

# Recent developments in the genetics of childhood epileptic encephalopathies: impact in clinical practice

Desenvolvimentos recentes na genética das encefalopatias epiléticas da infância: impacto na prática clínica

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## ABSTRACT

Recent advances in molecular genetics led to the discovery of several genes for childhood epileptic encephalopathies (CEEs). As the knowledge about the genes associated with this group of disorders develops, it becomes evident that CEEs present a number of specific genetic characteristics, which will influence the use of molecular testing for clinical purposes. Among these, there are the presence of marked genetic heterogeneity and the high frequency of *de novo* mutations. Therefore, the main objectives of this review paper are to present and discuss current knowledge regarding i) new genetic findings in CEEs, ii) phenotype-genotype correlations in different forms of CEEs; and, most importantly, iii) the impact of these new findings in clinical practice. Accompanying this text we have included a comprehensive table, containing the list of genes currently known to be involved in the etiology of CEEs.

**Keywords:** Dravet syndrome, Ohtahara syndrome, West syndrome, Lennox-Gastaut syndrome, Doose syndrome, Landau-Kleffner syndrome.

## RESUMO

Os avanços recentes em genética molecular permitiram a descoberta de vários genes para encefalopatias epiléticas da infância (EELs). À medida que o conhecimento sobre os genes associados a este grupo de doenças se desenvolve, torna-se evidente que as EELs apresentam uma série de características genéticas específicas, o que influencia o uso do teste molecular para fins clínicos. Entre as EELs, há a presença de acentuada heterogeneidade genética e alta frequência de mutações *de novo*. Assim, os principais objetivos deste trabalho de revisão são apresentar e discutir o conhecimento atual a respeito de i) novas descobertas em genética molecular das EELs, ii) correlações fenótipo-genótipo nas diferentes formas de EELs; e, mais importante, iii) o impacto desses novos achados genéticos na prática clínica. Acompanhando o texto, incluímos uma tabela contendo a lista de genes conhecidos atualmente como envolvidos na etiologia da EELs.

**Palavras-chave:** síndrome de Dravet, síndrome de Ohtahara, síndrome de West, síndrome de Lennox-Gastaut, síndrome de Doose, síndrome de Landau-Kleffner.

The encephalopathic effects of epileptic activity may occur in association with any form of epilepsy; however, it is more often present in a number of syndromes called childhood epileptic encephalopathies (CEEs). CEEs are conditions in which “the epileptic activity itself may contribute to severe cognitive and behavioral impairment above and beyond what might be expected from the underlying pathology alone (e.g., cortical malformation), and these can worsen over time”<sup>1</sup>.

Although the damaging effect of seizures can potentially happen in any form of epilepsy, in some syndromes this impairment is virtually always present. According to current classification<sup>1</sup>, the following syndromes are considered CEEs: early myoclonic encephalopathy (EME), Ohtahara syndrome (OS), epilepsy of infancy with migrating focal seizures (EIMFS), West syndrome (WS), Dravet syndrome, Doose syndrome or epilepsy with myoclonic atonic (previously astatic) seizures,

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Lennox-Gastaut syndrome (LGS), epileptic encephalopathy with continuous spike-and-wave during sleep (CSWS), and Landau-Kleffner syndrome (LKS). As widely recognized, each one of these different clinical entities have specific characteristics, including mainly clinical and EEG features, which make it possible to clinically recognize them; however, recent developments in the field of molecular genetics are helping to determine that there are many intermediary phenotypes, which can represent a great diagnostic challenge to clinicians. Patients presenting these transitional or less characteristic phenotypes are probably those who will benefit most of the recently available genetic diagnostic tools, which will help determining diagnosis and establishing an etiology. However, even for patients with a clinically well-defined syndrome within the group of CEEs a positive genetic test can define etiology. Therefore, the main objective of this review is to present and discuss current knowledge regarding i) new molecular genetic findings in this group of disorders; ii) the complex phenotype-genotype correlations observed in the CEEs; and, most importantly, iii) the impact of these new genetic findings in clinical practice.

## MOST COMMON CEEs

Early myoclonic encephalopathy (EME) is a neonatal epilepsy syndrome characterized by onset of myoclonic seizures usually within the first month of life and abnormal neurological signs at birth or at the moment of seizure onset<sup>2</sup>. The EEG presents with suppression-burst pattern with short paroxysmal bursts and longer periods of suppression, enhanced during sleep<sup>2</sup>. The syndrome has a poor prognosis with progressive deterioration and early death.

Ohtahara syndrome (OS), also called early infantile epileptic encephalopathy, is an age-dependent epileptic encephalopathy characterized by tonic seizures with onset at the neonatal period and EEG showing suppression-burst pattern with longer periods of bursts and shorter periods of suppression<sup>2</sup>. The prognosis is poor, with significant neurological impairment or death. Children with OS might evolve to West syndrome<sup>2</sup>.

Epilepsy of infancy with migrating focal seizures (EIMFS) is a rare epileptic syndrome characterized by onset of multifocal seizures within the first 6 months of life and an ictal EEG demonstrating seizures independently arising and moving sequentially from both hemispheres. The syndrome progresses as intractable seizures and further psychomotor delay<sup>3</sup>.

West syndrome (WS) is characterized by developmental delay, epileptic spasms and EEG showing hypsarrhythmia. It starts in the first year of life, usually after the third month. The spasms are usually refractory to anti-epileptic drugs, ACTH or steroids; therefore, the prognosis is often poor<sup>1</sup>.

Lennox-Gastaut syndrome (LGS) starts between 3 and 5 years-old. It is characterized by deterioration of cognitive and psychomotor skills, multiple seizure types (tonic, atonic,

atypical absences, generalized tonic clonic and focal), and EEG during wakefulness showing diffuse slow spike-and-waves (<2.5Hz). During sleep, EEG shows bursts of generalized fast spikes around 10 Hz<sup>4</sup>. Although LGS can evolve from WS, it may occur in a previously epilepsy free child. Both WS and LGS can be associated with structural lesions such as malformations of cortical development, vascular lesions, metabolic disorders, etc. However, several patients present with a normal MRI. Therefore, determining the etiology of CEEs in these patients represents an additional challenge.

Doose syndrome, or epilepsy with myoclonic atonic (previously astatic) seizures, is characterized by multiple seizure types such as atypical absence, atonic, tonic and myoclonic astatic seizures. Its onset is between 7 months and 6 years-old<sup>5</sup>, and the prognosis is variable. Disturbances in cognitive and psychomotor skills are often present. The EEG remains the best diagnostic tool available.

Dravet syndrome was described in 1978 under the name of severe myoclonic epilepsy of infancy<sup>6</sup>. It is characterized by febrile and afebrile generalized and unilateral, clonic or tonic clonic seizures, which occur in the first year of life in an otherwise normal infant. These can be later associated with myoclonus, atypical absences, and partial seizures, and high sensitivity even to low-degree fever is observed<sup>6,7</sup>. Between the first and fourth years of life, some degree of cognitive impairment and behavior abnormality is often present. Seizures are usually refractory to antiepileptic drug treatment. Photosensitivity may be present. However, photosensitivity can be difficult to evaluate because it may not be present during the whole course of the disease<sup>6</sup>.

Epileptic encephalopathy with continuous spike-and-wave during sleep (CSWS) is characterized by a typical EEG finding of continuous spike-and-wave discharges (usually diffuse, but sometimes focal) occurring in at least 85% of slow sleep in children with focal or, eventually, generalized seizures (electrical status epilepticus of sleep, ESES). Seizure onset usually occurs between 2 and 12 years and there is a marked neurological deterioration in cognitive, behavioral and/or motor domains<sup>8</sup>. The treatment must aim the disappearance of the ESES, which is the mechanism responsible for the encephalopathy.

Landau-Kleffner syndrome (LKS) or syndrome of acquired aphasia with convulsive disorder in children is an epileptic encephalopathy that occurs in previously normal children with normally developed age-appropriate language<sup>9</sup>. It is characterized by seizures and acquired aphasia, typically verbal auditory agnosia, with onset between 2 and 8 years. EEG during sleep of patients with LKS characteristically shows ESES.

## THE DIAGNOSIS OF CEE

The diagnosis of CEEs is still based on clinical features and EEG findings as described above. However, until

recently, the etiology in most patients was not established. The first important development to improve the determination of etiology in patients with CEE occurred in the years of 1980's with the advances in imaging techniques, especially the introduction of clinical MRI. These developments made it possible to perform *in vivo* diagnosis of malformations of cortical development. However, it also became clear that a significant proportion of patients with CEE do not have structural lesions<sup>1,7,10</sup>. It was only in the 21<sup>st</sup> century that significant advances in molecular genetics enabled the discovery that many patients with CEE actually have mutations in specific genes<sup>11</sup>.

## RECENT DEVELOPMENTS IN THE GENETICS OF CEE

Recent advances in molecular genetic technologies have allowed for the mapping and the discovery of several genes for different forms of epilepsies. Traditional approaches such as linkage analysis and candidate gene association studies enable to determine the chromosome position of genes potentially contributing to the disease by evaluating the segregation of genetic markers among affected individuals within large pedigrees or by comparing their allele frequencies between cohorts of affected and unaffected individuals. Over the last decade, new techniques for detecting variants associated with complex traits have emerged, such as genome wide association studies (GWAS), which interrogates a great number of single-nucleotide polymorphisms (SNPs) among a large group of individuals. DNA sequencing methods to detect potentially deleterious variants have also advanced from

the capillary electrophoresis technology (Sanger sequencing) to the next generation high throughput techniques, allowing for massively parallel sequencing that may include either the entire genomic sequence (whole genome sequencing, WGS) or be restricted to the protein coding sequences (whole exome sequencing, WES). Structural variations, such as deletions or duplications named copy number variants (CNVs) are also currently widely investigated by chromosome-microarrays using SNP-array technologies or arrays for complete genome hybridization (array-CGH).

This plethora of molecular genetics tools has helped to unravel the genetic factors underlying epilepsies such as the CEEs. As the knowledge on the genes associated with this group of disorders develops, it becomes evident that genetic heterogeneity is present in CEE, with many genes identified as harboring causative mutations in different patients. In addition, a surprising complex relationship between gene/mutations and phenotypes has also emerged. Therefore, we highlight the need to further assess the impact of these new molecular genetic findings in clinical practice. Below, we outline the main potentially deleterious variants currently reported for the different CEE phenotypes. The reader will clearly notice that a single phenotype (as defined by clinical and EEG aspects) is frequently associated with different causative mutations in different patients, as well as that, in several instances, mutations in the same gene may cause different CEE syndromes, exemplifying well the complex nature of the genotype/phenotype relationship, which is still in need of further studies. A comprehensive table of the genes associated with the different CEE phenotypes is presented (Table).

**Table.** List of genes associated with different childhood epileptic encephalopathies (CEEs).

Gene	Associated phenotype	References
<i>ADORA2A</i>	Acute encephalopathy with biphasic seizures and late reduced diffusion (AESD)	61
<i>ALG13</i>	Lennox-Gastaut Syndrome and/or Infantile Spasms	62
<i>ARFGEF2</i>	West Syndrome	63
<i>ARHGEF15</i>	Severe Early-onset Epilepsy	64
<i>ARHGEF9</i>	Severe mental retardation and epilepsy	65
<i>ARX</i>	Lennox-Gastaut syndrome Ohtahara Syndrome West Syndrome	16; 29; 30
<i>ASAH1</i>	Childhood-onset Epilepsy or Early-onset encephalopathy	66
<i>C10orf2</i>	Early Onset Encephalopathy Infantile onset Spinocerebellar Ataxia Syndrome	67; 68
<i>CACNA1A</i>	Lennox-Gastaut Syndrome and/or Infantile Spasms	62
<i>CACNA2D2</i>	Early infantile epileptic encephalopathies	69; 70
<i>CASK</i>	Ohtahara Syndrome	17
<i>CDKL5/ STK9</i>	Early onset encephalopathy Infantile Spasms and Mental Retardation Lennox-Gastaut syndrome West Syndrome	31; 71; 72; 73
<i>CHD2</i>	Dravet Syndrome Infantile Spasms Lennox-Gastaut syndrome	45; 62; 74; 75

Continue

## Continuation

<i>CHRNA7</i>	Congenital retinal dysfunction, Refractory epilepsy, Encephalopathy, Mental retardation, Repetitive hand movements, Severe muscular hypotonia and Macrocytosis. Severe encephalopathy with seizures and hypotonia	76; 77; 78
<i>CLCN4</i>	Severe Early-onset Epilepsy	64
<i>CNTNAP2</i>	Focal Epilepsy with Regression	79
<i>DCX</i>	Lennox-Gastaut Syndrome and/or Infantile Spasms	62
<i>DOCK7</i>	Epileptic Encephalopathy and Cortical Blindness	80
<i>EEF1A2</i>	Severe Early-onset Epilepsy	64
<i>ENG</i>	Early Infantile Epileptic Encephalopathy with suppression-burst	81
<i>ErbB4</i>	Early Mioclonic Encephalopathy	13
<i>FLNA</i>	Lennox-Gastaut Syndrome and/or Infantile Spasms	62
<i>FOLR1</i>	Childhood-onset Epilepsy or Early-onset encephalopathy	66
<i>FOXG1</i>	Rett syndrome with early-onset seizures	82; 83
<i>GABRA1</i>	Lennox-Gastaut Syndrome and/or Infantile Spasms	62
<i>GABRB3</i>	Lennox-Gastaut Syndrome and/or Infantile Spasms	62
<i>GABRG2</i>	Doose syndrome Dravet Syndrome Generalized epilepsy with febrile seizures plus (GEFS+)	45; 50; 84
<i>GNAO1</i>	Epileptic Encephalopathy with involuntary movements	85
<i>GRIN1</i>	Lennox-Gastaut Syndrome and/or Infantile Spasms	62
<i>GRIN2A</i>	Epileptic encephalopathy with continuous spike-and-wave during sleep Atypical rolandic epilepsy and speech impairment Landau-Kleffner syndrome	56; 58; 86; 87; 88
<i>GRIN2B</i>	Lennox-Gastaut Syndrome and/or Infantile Spasms Mental retardation and/or epilepsy	88; 62
<i>HCN1</i>	Early Infantile Epileptic Encephalopathy	89
<i>HDAC4</i>	Lennox-Gastaut Syndrome and/or Infantile Spasms	62
<i>HNRNPU</i>	Lennox-Gastaut Syndrome and/or Infantile Spasms	62; 90
<i>HOXD</i>	Early Infantile Epileptic Encephalopathy without Mesomelic Dysplasia	91
<i>IQSEC2</i>	Lennox-Gastaut Syndrome and/or Infantile Spasms	62
<i>JNK3</i>	Severe Developmental Epileptic Encephalopathy (Lennox-Gastaut syndrome)	42
<i>KCNH5</i>	Severe Early-onset Epilepsy	64
<i>KCNQ2</i>	Early onset epileptic encephalopathy (EOEE) Ohtahara Syndrome	18; 92; 93; 94
<i>KCNQ3</i>	Benign Familial Neonatal Seizures (BFNS) Early onset epileptic encephalopathy (EOEE)	65; 95; 96
<i>KCNT1</i>	Malignant migrating partial seizures of infancy (MMPSI) Ohtahara Syndrome	18; 22; 97
<i>KCTD7</i>	Progressive Myoclonus Epilepsy	65; 98
<i>KLF13</i>	Congenital retinal dysfunction, Refractory epilepsy, Encephalopathy, Mental retardation, Repetitive hand movements, Severe muscular hypotonia and Macrocytosis.	78
<i>MAGI2</i>	Early-onset Epileptic Encephalopathy Infantile spasms	99; 100; 101
<i>MBD5</i>	West Syndrome	90
<i>MECP2</i>	Early-onset Encephalopathy and Cortical Myoclonus Lennox-Gastaut syndrome and Rett syndrome	41; 102
<i>MEF2C</i>	Severe Intellectual Disability and Early-onset Epileptic Encephalopathy	103
<i>MTOR</i>	Lennox-Gastaut Syndrome and/or Infantile Spasms	62
<i>NECAP1</i>	Severe infantile epileptic encephalopathy	104
<i>NEDD4L</i>	Lennox-Gastaut Syndrome and/or Infantile Spasms	62
<i>NRG2</i>	Hypotonia, Feeding difficulty in infancy, Severe developmental delay, and Epileptic/ nonepileptic Encephalopathy associated with Delayed Myelination	105
<i>PCDH19</i>	Dravet Syndrome Infantile or early childhood onset epilepsy in female patients Lennox-Gastaut syndrome	45; 53; 106
<i>PCDHG</i>	Hypotonia, Feeding difficulty in infancy, Severe developmental delay, and Epileptic/ nonepileptic Encephalopathy associated with Delayed Myelination	105
<i>PIGA</i>	Early-onset Epileptic Encephalopathy	15
<i>PIGQ</i>	Ohtahara Syndrome	18
<i>PLCB1</i>	Early-onset epileptic encephalopathy Malignant migrating partial seizures in infancy	26; 62; 101

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## Continuation

<i>PNKP</i>	Early-onset Epileptic Encephalopathy Intractable Seizures and Developmental delay West Syndrome	100; 101; 107
<i>PNPO</i>	Neonatal epileptic encephalopathy	108
<i>POLG1</i>	Alpers syndrome Childhood progressive encephalopathy Severe Encephalopathy with Intractable Epilepsy	109; 110
<i>PRRT2</i>	Benign familial Infantile Epilepsy (BFIE) Infantile convulsions with choreoathetosis (ICCA) Paroxysmal kinesigenic dyskinesia (PKD)	111; 112
<i>RB1</i>	Infantile Spasms and Retinoblastoma	113
<i>SCN1A</i>	Acute Encephalopathy Doose Syndrome Dravet Syndrome Early Onset Epilepsy (EOE) Generalized Epilepsy With Febrile Seizures Plus (GEFS+) Lennox-Gastaut syndrome Malformations of Cortical Development (MCDs) Malignant Migrating Partial Seizures of Infancy West Syndrome	11; 20; 43; 47; 64; 114; 115; 116; 117; 118; 119; 120
<i>SCN1B</i>	Dravet Syndrome Generalized epilepsy with febrile seizures plus (GEFS+)	44; 52; 121
<i>SCN2A</i>	Dravet Syndrome Generalized epilepsy with febrile seizures plus (GEFS+) Intractable epilepsy Lennox-Gastaut syndrome Migrating focal seizures of infancy Ohtahara Syndrome West Syndrome	18; 19; 51; 65; 60; 122; 123
<i>SCN8A</i>	Epilepsy of infancy with migrating focal seizures Infantile epileptic encephalopathy and SUDEP Lennox-Gastaut syndrome	21; 62; 124
<i>SERPINI1</i>	Continuous Spike and Waves during slow-wave Sleep	55
<i>SLC19A3</i>	Epileptic spasms in early infancy Severe psychomotor retardation	125
<i>SLC25A22</i>	Early myoclonic encephalopathy Epilepsy of infancy with migrating focal seizures Neonatal Epileptic Encephalopathy with Suppression Burst	12; 24; 126
<i>SLC2A1</i>	Doose Syndrome GLUT1 deficiency with neurodevelopmental delay and severe ataxia	46; 127
<i>SLC35A2</i>	Early-onset Epileptic Encephalopathy	128
<i>SLC9A6</i>	Continuous Spike and Waves during slow-wave Sleep and Christianson syndrome	57
<i>SNAP25</i>	Severe Static Encephalopathy, Intellectual disability, and Generalized Epilepsy	129
<i>SPTAN1</i>	West Syndrome	39; 130
<i>SRGAP2</i>	Early infantile epileptic encephalopathy	131
<i>SRPX2</i>	Rolandic epilepsy associated with oral and speech dyspraxia and mental retardation	132
<i>STXBP1</i>	Borderline Early myoclonic encephalopathy and Ohtahara Syndrome Early infantile epileptic encephalopathy Lennox-Gastaut syndrome Ohtahara Syndrome West Syndrome	14; 38; 62; 101; 133; 134
<i>SYNGAP1</i>	Early-onset epileptic Encephalopathy	45; 66
<i>SYNJ1</i>	Childhood-onset Epilepsy or Early-onset encephalopathy	66
<i>SZT2</i>	Early-onset Epileptic Encephalopathy characterized by Refractory Epilepsy and Absent Developmental Milestones	135
<i>TBC1D24</i>	Familial Infantile Myoclonic Epilepsy Focal epilepsy and Intellectual disability syndrome Malignant Migrating Partial Seizures of Infancy (MMPSI) Ohtahara Syndrome	23; 136
<i>TCF4</i>	Pitt-Hopkins syndrome (PHS)	137
<i>TNK2</i>	Infantile onset Epilepsy and Intellectual Disability	138
<i>TOR1A</i>	Early Infantile Epileptic Encephalopathy	81
<i>TRPM1</i>	Congenital retinal dysfunction, Refractory epilepsy, Encephalopathy, Mental retardation, Repetitive hand movements, Severe muscular hypotonia and Macrocytosis.	78

### Early myoclonic encephalopathy (EME)

Up until the last decade, little about the etiology of EME was known, and a scarcity of familial cases had been reported. Linkage analysis of a family with severe neonatal epilepsies with suppression-burst pattern revealed genetic mapping to chromosome 11p15.5, followed by the identification of a missense mutation in the gene encoding a mitochondrial glutamate/H symporter, *SLC25A22*, cosegregating with the disease<sup>12</sup>. The authors then performed *SLC25A22* mutation screening in 25 additional EME patients, but found no mutation. Furthermore, a *de novo* translocation t(2;6)(q34;p25.3) has been reported in a patient with EME and profound psychomotor delay<sup>13</sup>. Fluorescence *in situ* hybridization (FISH) analysis revealed that one breakpoint disrupts the erythroblastic leukemia viral oncogene homolog 4 gene *ErbB4*, involved in the regulation of cell growth, proliferation and differentiation and that have been associated with schizophrenia<sup>13</sup>. More recently, mutations in two other candidate genes for EME have been reported. Targeted capture and sequencing of candidate genes for early onset epileptic encephalopathy (EOEE) detected a *de novo* splice site mutation in the syntaxin binding protein 1 gene (*STXBPI*), involved in the neurotransmitters release regulation, in a borderline patient with EME/OS<sup>14</sup>. This gene is also involved in the etiology of other CEEs, as it will be further presented in this paper. The other candidate gene is *PIGA*, encoding an enzyme required for the biosynthesis of a phosphatidylinositol glycan anchor, in which a nonsense mutation with an uncertain mode of inheritance was identified by WES in a sporadic case of EME previously diagnosed as OS<sup>15</sup>.

### Ohtahara syndrome (OS)

Although OS may arise from a variety of etiologies, mainly involving structural abnormalities, a number of different genes have recently been associated with this syndrome. The first report of a genetic basis for OS was a *de novo* 33-bp duplication identified by direct sequencing<sup>16</sup>. This deletion comprises the aristaless-related homeobox gene *ARX*, essential for the development of interneurons, and results in an expansion of the first polyalanine tract of the ARX protein. *ARX* mutations had already been implicated in a range of phenotypes including brain malformations with abnormal genitalia and nonsyndromic mental retardation, thus the identification of an *ARX* mutation in OS suggests a continuum between these phenotypes, with a common pathological mechanism possibly caused by impairment in the  $\gamma$ -aminobutyric acid (GABA) ergic interneurons<sup>16</sup>. Further studies contributed to increase the knowledge on the association of *ARX* with OS, with the report of additional mutations identified by direct sequencing. However, a percentage of OS cases still do not present *ARX* mutations<sup>17</sup>. Copy number variations (CNVs) have also been implicated in the etiology of OS, such as a *de novo* 2Mb deletion at 9q33.3–q34.11 identified by aCGH and a 111-kb deletion at Xp11.4 detected by genomic microarray

analysis<sup>17</sup>. Mutation analysis of the *STXBPI* gene, included in the 9q33.3–q34.11 region, revealed *de novo* missense, frameshift and splice-site mutations<sup>14</sup>. The 111-kb deletion comprises the calcium/calmodulin-dependent serine protein kinase gene *CASK*<sup>17</sup>. Interestingly, a *de novo* translation initiation mutation in the same *CASK* gene was detected in a second patient with OS<sup>17</sup>. Recently, genes encoding ion channels have also been associated with OS. One of them is the gene encoding the voltage-gated potassium channel Kv7.2 (*KCNQ2*), in which *de novo* missense mutations were found in patients with OS and neonatal epileptic encephalopathies resembling OS<sup>18</sup>. Another ion channel associated with OS is the voltage-gated sodium channel Nav1.2 (*SCN2A*), in which *de novo* missense mutations were also identified<sup>18</sup>. Mutations in both *KCNQ2* and *SCN2A* are involved in a wide clinical spectrum of EOEEs, which overlap each other including benign phenotypes such as benign familial neonatal seizures, but also severe forms of CEEs. Recently, a WGS study also revealed two novel genes for OS: *KCNT1*, which encodes the potassium channel KCa4.1, and *PIGQ*, encoding a subunit of an N-acetylglucosaminyltransferase involved in the glycosylphosphatidyl inositol (GPI) biosynthesis<sup>18</sup>.

### Epilepsy of infancy with migrating focal seizures (EIMFS)

The first genetic study in malignant EIMFS investigating genes encoding different ion channels yielded no deleterious mutations. Later, however, mutation screening of voltage-gated sodium channel subunit genes revealed *de novo* missense mutations in *SCN2A* (Nav1.2)<sup>19</sup>, *SCN1A* (Nav1.1)<sup>20</sup> and *SCN8A* (Nav1.6)<sup>21</sup>. In addition, WES analysis allowed for the detection of *de novo* missense mutations in another ion channel gene, *KCNT1* (KCa4.1)<sup>22</sup>. WES analysis also enabled the identification of novel candidate genes for EIMFS, such as the *TBC1D24* gene<sup>23</sup> and *SLC25A22*<sup>24</sup>. Furthermore, CNVs appear to account for a few cases of EIMFS. Distinct studies revealed a 598 Kb microduplication at chromosome 16p11.2<sup>25</sup>, an 11.06 Mb deletion of chromosome 2q24.2q31.1, comprising more than 40 genes including *SCN1A*<sup>20</sup> and a deletion of chromosome 20p13, disrupting the phospholipase C, beta 1 gene *PLCB1*<sup>26</sup>. Even with these recent advances regarding the genetic basis of EIMFS, the etiology of a number cases remain unclear, as other studies investigating candidate genes failed to identify potential disease-causing mutations<sup>22</sup>.

### West syndrome (WS)

The first evidence about the genetic basis of WS came from genetic linkage analysis, with the mapping of an X-linked form of WS to chromosome Xp11.4 and Xp21.3–Xp22<sup>27,28</sup>. Mutation screening of the *ARX* gene located within the candidate region in families with X-linked WS revealed a 24-bp duplication; an expansion of seven tandem triplets repeats, both resulting in an additional polyalanine stretch; and a 1.517 bp deletion promoting a frameshift<sup>29</sup>. Frameshift and missense

mutations were subsequently found in the same *ARX* gene in patients diagnosed with WS or those who evolved to WS from an OS phenotype<sup>30</sup>.

A second chromosomal locus for X-linked WS was identified distal to *ARX* in the Xp22.3 region, with the subsequent report of two apparently balanced X;autosome translocations detected by FISH and Southern blot hybridization<sup>31</sup>. In both cases, the breakpoint mapped to the cyclin-dependent kinase-like 5 gene, *CDKL5* (also known as serine/threonine kinase 9, *STK9*). However, screening for potentially deleterious *CDKL5* mutations in additional WS cohorts yielded negative results. Other chromosomal anomalies associated with WS include partial 4p trisomy<sup>32</sup>, balanced translocations t(X;18)(p22;p11.2)<sup>33</sup> and t(2;6)(p15;p22.3)<sup>34</sup>, microdeletions on chromosomes 9q34.11 and 15q13.3<sup>35</sup>, duplications on chromosome 14<sup>36</sup> and a 0.5 Mb triplication (partial tetrasomy) of chromosome 17q25.3<sup>37</sup>. Additionally, mutation screening of *STXBPI* and the  $\alpha$ -II spectrin gene *SPTANI*, both located within the microdeleted region on chromosome 9q34.11, revealed a *de novo* *STXBPI* missense mutation<sup>38</sup> and an in-frame 3 bp *de novo* deletion, a 6 bp and a 9 bp *de novo* duplications in *SPTANI*<sup>39</sup> in patients with WS. However, further *STXBPI* and *SPTANI* mutation screening in other cohorts revealed no mutations<sup>39</sup>. Other studies, usually single case-reports, found mutations in several other genes. A few cases of mitochondrial DNA mutation have also been reported. This genetic heterogeneity could be explained by the multiple mechanisms/lesions which can ultimately lead to the WS phenotype, including malformations of cortical development and a primarily mitochondrial disorder.

### Lennox-Gastaut syndrome (LGS)

The etiology of LGS is highly heterogeneous, with the majority of cases resulting from a brain structural abnormality, but also including genetic factors. Mutations in a variety of genes that might be associated with LGS or LGS-like phenotypes have been reported, although there is still scarcity of systematic genetic analyses of cohorts with LGS. Among these genes, some have been already associated with other types of CEEs, such as *SCN1A*, *SCN2A*, *CHD2*, *CDKL5*, *ARX* and *STXBPI*. However, other studies failed to detect causative mutations in patients with LGS in these candidate genes. Most of the mutations identified to date were detected using WES or targeted massively parallel sequencing, which also allowed for the identification of *de novo* mutations in several other genes.

Several pathological CNVs have also been identified in patients with LGS: a microduplication of 15q11–q13 was reported in patients with late-onset LGS<sup>40</sup>. Furthermore, a 22q13.3 deletion, a 2q23.1 deletion, a duplication encompassing the *MECP2* gene, and a deletion including the chromodomain helicase DNA binding protein 2 gene (*CHD2*), were also detected by aCGH in patients with LGS<sup>41</sup>. Another chromosome abnormality identified in a patient with a severe

developmental delay and CEE consistent with LGS was a balanced translocation t(Y;4)(q11.2;q21), which truncates the c-Jun N-terminal kinase 3 (*JNK3*) gene<sup>42</sup>.

### Doose syndrome

Since the description of Doose syndrome, hereditary factors have been suspected of being involved, most likely presenting a polygenic inheritance. The hypothesis of a genetic etiology for this phenotype was later supported by studies showing affected members in families with generalized febrile seizures plus (GEFS+) harboring mutations in *SCN1A*<sup>43</sup>, *SCN1B*<sup>44</sup> and *GABRG2*. However, only one member of each family investigated had Doose syndrome, and these individuals all had some atypical features. Moreover, subsequent studies of these candidate genes in sporadic and familial cases of Doose syndrome yielded no causative mutations. Additional studies investigating several other candidate genes also did not find causative mutations in patients with typical Doose syndrome.

To date, the majority of mutations associated with Doose syndrome were identified by target sequencing of *SCN1A*. In addition, two patients with Doose syndrome from the same large pedigree and a patient from another cohort showed missense mutations in *GABRG2*<sup>45</sup>. This same study performed targeted massively parallel sequencing, which also enabled the identification of two *de novo* frameshift mutations in the *CHD2* gene in two other patients with Doose syndrome<sup>45</sup>. More recently, another gene has risen as a potential candidate for Doose syndrome, the *SLC2A1*, which encodes the glucose transporter 1 (GLUT1), associated with a severe metabolic encephalopathy involving movement disorder and epilepsy<sup>46</sup>. However, multiplex ligation-dependent probe amplification analysis (MLPA) did not reveal any structural rearrangements in *SLC2A1*. The importance of seeking mutations in *SLC2A1* (GLUT1) is that these patients appear to respond to ketogenic diet which should be introduced when molecular diagnosis is confirmed<sup>7,46</sup>.

### Dravet syndrome

Initially, linkage studies allowed for the identification of a locus for GEFS+ on chromosome 2, with subsequent detection of mutations in *SCN1A*<sup>43</sup>. Clinical similarities between some patients with GEFS+ and Dravet syndrome motivated Claes et al.<sup>47</sup> to further investigate mutations in *SCN1A* in patients with Dravet syndrome; thus, leading to the discovery of the first mutations in patients with Dravet syndrome. After this first report, several mutations in *SCN1A* have been identified, with an overall frequency of mutations of approximately 70–80% in patients with Dravet syndrome. Therefore, *SCN1A* can be considered today as one of the most clinically relevant genes for genetic epilepsy<sup>48</sup>. Interestingly, mutations in *SCN1A* in patients with Dravet syndrome frequently arise *de novo*; while in GEFS+ they are usually inherited as an autosomal dominant trait<sup>48</sup>. In addition, structural changes, CNVs,

in *SCN1A* have been identified in a percentage of patients with Dravet syndrome, making it important to use more than one molecular technique to completely study potential deleterious changes in *SCN1A* in patients with this phenotype<sup>49</sup>.

Several studies have been performed to identify novel candidate genes for Dravet syndrome in *SCN1A*-negative patients. *GABRG2* nonsense mutations have been identified, one in a family with GEFS+ and the other in dizygotic twins with Dravet syndrome<sup>50</sup>. However, another study failed to identify mutations in *GABRG2* in a group of patients with Dravet syndrome. In addition, nonsense and missense mutations in *SCN2A* were found in other cohorts<sup>51</sup>. Homozygous missense mutations in *SCN1B* have also been identified<sup>52</sup>. Depienne et al.<sup>53</sup> investigated micro-rearrangements by high-density SNP microarrays, which led to the discovery of a hemizygous deletion encompassing the protocadherin 19 gene (*PCDH19*). Subsequent *PCDH19* target sequencing of additional subjects led to the identification of nonsense, frameshift and missense mutations. Recent WES and target sequencing studies analyzing cohorts of patients with CEE presenting some features of Dravet syndrome also revealed mutations in additional candidate genes. In addition, although Dravet syndrome is fundamentally considered a monogenic disease, the hypothesis of a complex inheritance in some patients has recently emerged, with the identification of a few modulating genes that might be involved in the etiology of Dravet syndrome. Therefore, it is clear that even in a somewhat clinically well-defined phenotype such as Dravet syndrome the presence of marked genetic heterogeneity occurs.

### Epileptic encephalopathy with continuous spike-and-wave during sleep (CSWS)

To date, little is known about the genetic basis of CSWS, with only one concordant pair of monozygotic twins reported<sup>54</sup> and few mutations identified. Later, though, a missense mutation in the neuroserpin gene *SERPINI1* (also known as proteinase inhibitor 12 gene, *PII2*) was found in one patient who presented EEG activity suggestive of CSWS<sup>55</sup>.

It is currently recognized that there is a continuous spectrum comprising rolandic epilepsy, CSWS and LKS, suggesting that these phenotypes may share a common genetic etiology. This assumption is supported by the recent finding of different types of *de novo* or inherited mutations in *GRIN2A* in patients with CSWS belonging to families segregating epilepsy-aphasia syndrome disorders. In these families there were patients with variable phenotypes such as LKS, CSWS, and atypical rolandic epilepsy and speech impairment<sup>56</sup>. *GRIN2A* encodes a subunit of the N-methyl-D-aspartate receptor, involved in the mediation of excitatory neurotransmission. More recently, an inherited homozygous splice-site mutation was identified in *SLC9A6* in a patient with clinical features of Christianson syndrome and CSWS<sup>57</sup>. *SLC9A6* encodes a sodium-hydrogen exchanger protein and had already been implicated in Christianson syndrome. In addition,

CNVs localized in genes that may be involved in predisposition to electrical status epilepticus during sleep have also been detected in patients with CSWS<sup>59</sup>.

### Landau-Kleffner syndrome (LKS)

Up until recently, scarce information regarding the genetic factors involved in the etiology of LKS was available, with only few cases reported<sup>9</sup>. Lately, investigation of CNVs in LKS patients using array-CGH led to the identification of a 15q13.3 microdeletion<sup>59</sup> and rare CNVs such as a microdeletion on chromosome 16p13, comprising the *GRIN2A* gene<sup>58</sup>. Subsequent *GRIN2A* mutation screening by target sequencing and WES revealed mutations in familial and isolated patients with LKS<sup>56</sup>. The identification of several *de novo* and inherited mutations in *GRIN2A* in both LKS and CSWS supports the hypothesis of a clinical spectrum with a similar genetic basis for both disorders<sup>56</sup>.

### IMPACT OF THE NEW GENETIC FINDINGS IN CLINICAL PRACTICE

As described above, the recent genetic findings in the group of CEEs are starting to shed some light on the different molecular mechanisms underlying several types of CEEs. It also becomes clear that genetic heterogeneity is a rule with different genes causing the same phenotype, as well as clinical heterogeneity with several genes causing different subtypes of CEE. The presence of genetic heterogeneity and clinical variability represent a major challenge when assessing the impact of these genetic discoveries in clinical practice. In addition, the vast range of molecular genetic technologies currently available can overwhelm the clinician, thus decision making regarding the most suitable technique for detecting genetic variants for each patient is not an easy task.

Nonetheless, the establishment of a correct molecular diagnosis has important practical applications as well as significant emotional impact for patients and parents. The fact that most abnormalities present in patients with CEE are *de novo* mutations has important implications for genetic counseling, since parents will most likely be found not to have these mutations and, therefore, the risk of recurrence in the same sibship will be the same as in the general population (except in rare cases of somatic mosaicism present in one of the parent's germ line)<sup>48</sup>. Furthermore, one cannot minimize the positive emotional impact of a molecular diagnosis for the parents of children with CEE. In general, once a cause for the disease is determined, even when curative therapies cannot be adopted, parents stop searching for a diagnosis and can concentrate on treatment options and rehabilitation.

In addition, the specific diagnosis can influence treatment decisions such as the need to avoid sodium-blockers antiepileptic drugs such as carbamazepine and phenytoin in Dravet syndrome and *SCN1A* mutation-positive patients, or



the specific indication of the use of ketogenic diet in patients with *GLUT1* mutations<sup>48</sup>.

Although very genetically heterogeneous, there are a few genes for which specific mutation screening may still be useful in the context of CEEs. One of these is *SCN1A*, which harbors mutation in almost 80% of patients with Dravet syndrome. In addition, a few mutations in *SCN1A* have also been reported in other types of CEEs. Therefore, one may consider genetic testing for *SCN1A* useful in all CEEs, although the most important indication of *SCN1A* genetic testing is still within the clinical limits of Dravet syndrome.

Another gene for which mutation screening may be very useful for clinical purposes in patients with CEEs is *ARX*. Mutations in this gene are mainly found in OS, but also in WS patients that evolved from OS or from families with OS affected members and even in a patient that later evolved to LGS<sup>30</sup>. It has been suggested that *ARX* testing should be performed in children younger than one year old with OS and a movement disorder, as well as in children with unexplained neurodegeneration, progressive white matter loss, and cortical atrophy.

*STXBPI* should also be considered for genetic testing in OS, as several mutations have been associated with this phenotype. For other CEE, however, the clinical utility of *STXBPI* genetic test remains unclear, as mutations have been reported only in a single patient with WS not preceded by OS, and in a few patients with LGS and Dravet syndrome.

*GRIN2A* is another gene that has recently emerged as a strong candidate for epilepsy-aphasia spectrum disorders that include LKS and CSWS<sup>56</sup>. Thus, *GRIN2A* genetic testing appears to be particularly relevant for these phenotypes.

*KCNQ2* and *SCN2A* genetic testing should be considered for patients with EOEE, although genotype-phenotype correlations are not yet well understood<sup>60</sup>. However, it has been recognized that *KCNQ2* screening should be performed for refractory neonatal seizures of unknown origin. In addition, mutations in *PCDH19* should be considered in female patients with Dravet-like syndrome and some degree of cognitive delay and *CDKL5* mutation should be contemplated in female patients with early onset severe intractable seizures or infantile spasms with or without Rett-like phenotype. Many other genes also appear to contribute to the etiology of certain specific phenotypes within the group of CEEs, but not in a frequency that justify a specific genetic testing.

It is important to consider that with the dissemination of genomic strategies of molecular diagnosis it is possible

to adopt tests that will interrogate all candidate genes listed above at once. These can be performed as part of NGS gene panels, which should include the most suitable candidate genes for the phenotype studied<sup>60</sup>. Alternatively, high throughput strategies such as WES or even WGS can also be applied<sup>14,18</sup>. These can be useful especially when it is not clear which candidate gene is involved or for the discovery of new genes that might be responsible for the disease. The type of test indicated, target sequencing with gene panels or WES/WGS, will depend mainly on whether a specific clinical diagnosis has been achieved (e.g. Dravet syndrome) or not. Obviously, questions regarding costs are also relevant when ordering genetic tests and one should keep in mind that costs for WES/WGS are decreasing rapidly, making these alternative more attractive lately.

In addition, there are important questions regarding the most indicated molecular method for the different types of genetic defects sought<sup>48,49</sup>. In this way, it is important to point-out that a small percentage of patients with Dravet syndrome and mutations in *SCN1A* have pathological CNVs instead of sequence mutations<sup>48,49</sup>. In addition, pathological CNVs have been widely reported in patients with different degrees of mental retardation associated or not with other clinical findings, including epilepsy. Since sequencing techniques can overlook CNVs, an alternative method such as chromosomal microarray should also be considered to complement genetic investigation<sup>48,49</sup>. Moreover, there are other limitations in the use of NGS, such as sequences of genes containing multiple repeats that may interfere with correct mapping and reading, thus resulting in low sequence coverage<sup>14</sup>. Therefore, the clinician should always be aware that even the most current technology in molecular diagnosis is not a guarantee of a flawless technique.

In conclusion, it is important to recognize that the most accurate technique for diagnosis may vary according to the genetic information already available and the phenotype investigated. When a potential candidate gene is more likely, one should consider targeted sequencing which may still be more cost-effective. However, in cases where there is scarce genetic information available, WES and WGS may reveal novel causative genes. In addition, there are a number of technical questions (e.g. whether important candidate genes will be well covered) that should be considered when using gene panels and WES in order to choose the most suitable technology. Furthermore, CNV analysis should also be considered when investigating patients with CEEs.

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