute carrier family 25 (mitochondrial carrier: glutamate), member 22), STXBP1 (Syntaxin binding protein 1) (Saitsu et al., 2012), SPTAN1 (spectrin, alpha, non-erythrocytic 1), KCNQ2 (potassium voltage-gated channel, KQT-like subfamily, member 2), ARHGEF9 (Cdc42 guanine nucleotide exchange factor (GEF) 9), PCDH19 (protocadherin 19), PNKP (polynucleotide kinase 3'-phosphatase), SCN2A (sodium channel, voltage-gated, type II, alpha subunit), PLCB1 (phospholipase C, beta 1 (phosphoinositide-specific)), SCN8A (sodium channel, voltage gated, type VIII, alpha subunit) (OMIM 308350, 300203, 609302, 602926, 182810, 602235, 300429).

Epileptic encephalopathies. Syntaxin binding protein 1 (STXBP1) appears to play a role in release of neurotransmitters via regulation of syntaxin, a transmembrane attachment protein receptor. Mutations in this gene have been associated with **infantile epileptic encephalopathy-4**. Suls et al. (2013) described de novo loss-of-function mutations in **CHD2** (Chromodomain-helicase-DNA-binding protein 2) in fever-sensitive myoclonic epileptic encephalopathy ("Dravet-like epilepsy") and Carvill et al. (2013) identified de novo CHD2 and **SYNGAP1** (synaptic Ras GTPase activating protein 1) mutations as novel causes of epileptic encephalopathies. CHD most probably modifies the chromatin structure thus altering access of the transcriptional apparatus to its chromosomal DNA template. SYNGAP1 is associated with NMDA receptors

at synapses. De novo CHD2 and SYNGAP1 mutations accounted for 1.2% and 1% of 500 patients respectively. Analysis included 19 known and 46 candidate epileptic encephalopathy genes and found pathogenic mutations in 10% of the cohort. Defects in the SYNGAP1 gene are a cause of mental retardation autosomal dominant type 5 (MRD5).

GLUT1 deficiency syndrome (G1D) is a genetic condition, i.e., a disease caused by an alteration or mutation in a gene that primarily affects the brain. G1D is a rare disorder. Fewer than 300 cases have been reported since the disease was identified in 1991. G1D affects males and females of all races and ethnicities equally.

Most affected individuals experience difficult to treat seizures within the first few months of life. Babies with G1D seem to be "normal" at birth, but over time may show signs of delayed brain growth. Common symptoms of G1D are: Developmental delays and learning disabilities, stiffness (spasticity), ataxia, dysarthria, episodes of confusion, lethargy, headaches, muscle twitches (myoclonus), involuntary irregular eye movements (particularly in early infancy). Less common symptoms of G1D include: spells of uncontrollable movements while awake (dyskinesia), constant movements at rest and while awake (chorea), alternating hemiplegia, and hemolytic anemia.

Low, and otherwise unexplained, glucose values which are commonly found in the spinal fluid of affected individuals suggest the diagnosis of G1D.

Genetic testing (direct DNA analysis) will confirm the diagnosis: G1D is caused by a defect in the SLC2A1 gene. The SLC2A1 gene makes the glucose transporter protein type 1 (GLUT1), which aids the transportation of glucose across the blood-brain barrier.

G1D can be inherited as an autosomal dominant genetic condition meaning that only one nonworking copy of the gene in each cell is enough to cause the disorder. Most cases, however, are due to new spontaneous mutations. In these instances, there is typically no familial history of the disorder. For affected individuals, there is a 50% chance in each pregnancy to pass the nonworking copy of the gene to a child. Unfortunately, due to the variability of symptoms, it is difficult to predict the severity of the condition in a child of an affected parent.

Autosomal Dominant Nocturnal Frontal Lobe Epilepsy (ADNFLE). ADNFLE is a partial (localization-related) epilepsy disorder. Signs and symptoms consist of brief violent complex seizures during sleep with arm and leg movements (hand/fist clenching, arm raising/lowering, and knee bending) and vocalizations such as yelling, moaning, shouting, or crying. Seizures often occur in clusters and typically first manifest in childhood. ADNFLE is often misdiagnosed as nightmares, night terrors, other parasomnias and various psychiatric disorders.

Malfunction in thalamocortical loops is considered the primary cause. Arguments for this assumption are: 1) Thalamocortical loops are important in sleep and ADNFLE seizures originate in the frontal cortex; 2) K-complexes are almost invariably present at the start of seizures "initial (spike-wave) complex" according to Wieser (1983) and El Helou et al. (2008); 3) Both the thalamus and cortex receive cholinergic inputs and acetylcholine receptor subunits comprise the three known causative genes for ADNFLE. These receptor subunits are expressed presynaptically by neurons that release the inhibitory transmitter GABA. Therefore, the mutation in the nicotinic acetylcholine receptor α-4 subunit could lead to reduced GABA release, causing hyperexcitability.

Pathophysiology. There are four known loci for ADNFLE, three with known causative genes (Table 2). These genes encode various nicotinic acetylcholine receptor α and β subunits CHRNA4, CHRNB2, and CHRNA2.

CHRNA4. The first mutation associated with ADNFLE is a serine to phenylalanine transition. The gene encodes a nicotinic acetylcholine receptor α subunit (Steinlein et al., 1995). Using the numbering based on the human CHRNA4 protein, this mutation is called S280F (Matsushima et al., 2002). Receptors containing this mutant subunit are functional, but desensitize much faster and recover from desensitization at a much slower rate compared to wild-type only receptors (Weiland et al., 1996). Interestingly, these mutant receptors also have a decreased single channel conductance than wild-type and have a lower affinity for acetylcholine (Kuryatov et al., 1997; Bertrand et al., 2002).

The second discovered ADNFLE mutation was also in CHRNA4. This mutation, L259_I260insL, is caused by the insertion of three nucleotides (GCT) between a stretch of leucine amino acids and an isoleucine. As with the S248F mutation, the L259_I260insL mutation is located in the second transmembrane spanning region. Electrophysiological experiments have shown that this mutant is tenfold more sensitive to acetylcholine than wild-type. The S252L mutation also has been as-

sociated with ADNFLE. Another mutation in CHRNA4 associated with ADNFLE is T265M, again located in the second transmembrane spanning segment. However, this mutation is less well studied.

Mesial temporal lobe epilepsy with hippocampal sclerosis (MTLEHS)

MTLEHS is the prototype of a "focal" (partial = localization-related) epilepsy. It is mentioned here, because Kasperavičiūtė et al. (2013) report an association between MTLHS with febrile seizures in childhood (MTLEHS+FS) and Single Nucleotide Polymorphisms near and in SCN1A (sodium channel gene cluster on chromosome 2q24.3 [rs 7587026, within an intron of the SCN1A gene]). We participated in this study which comprised of 1018 patients *with* MTLEHS and 7552 control subjects. Patients with MTLEHS with (n = 757) and *without* (n = 803) febrile seizures were compared. Furthermore a cohort of 172 individuals with febrile seizures, who did not develop epilepsy during prospective follow-up to age 13 years were analysed. In this group, in the MTLS *without* FS, and in the control subjects no association was found for rs 7587026 and febrile seizures.

This study is important, because MTLEHS is frequent, typically pharmacoresistant, making it the commonest epilepsy form for which resective neurosurgical treatment is undertaken. The cause of MTLEHS is unknown, but there is an association with childhood febrile seizure (Wieser, 2004). MTLEHS has rarely been described in families with genetic epilepsy with febrile seizures plus (GEFS+) (Abu-Khalil et al., 2001) or familial febrile seizures (Mantegazza et al., 2005) associated with SCN1A mutations. In familial MTLE, some family members may have hippocampal sclerosis (Striano et al., 2008). Together, this evidence suggests a genetic susceptibility to MTLEHS, though heritability of MTLEHS is not known.

Genetic Testing in the Epilepsies

As highlighted at the beginning, the utility and state of knowledge has been expertly summarized in the Report of the ILAE Genetics Commission (Ottman et al., 2010).

DNA extraction for genetic testing. A sample of approximately 15 mL venous blood is treated with detergents to break open the cell membrane spilling the contents. Enzymes are used to break down all the protein, RNA, sugars and fats in the solution. Genetic test-

ing is offered by several private and University institutions. Extensive information about the available clinical genetic tests can be found at the **Gene Tests website** (http://www.genetests.org). It comprises a *Laboratory Directory* of over 600 international laboratories offering molecular genetic testing, biochemical genetic testing, and specialized cytogenetic testing for more than 3000 inherited disorders and a *Clinic Directory* of over 1000 international genetics clinics providing diagnosis and genetic counseling services to patients and their families. The site also contains authoritative reviews on the genetics of several epilepsy syndromes, with links to *GeneReviews™* chapters and related information. *GeneReviews™* is NIH-funded and developed and maintained by the University of Washington, Seattle.

DNA Sequencing. Many laboratories, such as *CD Genomics*, provide a complete sequencing solution. Highly flexible DNA sequencing packages are tailored to meet individual needs and are equipped with high-throughput sequencers, such as ABI 3730xl. *CD Genomics* reported that they extended their large scale sequencing with Roche 454 GS-FLX System, ABI SOLID sequencing system and Illumina Solexa 1G Genome Analyzer using the Next-Gene sequencing technology.

Genes responsible for the side effects of AEDs can be included. A Japanese Group (Hirosaki University) developed and tested a new version of the EpiGene that contains 35 genes and includes genes responsible for the side effects of AEDs (Sugawara et al., 2013). These authors showed that for some epilepsy phenotypes it is becoming possible to predict the most efficacious antiepileptic drugs for patients based on their genetic makeup (Yamada et al., 2013; Sugawara et al, 2013). In a similar way pharmacoresistance can be determined by genetic studies (Mirza et al., 2011; Lachos et al., 2011). Thus, the development of individualized medicine is expected to greatly improve the management of epilepsy patients (Striano and Striano, 2013).

Estimated Costs. At present the cost per sample could be up to 3250 EUR (gene panel: 2250 EUR, MLPA (Multiplex Ligation-dependent Probe Amplification): 250 EUR, Sequence analysis: 750 EUR). In the future this might be less (about 1000 EUR??). The isolated DNA can be stored for future research. The sensitivity is 95%. Results are reported in about 8 weeks.

CONFLICT OF INTEREST DISCLOSURE

The author has no conflict of interest to declare.

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