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Review

The genetics of monogenic idiopathic epilepsies and epileptic encephalopathies

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ABSTRACT

The group of idiopathic epilepsies encompasses numerous syndromes without known organic substrate. Genetic anomalies are thought to be responsible for pathogenesis, with a monogenic or polygenic model of inheritance. Over the last two decades, a number of genetic anomalies and encoded proteins have been related to particular idiopathic epilepsies and epileptic encephalopathies. Most of these mutations involve subunits of neuronal ion channels (e.g. potassium, sodium, and chloride channels), and may result in abnormal neuronal hyperexcitability manifesting with seizures. However non-ion channel proteins may also be affected. Correlations between genotype and phenotype are not easy to establish, since genetic and non-genetic factors are likely to play a role in determining the severity of clinical features. The growing number of discoveries on this topic are improving classification, prognosis and counseling of patients and families with these forms of epilepsy, and may lead to targeted therapeutic approaches in the near future. In this article the authors have reviewed the main genetic discoveries in the field of the monogenic idiopathic epilepsies and epileptic encephalopathies, in order to provide epileptologists with a concise and comprehensive summary of clinical and genetic features of these seizure disorders.

1. Introduction

Idiopathic epilepsies represent up to 47% of all epilepsies, and they are thought to have a genetic origin with a monogenic or polygenic model of inheritance. During the last 2 decades, several epilepsy-causing gene mutations have been discovered, improving our knowledge on the classification of epilepsies and epileptic encephalopathies and the epileptogenic mechanisms and therapeutic approaches. However, to date, only about 2% of the idiopathic epilepsies are considered to be monogenic, and numerous issues still remain unclear.[1] In majority of the monogenic epilepsies (Table 1), the mutated genes encode ion channel subunits (Table 2) (e.g., voltage-gated sodium and potassium channel subunits) that mediate neuronal excitability and whose gain or loss of function result in abnormal generation and propagation of action potentials.[2] However, epilepsy-causing genes coding for non-ion channel proteins have been mapped (Table 2); in these cases, identification of epileptogenic mechanisms responsible for seizure induction is less clear and functional interaction with ion channels is supposed. Genotype–phenotype correlations have not been completely clarified, since several undefined genetic and environmental factors are thought to play a role in determining the phenotype: some epileptic syndromes, in particular the group of idiopathic generalised epilepsies, may have complex polygenetic traits; furthermore, monogenic epilepsy syndromes may have been derived from mutations of different genes.[1] Finally, a specific mutation (e.g., missense sodium channel alpha 1 subunit [*SCN1A*] mutations) may underlie more phenotypes (from febrile seizures plus to the Dravet syndrome [DS]), but a specific phenotype may also be derived from different mutations on a single gene (e.g., missense or nonsense or other type of *SCN1A* mutations). In this article, we have reviewed the main genetic discoveries in the field of monogenic idiopathic epilepsies and epileptic encephalopathies to provide epileptologists a rapid and comprehensive summary of the clinical and genetic features of these forms.

2. Early infantile epileptic encephalopathy/ohtahara syndrome

Early infantile epileptic encephalopathy (EIEE) (OMIM #308350), also known as the Ohtahara syndrome (OS),[3] is

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Table 1
Monogenic epileptic syndromes and encephalopathies. List of abbreviation: PB, phenobarbital; ACTH, adrenocorticotropic hormone; VPA valproic acid; CBZ, clobazam; CZP, clonazepam; GVG, vigabatrin; ESM, ethosuximide; LZP, lorazepam; PHT, phenytoin; LEV, levitiracetam; TPM, topiramate; CBZ, carbamazepine; LTG, lamotrigine; ZNS, zonisamide; IVIG, intra venous immunoglobulin.

Syndrome	Age of onset	Seizure type	Inter-ictal EEG features	Therapeutic options
EME	Neonatal period	Fragmentary and erratic myoclonias, simple partial seizures, massive myoclonus, tonic spasms	Suppression burst pattern	PB, steroids, ACTH, other AEDs
EIEE-OS	Neonatal period – first months of life	Tonic spasms, erratic focal motor seizures, generalized tonic seizures	Suppression burst pattern	VPA, CBZ, CZP, GVG, ACTH, Steroids, IVIG
BFNS BFNIS BFIS	First days of life Neonatal period 3m-12m	Focal tonic–clonic convulsions, generalized convulsions	Normal; focal or multifocal abnormalities or 'théta pointu alternant' pattern	PB
GEFS+	Early infancy or childhood (6m-6y)	FS, FS+, GTCS, AbS, AtS, focal seizures, MyS	Normal; focal or generalized spike and waves complexes	VPA, ESM, CBZ, PB
DS	Early infancy (before 1 year of age)	Febrile seizures, tonic–clonic, tonic, atonic, absences, myoclonic jerks, partial seizures	Normal during the first 12m of life; Focal or generalized spike and waves complexes	VPA, PB, CPZ, LPZ, ESM, PTH, STP
EFMR	Early infancy or childhood (6-36m)	Febrile seizures, tonic–clonic, tonic, atonic, absences, myoclonic jerks, partial seizures	Focal or multifocal or generalized spike-and-wave complexes	VPA, PB, TPM, LZP, CLB
ISSX	Before 1 year of age	Infantile spasms	Hypsarrhythmia	VPA, CBZ, LEV, ESM, CLB, LTG
RTT	After 2 year of age	GTCS, absence seizures, myoclonic seizures, tonic seizures, atonic seizures	Slow waves, focal or multifocal paroxysmal activity	
EOAE	Before 4 year of age	Absence seizures	3 Hz diffuse spike and waves complexes	VPA, ESM
JME	Late childhood–early adulthood	Myoclonic seizures, GTCS, absence seizures	Diffuse spike and waves complexes; photosensitivity	VPA, CZP, TPM, LTG, ZNS
ADPEAF/ADLTE	4–50 years	Simple and/or complex focal (temporal seizures), with or without secondary generalization	Normal or with epileptic anomalies in temporal regions	VPA, CBZ, PHT
ADFNLE	First two decade	Nocturnal (and rarely daily) seizures with frontal semiology	Normal (waking) or with epileptic anomalies in frontal regions (sleep)	CBZ, ZNS

characterised by the early onset of tonic spasms that occur with or without clustering, seizure intractability, a characteristic interictal suppression burst (SB) pattern on the EEG that is persistently observed in both waking and sleeping states, and a remarkable age-dependent evolution into the West syndrome (WS) (reported in 75% of the cases).[4] In addition to tonic spasms, partial seizures, such as erratic focal motor seizures, are observed in about one-third to one-half of the patients. Prognosis is very poor with severe drug resistance and psychomotor retardation. The mortality rate is high, especially in the early stage of the disorder.[4] The causes of EIEE are heterogeneous. Several brain malformations, neuronal migration disorders, and metabolic disorders have been found as the underlying causes of symptomatic OS.[5] Two causative genes are thought to be involved in the pathogenesis of the cryptogenic cases of OS: the aristaless-related homeobox (*ARX*) and the syntaxin-binding protein 1 (*STXBP1*) genes. The *ARX* gene is considered to have an important role in neuronal proliferation, differentiation of the embryonic brain, and interneuronal migra-

Table 2
Genes and encoded proteins involved in the genetic epileptic syndromes and encephalopathies.

Protein	Subunit	Gene	Gene locus	Phenotype
Neuronal nicotinic acetylcholinic receptor	α2-subunit	CHRNA2	8p21	ADNFLE
	α4-subunit	CHRNA4	20q13	ADNFLE
	β2-subunit	CHRNB2	1q21	ADNFLE
M-current protein channel	Kv7.2	KCNQ2	20q13	BFNS
	Kv7.3	KCNQ3	8q24	BFNS
Voltage gated Sodium channel	α1-subunit	SCN1A	2q24	GEFS+ SMEI IGE-GTC MAE
	α2-subunit	SCN2A	2q23-q24.3	BFNIS BFIS SMEI
	β2-subunit	SCN2B	19q13	GEFS+ EOAE+FS plus
GABA receptor	α1-subunit	GABRA1	5q34-q35	JME
	γ2-subunit	GABRG2	5q34	GEFS+ CAE
Leucine rich glioma inactivated 1		LGI1	10q24	ADPEAF/ADLTE
Glucose transporter type 1		SLC2A1	1p35-p31.3	EOAE
EF hand motif containing 1		EFHC1	6p12-p11	JME
Protochaderin		PCDH19	Xq22	EFMR
Cyclin-dependent kinase-like 5		CDKL5/STK9	Xq28	ISSX-RTT
Aristaless related homeobox		ARX	Xp22.13	OS
Sintaxin binding protein 1		STXBP1 (MUNC18-1)	9q34.1	OS
Solute carrier family 25 member 22		SLC25A22	11p15.5	EME

tion and acts as a transcription factor in the development of γ-aminobutyric acid (GABA)ergic interneurons.[6] Phenotypes associated with *ARX* mutations include both malformative and non-malformative syndromes. Malformation syndromes (e.g., X-linked lissencephaly with an absent corpus callosum, the Proud syndrome, X-linked myoclonic epilepsy with spasticity and intellectual disability, and hydranencephaly with abnormal genitalia) have been related to *ARX* mutations with loss-of-function (nonsense or missense mutations in the homeobox domain).[7–9] However, *ARX* mutations with gain-of-function (expansion of polyalanine tracts, missense mutations outside the homeodomain, and deletion of exon 5) cause non-malformation syndromes (e.g., Partington syndrome, non-syndromic mental retardation, and X-linked infantile spasms syndrome (ISSX) that include WS and OS). Shinozaki et al. found that expansion of the first polyalanine tract with 11 expanded alanine residues causes EIEE; however, the insertion of 8 alanine residues into the second polyalanine tract, the most common type of *ARX* anomaly, results in X-linked mental retardation, ISSX, and the Partington syndrome.[10] The human *ARX* protein was shown to be a potent transcriptional repressor, so the expansion of either the first or the second *ARX* polyalanine tract enhances the transcriptional repression activity in a manner dependent on the length of the alanine expansion.[11] The longer expansion of the polyalanine tract causes the more earlier and severe phenotype (EIEE/OS), while the shorter expansion leads to the less severe and later-onset WS.[12] Pleiotropic mutations of the *ARX* gene cause a variety of phenotypes that are considered to share a common pathological mechanism related to the structural and functional disturbance of interneurons, called 'interneuronopathies'.[13,14] This hypothesis was supported by experimental data (from *ARX*-knockout mice) demonstrating that *ARX* protein deficiency results in the loss of GABAergic interneurons and anomalous distribution of residual cells in the cortex and basal ganglia.[15] Consequently, GABAergic network dysfunction seems to play a crucial role in the pathogenesis of SB and the hypsarrhythmic pattern. The syntaxin-binding protein 1 (*STXBP1*) or the *MUNC18*-1 gene encodes a neuron-specific protein that is essential for synaptic vesicle release.[16,17] Many authors have considered *STXBP1* haploinsufficiency as a possible cause of EIEE. Saitsu et al. described several mutations (frameshift, nonsense, splicing, and recurrent missense mutations) in patients with EIEE suggesting that *STXBP1* aberration is associated with the early onset of epilepsy and invariable development of mental retardation and might be an important cause for cryptogenetic EIEE.[18,19] It remains to elucidate how haploinsufficiency of *STXBP1* leads to EIEE. The authors did not identify any brain malformation in the 5 subjects with EIEE who had *STXBP1* defects, but they described extensive neuronal cell death in the brainstem that, in addition to the impaired synaptic vesicle release, might contribute to EIEE pathogenesis. In addition, a recent study showed that mutations in *STXBP1* are not limited to patients with OS but are also present in patients with early-onset epileptic encephalopathy, which does not fit into either OS or WS. This strongly supports the hypothesis that mutations in *STXBP1* could cause many types of epileptic disorders.[20,21]

3. Early myoclonic encephalopathy

Early myoclonic encephalopathy (EME) (OMIM #609304) is an age-related, generalised epilepsy of non-specific etiology[22] and was first described by Aicardi and Goutieres in 1978.[23] EME is characterised by the very early onset of fragmentary and erratic myoclonias and is frequently associated with partial seizures. Interictal EEG shows an SB pattern, with a short burst and a long suppression, enhanced by sleep.[24,25] Unlike the OS, EME shows no specific evolution with age, and the prognosis is very poor with no effective treatment.[4,26] The etiology of EME remains unknown in majority of the patients. It has been hypothesised that genetic factors and/or inborn errors of metabolism play a crucial role in the pathogenesis of this encephalopathy, since patients with EME and several inborn errors of metabolism (e.g., methylmalonic acidemia, nonketotic hyperglycinemia, propionic aciduria, Zellweger syndrome, D-glyceric acidemia, sulfite and xanthine oxidase deficiency, and Menkes disease) have been reported, with a high incidence of familial cases.[24,26–29] Ohtahara and Yamatogi argued that EME could be due to extensive cortico-subcortical dysfunction as a consequence of multiple severe metabolic disorders rather than a specific genetic abnormality.[4] Computed tomography and magnetic resonance imaging seldom show abnormalities in the early stage of the disease, which may appear several months later. Molinari et al. identified a monozygous missense mutation (p.Pro206Leu) in exon 8 of the *SLC25A22* gene (solute carrier family 25 member 22; also known mitochondrial glutamate carrier 1 [GC1]) in 4 children with EME.[30] The *SCL25A22* gene is mapped on chromosome 11p15.5 and encodes a mitochondrial glutamate/H^+ symporter.[31] Functional analyses of fibroblasts have supported the hypothesis that this mutation altered an amino acid (proline 206) that is probably a residue strongly implicated in glutamate transport. Furthermore, expression studies pointed out that *SLC25A22* gene expression is limited to the brain, especially in those regions involved in the genesis and control of myoclonic seizures, such as substantia nigra,[32,33] the cranial nerves nuclei III, the red nuclei, and olivary complexes.[34,35] In addition, Berkich found that *SLC25A22* is more abundant in astrocytes than in neurons, so a defect in this protein may cause glutamate accumulation in the astrocyte cytosol and glutamate liberation in the synaptic cleft, which may be involved in the generation of epileptic-like discharges in the brain.[36] Recently, Molinari described a new homozygous missense mutation in the *SLC25A22* gene of an Algerian boy with severe epileptic encephalopathy associated with SB pattern on EEG and brain abnormalities on MRI.[37] The authors detected a homozygous substitution (p.Gly236Trp) that led to the change of a highly conserved residue within the V helix of the internal channel. The complete loss of the uniport and transport activity of the *SLC25A22* mutant protein demonstrated that the G236 residue is crucial for *SLC25A22* activity, even if in vitro functional expression analyses in *Escherichia coli* showed that it had no functional transport activity. Then, how mutations in *SLC25A22* cause epilepsy remains an unsolved question, but these findings suggest that defective GC1 function could result in a severe alteration of glutamate metabolism in glial cells and lead to alteration of normal brain function, especially neuronal excitability.

4. Benign familial neonatal seizures, benign familial neonatal/infantile seizures, and benign familial infantile seizures

Benign familial seizures include benign familial neonatal seizures (BFNS), benign familial neonatal/infantile seizures (BFNIS), and benign familial infantile seizures (BFIS) and are classified on the basis of the age of onset. BFNS (also known as benign familial neonatal convulsions or benign familial epilepsy type 1; OMIM #121200), the first identified central nervous system channelopathy and the best recognised disease model for genetically determined human epilepsies, is a rare, monogenic, autosomal dominant, and benign familial epilepsy syndrome.[38] It is characterised by unprovoked and brief cluster of focal tonic–clonic convulsions occurring within the first days of life and frequently flowing into status epilepticus. In addition, apnoeic spells and generalised seizures may occur. No specific EEG trait characterises BFNS: interictal EEG is most commonly normal, and if

present, anomalies are usually transient.[39,40] Majority of the individuals with BFNS can be kept seizure-free by using phenobarbital. Seizures disappear spontaneously within 2 months of life. However, about 10–15% of the children with BFNS develop seizures later in life, with a variable age of onset and duration; in this eventuality, seizures are mainly generalised tonic or tonic–clonic seizures, and EEG may be characterised by centrotemporal spikes and sharp waves or benign epilepsy with centrotemporal spikes.[41] In addition, some affected children will suffer from recurrent febrile seizures or photosensitive myoclonic epilepsy. BFNS is rarely associated with peripheral nerve hyperexcitability (myokymia),[42] therapy-resistant epileptic encephalopathy shortly after birth, and a variable degree of mental retardation.[43,44] BFNS is linked to mutations in the *KCNQ2* and *KCNQ3* genes,[45–48] which are members of a family of voltage-gated potassium channel genes (*KCNQ1–5*). *KCNQ2* and *KCNQ3* are predominantly expressed in the brain,[49] mainly in the hippocampus, temporal cortex, cerebellar cortex, and medulla oblongata, from late foetal life to early infancy, coinciding with the time in which BFNS occurs.[50,51] They encode the voltage-gated Kv7.2 and Kv7.3 channels that produce a neuronal muscarinic-regulated potassium current (M-current), a slow activating non-inactivating potassium current important in the modulation of the resting membrane potential. This action limits the repetitive firing of many neurons. More than 60 mutations have been described in the BFNS families, with the majority involving *KCNQ2*. Approximately half of the *KCNQ2* mutations described in BFNS are truncations, splice-site defects, or deletions or insertions of a small number of bases that cause frameshifts; about 60% of these mutations are in the C-terminus and are predicted to cause truncation of the C-terminus with haploinsufficiency.[43,52–56] Missense mutations have been reported in *KCNQ3*. No major phenotypic differences are observed between patients with BFNS caused by a *KCNQ2* mutation and those with BFNS caused by a *KCNQ3* mutation. Because of the small number of families with BFNS, genotype–phenotype correlations are speculative.[57] Penetrance is incomplete (85%); anticipation has not been observed.[38] The majority of newborns diagnosed with BFNS have an affected parent; however, sporadic BFNS has also been reported. In BFNIS (OMIM #607745), seizures appear in neonates, and in BFIS (OMIM #601764), they begin between the 3rd and the 12th month of life. Seizures are usually of the partial type, with or without secondary generalisation. Mutations in the voltage-gated sodium channel alpha 2 subunit (*SCN2A*) have been reported in BFNIS[58] and BFIS.[59,60] Increased sodium current, derived from the gain-of-function of the sodium channel and explaining a neuronal hyperexcitability resulting in seizures, has been reported in BFNIS.[61] Benign infantile seizures may also be associated with paroxysmal dyskinesia, a movement disorder in the form of choreoathetosis or dystonia, generating the infantile convulsions with choreoathetosis (ICCA) syndrome. The ICCA syndrome is inherited in an autosomal dominant fashion and is linked to mutations of the 16p12-q12 chromosome, but the ICCA gene has not been mapped: this critical area displays complicated genomic architecture and is the site of deletions and duplications associated with other diseases.[62]

5. Genetic epilepsy with febrile seizures plus and DS?

Genetic epilepsy with febrile seizures plus (GEFS+) (OMIM #604233) is a familial, autosomal dominant epileptic syndrome with a large pattern of intrafamilial and extrafamilial phenotypic variability. Patients with GEFS+ may suffer from febrile seizures (FS) after the 6th year of age (called febrile seizures plus [FS+]) and afebrile myoclonic, absence, atonic, or partial seizures may appear.[63] FS and FS+ represent the milder form of GEFS+, whereas severe myoclonic epilepsy of infancy (SMEI) or the DS (OMIM #607208) represent the most severe form. SMEI is an epileptic encephalopathy that starts during the first year of life, especially around the 6th month, with recurrent and long-lasting febrile seizures, also known as febrile status epilepticus. Drug-resistant myoclonic, complex partial, and atypical absence seizures can appear after 12 months of life. Hot water seizures and photosensitivity are present in about 50% of the patients.[64] Regression of the normally acquired mental capacities may start from the 2nd year, often related to episodes of status epilepticus.[63–65] Interictal myoclonus, ataxia, and pyramidal signs may complete the clinical picture. Japanese authors described patients with incomplete SMEI phenotype and have named these variants as borderline severe myoclonic epilepsy of infancy (SMEB) and intractable childhood epilepsy with generalised tonic–clonic seizures (ICE-GTC).[66,67] In GEFS+, SMEI, SMEB, and IGE-GTC, mutations in the voltage-gated *SCN1A* gene have been discovered. The *SCN1A* gene (chromosome 2q24.3) is mainly expressed in the cerebral tissue and is implicated in the generation and propagation of action potentials.[2] About 10% of the GEFS+ patients have *SCN1A* mutation. In SMEI patients, mutations in the encoding exons, which are de novo in 95%, are present in about 80% of the cases, and they include missense (39%), nonsense (22%), frameshift (19%), splice-site (10%), genomic rearrangements (deletions, duplications, amplifications, and translocations) (7%), in-frame deletions (2%), and other types (silent and complex mutations) (1%) of mutations.[68,69] Recently, the first cases of microdeletion limited to the *SCN1A* noncoding exons located at 5′ promoter region, with the coding sequence preserved, have been found, indicating the critical involvement of this upstream region in the molecular pathology of DS.[70] Functional studies in animal models with SMEI suggest that recurrent seizures and ataxia can result from a cell-specific reduction of sodium current in interneurons and Purkinje neurons.[2] Genotype–phenotype correlations showed that a severe clinical picture (e.g., SMEI) is more frequently observed in association with nonsense mutations, which generate a truncated alpha subunit, and missense mutations affecting the pore-forming region (S5–S6), which modify the amino acid polarity, and consequently, the sodium current. A recent large genotype–phenotype study of patients with *SCN1A* mutations revealed that, compared to missense mutations, truncating mutations were associated with earlier mean onset of prolonged seizures, myoclonic seizures, and atypical absence seizures.[71] In contrast, missense mutations in GEFS+ are usually located outside the pore-forming region.[2,72] Some case reports have shown that nonsense mutations can be associated with phenotypes less severe than SMEI, such as GEFS+.[70] In SMEB or ICE-GTC, missense mutations are more frequently found.[68] It is a common opinion that several factors may account for the large pattern of phenotypic heterogeneity. In particular, stochastic events during development, environmental factors (e.g., viral infections and vaccination), and genetic factors (e.g., anomalies in modifier genes, mosaicisms, and the timing of mutagenesis) may influence the final phenotype of patients carrying *SCN1A* anomalies.[73–76] It has been recently reported that diphtheria–tetanus–pertussis vaccination might trigger the earlier onset of DS in children who, because of an *SCN1A* mutation, are destined to develop the disease, without influencing other clinical aspects (e.g., intellectual outcome and subsequent seizure type).[77] Regarding genetic factors, studies on the mouse model for GEFS+ carrying *SCN1A* mutations have shown that voltage-gated ion channel variants in *SCN2A*, *SCN8A*, and *KCNQ2* can modify the phenotype ('modifier genes'), influencing clinical presentation and severity.[78] Several authors have reported mutations in *SCN1A* in the form of mosaicism as an important cause of familial variability (e.g., SMEI children who have inherited mutations from asymptomatic or slightly affected parents). In a recent study, mosaicism was found in 7% of the families with DS.[79]

The hypothesis suggested is that the *SCN1A* gene is dosage-sensitive and has a critical threshold with a phenotype depending on the percentage of functional sodium channels: in case of haploinsufficiency (50% functional Na^+ channel reduction) SMEI is observed; in case of mosaicism (<50% functional Na^+ channel reduction), milder phenotypes are reported. However, these observations are derived from blood lymphocytes and not from neurons.[80–84] Finally, a twin study showed that de novo mutations in *SCN1A* may occur at any time, from the premorula stage of the embryo (causing disease in the subject) to adulthood (with mutations in the germ-line cells of parents causing disease in the offspring).[85] Till now, in DS, hundreds of mutations were found in *SCN1A*, while only few mutations were identified in the paralog gene *SCN2A*, which encodes the alpha2 subunit, associated with BFNIS and BFIS and other various intractable childhood epilepsies.[86,87] Mutations of the *SCN1B* gene and the GABA receptor gamma2 subunit (*GABRG2*) gene were identified in a few families with the GEFS+ spectrum.[88,89]

6. Epilepsy and mental retardation limited to females

Epilepsy and mental retardation limited to females (EFMR) (OMIM #300088) is an epileptic encephalopathy first described in 1971[90] and then in 1997.[91] In EFMR, generalised febrile seizures start around the first year of age. Then afebrile partial, absence, and myoclonic seizures may appear. Episodes of febrile or afebrile status epilepticus are also possible. Mental abilities are normally acquired at the time of the first seizures, but successively, slowing of psychomotor development with different degrees of mental retardation is observed. Behavioural problems can manifest as autistic, obsessive, or aggressive features.[92] The gene responsible for EFMR, the *PCDH19* gene, has been recently discovered.[93,94] *PCDH19*, located on chromosome Xq22, encodes protocadherin 19, a protein with an unclear biologic role: the gene is expressed in the developing brain and may take part in neuronal connection and signal transduction. The genetic mechanism underlying the phenotypic expression of EFMR has not been completely elucidated. As specified by the name, EFMR affects the females and spares the males. Males are obligate carriers and do not develop the phenotype. Different mechanisms have been hypothesised to explain this pattern of inheritance: a dominant negative effect of the mutant protein in carrier females or the presence of a compensatory factor in males or the pathogenetic presence of mosaicism for the *PCDH19* gene in females (due to the random X inactivation process) compared to the homogeneous expression of the *PCDH19* mutated gene in males.[93] This last mechanism, called 'cellular interference', which assumes that only the co-existence of *PCDH19*-positive and *PCDH19*-negative cells is pathogenic, appears to be more probable. In addition, unrelated females with de novo *PCDH19* mutations have been described, highlighting the importance of testing *PCDH19* in females with early-onset epilepsy, intellectual impairment, and autistic features, regardless of family history.[90] It is evident that DS and EFMR share clinical features, but it is actually discussed if *PCDH19* is a new gene for DS or if EFMR is a DS-like epileptic encephalopathy 'per se'.[94] From the case series available to date, several clinical differences have been highlighted: EFMR seems to have a slightly older age of onset, no photosensitivity, less frequent status epilepticus and absence and myoclonic seizures, typical clusters of brief seizures, frequent focal seizures, and lastly, a milder degree of developmental regression and an easier control of epileptic events.[94–96] Another recent study on related and unrelated patients with *PCDH19* mutations have shown how the epileptic phenotype may be highly variable between families but also within affected members of the same family. In addition, this study has expanded the clinical spectrum of *PCDH19*-related epileptic disorders, since a family with GEFS+ features carried *PCDH19* anomalies.[97]

7. Issx-rett syndrome

The Rett syndrome (RTT) (OMIM #312750) is a progressive neurodevelopmental disorder characterised by acquired microcephaly, repetitive stereotyped hand movements, regression of mental capacities with communication dysfunction, loss of acquired speech, and cognitive impairment. Approximately 80% of the patients with RTT develop epilepsy.[98] Mutations in the methyl-CpG-binding protein 2 (*MECP2*) gene, located on Xq28, account for 80% of the patients with RTT. *MECP2* mutations are usually lethal in males, but living males with RTT carrying different types of mosaicism or mild forms of *MECP2* gene mutations have been reported.[99] Besides the classical form, different variants of RTT exist such as the congenital form, the 'forme fruste' and late childhood regression, and the infantile onset seizures type (Hanefeld syndrome). Mutations in the cyclin-dependent kinase-like 5 (*CDKL5*/*STK9*) gene have been reported in patients with phenotype overlapping that of Hanefeld syndrome and ISSX (OMIM #308350).[100–102] The *CDKL5*-associated phenotype are characterised by onset of encephalopathy with infantile spasms in the first few months of age, late drug-resistant seizures, hypotonia, and RTT-like features.[103]

CDKL5 and *MECP2* play an important pathogenic role in the genesis of RTT since cyclin-dependent kinase phosphorylates *MECP2*. Clinical overlapping features between patients with *MECP2* and *CDKL5* mutations are believed to depend on the same molecular pathway and the similar temporal and regional patterns of expression during development shared by the 2 proteins.[104] Although *MECP2* is the only known substrate of *CDKL5*, epileptic seizures associated with *CDKL5* mutations may result from abnormal phosphorylation of other unidentified proteins. In addition, differences among patients with *CDKL5*-associated encephalopathy have been reported, and this clinical heterogeneity in unrelated patients may be due to genetic factors such as X-inactivation of the same *CDKL5* gene and polymorphisms affecting the target genes of *CDKL5* and/or *MECP2*.[103]

8. Early-onset absence epilepsy

Absence seizures are epileptic manifestations that may start in children typically between the 4th and the 10th year of age (childhood absence epilepsy [CAE]). Less commonly, absence seizures may arise before the 4th year of age (early-onset absence epilepsy [EOAE]) and may be associated with other neurological disorders (other types of seizures, developmental delay, and movement disorders).[105] Mutations in 3 different genes have been reported in children with absence seizures: anomalies of the *GABRG2* gene have been described in patients with febrile seizures and CAE[106,107] and mutations in the *SCN1B* and *SCL2A1* genes have been reported in children with EOAE, with[108] or without[109] febrile seizures. A deletion of 5 amino acids in the extracellular immunoglobulin-like domain of the *SCN1B* gene, with potential loss of function of the gene, has been described in a single family with FS+ and EOAE. The authors hypothesised that *SCN1B* mutations, more often associated with GEFS+, may have a role in the elicitation of absence seizures. The *SCL2A1* gene encodes glucose transporter type 1 (GLUT1), a glucose transporter across the blood-brain barrier. *SCL2A1* is responsible for the GLUT1 deficiency syndrome (infantile-onset epilepsy with heterogeneous type of seizures, complex movement disorders, ataxia, intellectual disability, macrocephaly, and diagnostic hypoglycorrhachia with normoglycaemia and a cerebrospinal fluid/blood glucose ratio of less than 0.4)[110] and a large milder phenotypic spectrum

characterised by normal glycorrhachia, movement disorders, often normal mental capacities, and seizures (in particular absence seizures).[111] Starting from these observations, Suls et al. have found mutations in the *SCL2A1* gene in 4 (12%) of a cohort of 34 children with EOAE (3 exonic missense mutations and 1 intronic splice-site mutation). The intronic mutation creates a new splice acceptor site, generating an aberrant *SLC2A1* transcript; the missense mutations reduce the transport capacity of GLUT1, probably without affecting glucose binding, protein stability, or intracellular transport mechanisms. Clinically, the mutated patients presented with absence seizures, with onset before 4 years of age, as the predominant seizure type, in association with generalised tonic–clonic seizures (3/4) and myoclonus (1/4). The epilepsy was easily controlled in some and refractory in others; intellect ranged from normal to moderately impaired. Subtle paroxysmal dyskinesia was observed in 1 case. Thus, the earlier age of onset is the sole feature that can help distinguish the seizure phenotype of EOAE from CAE. In addition, the authors preliminarily reported a marked reduction of epileptic activity on EEG in 2 of the mutated patients receiving a ketogenic diet. In fact, it was noted that the ketogenic diet may control seizures in cases of GLUT1 deficiency syndrome.[109] Lastly, a recent study performed by the same group of authors demonstrated that the epileptic phenotypic spectrum of GLUT1 deficiency is greater than that recognised previously. In fact, the authors have reported 12 patients with *SCL2A1* mutations and epilepsy, including absence epilepsies with onset from early childhood to adult life, and various common forms of idiopathic generalised epilepsy.[112]

9. Juvenile myoclonic epilepsy

Juvenile myoclonic epilepsy (JME) or the Janz syndrome (OMIM #254770) is characterised by myoclonic seizures without loss of consciousness. Myoclonic seizures usually start around puberty, involve mainly the arms, and can develop in the form of myoclonic jerks, which can cause sudden fall. In addition, generalised tonic–clonic and absence seizures may appear. Mutations of several genes have been reported in patients with JME. Mutations of the EF-hand motif containing 1 (*EFHC1*) gene has been related to classical JME,[113] but anomalies of the $GABA_A$ receptor alpha 1 subunit (*GABRA1*) and the voltage-gated chloride channel CIC-2 (*CLCN2*) genes have been discovered in cases of idiopathic generalised epilepsy, including JME.[114–116] Higher frequency of *CHRNA4* 1674(+11)C>T polymorphism has been observed in patients with JME, suggesting that the *CHRNA4* may be one of the candidate genes for this epileptic syndrome.[117] The *EFHC1* gene encodes the EF-hand-containing calcium binding protein, which most likely plays a role in calcium homeostasis. $GABA_A$ receptors are ligand-gated chloride channels, which carry out inhibitory functions in the central nervous system.[118] The $GABA_A$ receptor is a heteropentameric protein complex made of 19 different classes of subunits (α1–6, β1–4, γ1–3, δ, ε, θ, π, and ρ1–2). The majority of the mutations occurring in one of these subunits reduce the inhibitory chloride currents.[118] Chloride currents are also altered in case of *CLCN2* gene mutations, since anomalies of the CIC-2 channels determine the impairment of chloride efflux, with intracellular accumulation of chloride; this may lead to impairment of GABAergic neuronal transmission.[116,118]

10. Autosomal dominant nocturnal frontal lobe epilepsy

Autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE) is characterised by brief (5 s–5 min) motor hyperkinetic seizures of frontal origin with tonic or dystonic features presenting in clusters during the night in non-REM sleep and most commonly, in stage 2 sleep. Daytime seizures may rarely occur. ADNFLE usually begins in the first 2 decades and is lifelong, but with older age, seizures may become milder and less frequent.[119,120] The term ADNFLE should only be used in case of presence of the typical clinical features associated with a positive family history for other affected individuals and/or a mutation in either *CHRNA4* (ADNFLE type 1; OMIM #600513), *CHRNB2* (ADNFLE type 3; OMIM #695357), or *CHRNA2* (ADNFLE type 4; OMIM #610353) genes, since the clinical features of ADNFLE are indistinguishable from those of nonfamilial nocturnal frontal lobe epilepsy.[121–123] The estimated penetrance is 70%. Mutations in *CHRNA4*, *CHRNB2*, or *CHRNA2*, which encode the neuronal acetylcholine receptor (α4, β2, and α2 subunit, respectively) can be found in around 10–20% of the individuals with a positive family history but only in around 5% of the individuals with a negative family history.[124–127] The pore-forming M2 transmembrane segments are affected by these mutations, and increased acetylcholine sensitivity is believed to be the main defect of the mutation.[1] In addition, mutations in the corticotropin-releasing hormone (*CRH*) gene of locus 15q24, which contains the *CHRNA3*, *CHRNA5*, and *CHRNB4* genes, have been identified in patients with ADNFLE.

11. Autosomal dominant partial epilepsy with auditory features or autosomal dominant lateral temporal epilepsy

This inherited epileptic syndrome was first described and named by Ottman in 1995 as autosomal dominant partial epilepsy with auditory features (ADPEAF), since partial seizures with auditory features arising from the temporal lobe are the main manifestations.[128] However, considering that ictal symptoms originating from the temporal lobe are not limited to auditory features, the term has been changed to autosomal dominant lateral temporal epilepsy (ADLTE) (OMIM #600512).[129] Seizures in ADLTE are described as focal, typically with auditory auras (e.g., ringing, singing, and whistling), with or without temporal sensory symptoms (e.g., aphasia, vertigo, and olfactory and visual phenomena), with a possible secondary generalisation with tonic–clonic manifestations. Seizures, which usually begin in young patients, may be triggered by exterior stimuli (e.g., noise or sound) and are considered to be benign and easy to control with antiepileptic drugs.[130] The leucine-rich glioma-inactivated 1 (*LGI1*) gene has been identified as the cause of familial (ADLTE) and nonfamilial partial epilepsy with auditory features (called idiopathic partial epilepsy with auditory features [IPEAF]). Mutations in *LGI1* have been found in about 50% of the ADLTE patients and in about 2% of the IPEAF patients,[131–134] and the penetrance of the mutations is around 67%.[135] The *LGI1* gene is located at 10q23.33; it is expressed mainly in the brain, with neuronal rather than glial predominance. The LGI1 protein product is not a neuronal ion channel, and its mutations may be more easily associated with mechanisms of epileptogenesis. Its biological role, and in particular, its involvement in neuronal transmission, remains unclear. The rapidly inactivating Kv1 potassium channel and ADAM22, a neuronal transmembrane receptor, are associated with the LGI1 protein, but no mutations in these 2 genes have been discovered in *LGI1*-negative ADLTE families.[136,137] Finally, a recent hypothesis suggests that the *LGI1* gene may be implied in structural brain development, and its mutations may result in cortical abnormalities of the temporal lobe, which are not visible on standard MRI but may be identified by new imaging techniques such as diffusion tensor imaging.[138]

12. Conclusions

In this review, we have summarised the rapid progress in the field of genetics, which allowed the identification of epilepsy-causing gene mutations underlying idiopathic epilepsies and

epileptic encephalopathies and resulted in the improvement of classification, prognosis, and counselling. An intriguing and hopeful challenge is the engine of targeted antiepileptic drugs, which may act on the basis of a well-known gene anomaly. For example, ezogabine (retigabine) is a new drug for adjunctive therapy of partial-onset seizures with a novel mechanism of action that consists of the opening of neuronal voltage-gated potassium KCNQ2 and 3 channels, thus promoting membrane repolarisation and opposing rapid repetitive discharges. However, it should be kept in mind that monogenic determined epileptic syndromes account only for a minority of the idiopathic epilepsies, and consequently, genetic tests should be performed after accurate clinical selection of families and probands. It is hoped that, in the near future, other epilepsy-causing genes will be discovered and other genetic and non-genetic factors responsible for the epileptic phenotypes will be clarified.

Conflicts of interest

The authors report no conflicts of interest.

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