Genomic studies in epilepsy

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Abstract

Epilepsy is a progressive and disabling disease if not diagnosed early; for this reason, it has been the subject of research, specially in cases with idiopathic etiology. Approximately between 1 and 2% of the world population have epilepsy. In Mexico the prevalence is from 10 to 20 patients per 1000 inhabitants. Lately, the scientific community has been trying to create, adapt, and use biomolecular tools to study its pathophysiology so that, hopefully, in a near future we are able to intervene in the natural history of this disease. The aim of this work is to cite evidence about some of the molecular biology techniques in order to support and encourage investment in neurogenomical research; as a necessary tool in the study of epilepsy.

Key words: Epilepsy. Biomolecular Tools. Neurogenomics.

Introduction

The International League Against Epilepsy (ILAE) defines an epileptic seizure as the occurrence of signs and/or symptoms due to an excessive synchronous or asynchronous abnormal neuronal activity, and epilepsy as a disease characterized by the long-term predisposition to generate epileptic seizures, as well as, by the neurobiological, cognitive, psychological, and social consequences of this condition¹.

In the world, there are >50 million people suffering from epilepsy, of which 80% live in developing countries with a prevalence of 7-14 per 1000 inhabitants, unlike the developed countries with a proportion of 4-10 per 1000 habitants².

In Mexico, a prevalence of 10-20 per 1000 habitants has been found; therefore, it can be estimated that there are approximately 1-2 million Mexicans affected³.

Etiologically, epilepsy can be classified into the following groups: symptomatic or secondary (where there is a known cause, such as tumor, neuroinfection, and congenital brain malformation), idiopathic (when genetic factors are suspected, inherited, or *de novo*, etc.), and cryptogenic (type of epilepsy in which it cannot be associated to a certain cause)⁴. Around 20-30% of epilepsies are caused by acquired conditions and 70-80% are related to one or more genetic factors⁵.

Epilepsy is considered a public health problem, due to its high morbidity and psychosocial repercussions (stigmatization or rejection) and economic (unemployment, pharmacological, and hospitalization expenses); therefore, it should be a reason for interest, investment, and research to understand the disease and provide the best care to this sector of the population. Considering the proportion of epilepsy related to genetic factors, 5 it is crucial to know the clinical, physiological,

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Date of reception: 29-07-2016
Date of acceptance: 15-03-2017
DOI: 10.24875/HGMX.M19000001

Available online: 21-03-2019
Rev Med Hosp Gen Mex. 2019;82(1):33-38
www.hospitalgeneral.mx

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Figure 1. Variations in the genome of a single base. Variants of a single nucleotide within a DNA sequence can be classified as SNP > 1% or as a point mutation <1% according to their frequency in the study population.

and genomic tools used in the diagnosis in this type of patients.

Since the publication in 1951 in JAMA by the epileptologist William G. Lennox, it was possible to confirm the importance of the genetic causes in some types of epilepsy, observed in their studies in twins⁶. Later, Watson and Crick (1953) propose the helical structure, antiparallel, and complementary to DNA⁷, researchers have used these principles for the development of molecular technology to understand and analyze the genetic material of all kinds of organisms, including humans, interest in the study of inheritance and genes, using genomics (a discipline that deals with the study of genomes, genes, and their functions, as well as related biotechnological techniques)⁸.

Advances in genomic technology are providing tools for the study of genetic factors that may be involved with different types of epilepsy. Some of the main types of studies used in epilepsy research are described below: full genome-wide association studies (GWAS), sequencing, next-generation sequencing (NGS), sequencing of whole genome (whole genome sequencing/[WGS]), complete exome sequencing (whole exome sequencing/[WES]), chromosomal microarrays (RNA and DNA microarrays) by comparative genomic hybridization (CGH) to detect copy number variations (CNVs), insertions and deletions, single-nucleotide polymorphisms (SNPs), or point mutations, (Fig. 1).

Full Genome Association Studies (GWAS)

In genetic epidemiology, a complete genome association study (GWA) uses high-throughput technologies to analyze hundreds of thousands of SNPs (SNPs, generally referring to a single-base variant in the human genome) and relates them to measurable traits,

as well as with various clinical conditions. These are studies designed to identify common genetic variants between two or more populations that contribute to a risk of disease⁹.

As an example, in 2014, the ILAE published a meta-analysis of 12 cohorts where they performed a complete genome association on 8696 patients with epilepsy and 26,157 controls. They found association of risk in the loci 2q24.3 ($p=8.71 \times 10^{-10}$) that involves the gene SCN1A and in the loci 4p15.1 ($p=5.44 \times 10^{-9}$) that involves the PCDH7 gene in patients with focal and generalized epilepsy. For patients with generalized epilepsy at the 2p16.1 loci ($p=9.99 \times 10^{-9}$), which implicate the VRK2 or FANCL genes, they could not determine an SNP with statistical significance related to focal epilepsy¹⁰. Feenstra et al.¹¹ studied through GWA children with febrile seizures as an adverse effect after the administration of the triple viral vaccine (rubella, measles, and mumps), children who did not have febrile seizures after the vaccine and finally children without a history of febrile seizures as controls. They found two risk loci related to febrile seizures after vaccination rs273259 ($p=5.9 \times 10^{-12}$ and $p=1.2 \times 10^{-9}$) involving the gene IFI44L and rs1318653 ($p=9.6 \times 10^{-11}$ and $p=1.6 \times 10^{-9}$) that involves the CD46 gene, with p values against the controls and against children who did not have febrile seizures after the vaccine, respectively. On the other hand, they found four risk loci for febrile seizures, in general, two were in known genes related to epilepsy (SCN1A and SCN2A).

Copy Number Variations (CNVs)

CNVs are defined as a DNA segment equal to or >1 kb whose number of copies is variable (duplicated or deleted) when compared to a reference genome (Fig. 2).

Figure 2. Copy number variations (CNVs). Variation in the number of copies, by loss (deletion) or gain (duplication) of a DNA segment greater than one kilobase with respect to a reference genome.

CNVs are an important source of normal genetic variation (in a frequency $>1\%$), but some may participate as risk factors or causes of disease^{5,12}. CNVs can be detected with DNA microarrays by means of CGH, array CGH, (Fig. 3)

Some rare CNVs (frequency $<1\%$) involve genes from known diseases and may be related to 5-10% in cases of childhood epilepsy^{13,14}. Helbig et al. reported the role of CNVs in patients with epilepsy, finding 88 rare CNVs in 71 patients (31.8%) >100 kb related to the disease¹⁵.

In general, research in generalized and focal epilepsy has identified recurrent microdeletions in up to 3% of

patients with idiopathic generalized epilepsy and 1% focal epilepsy. The microdeletions in the chromosomal regions 15q13.3 and 16p13.11 are the most frequently identified variants^{16,17}.

Next Generation Sequencing (NGS)

DNA sequencing refers to the determination of the order of the nucleotides of a given sequence, from some base pairs (bp) to the sequence of complete genomes. The NGS, also called mass sequencing in parallel, means that millions of small DNA fragments (around 100 bp) can be sequenced at the same time¹⁸.

Figure 3. Next-generation sequencing (NGS) determines the order of the nucleotides of a specific sequence. It can be used to determine only the coding part of a sequence (exome) or the whole sequence (genome).

At present, two types of sequencing are performed for the study of epilepsy: complete genome sequencing and complete exome sequencing (Fig. 3).

Complete Genome Sequencing (WGS)

It refers to the determination of the order of the nucleotides of the whole genome (both the coding and non-coding sequences) which covers around 3000 million bp¹⁹.

Complete Exome Sequencing (WES)

This technique allows exploring 180,000 exons or coding regions (more or less 30 million bp), which corresponds to approximately 1% of the human genome²⁰, it is estimated that 85% of the variations related to hereditary diseases are found in the exome¹⁸.

Helbig et al. evaluated the performance of exome sequencing as a diagnostic method in patients with epilepsy, finding 38.2% positive results compared to controls with $p=0.004$ value, concluding that this technique is a useful diagnostic tool, especially in severe epilepsy of early onset²¹.

In the past 10 years, the advancement of complete genome sequencing or exome techniques has allowed the identification of new genes and genetic variants involved in family epilepsies, severe epilepsies, and epileptic encephalopathies, which has had an important impact in the diagnosis of this disease. The current rate in the diagnosis of epilepsy by NGS ranges from 20% to 30% and specifically with WES is approximately 25%²².

Candidate Genes Related to Epilepsy

Some of the major genes involved in generalized epilepsy are described below:

SCN1A codes for the alpha-1 subunit of the voltage-dependent sodium channel. The transmembrane alpha subunit forms the central pore of the channel. This ion channel is critical for the generation and propagation of action potentials. The channel responds to the voltage difference across the cell membrane to create a pore that allows sodium ions to pass through the membrane. The influx of sodium creates an action potential, which is critical for signaling within the brain. Mutations of loss of function cause a reduction of

sodium currents and alteration of the signaling of the hippocampal GABAergic interneurons. Allelic variants of this gene are associated with generalized epilepsy with febrile seizures and epileptic encephalopathy. In 70-90% of cases, Dravet syndrome is caused by a *de novo* mutation in SCN1A, which often leads to a non-functional protein^{23,24}.

SCN2A encodes the alpha-II subunit of the voltage-dependent sodium channel and is found in the initial segment of the axon, nonsense mutations are observed in patients with epileptic encephalopathies where their expression is reduced on the cell surface, resulting in a net loss of function. This mutation is related to four different phenotypes such as benign neonatal and infantile epilepsy, autism and intellectual disability, infantile spasms, and early-onset epileptic encephalopathies including Ohtahara syndrome and severe neonatal epilepsy. All phenotypes within the SCN2A spectrum include cognitive disturbances, seizures, and movement disorders^{23,24}.

CACNA1A codes for the alpha-1 subunit of voltage-dependent calcium channels and mediates the entry of calcium ions into excitable cells; it is also included calcium-dependent processes including muscle contraction, hormone release, and neurotransmitter release. Mutations in this gene are related to episodic ataxias, spinocerebellar degeneration, and familial hemiplegic migraine, generalized epilepsies such as absences or Dravet syndrome, and tonic paroxysms^{23,24}.

Regarding focal epilepsy, the main candidate genes are described below:

GRIN2A encodes the alpha-2 subunit of the glutamate receptor N-methyl-D-aspartate, it is involved in long-term potentiation, an activity-dependent increase in the efficiency of synaptic transmission; the interruption of this gene is associated with the disorder of focal rolandic epilepsy, atypical benign partial epilepsy, Landau-Kleffner syndrome, and some learning disorders^{23,24}.

DEPDC5 codes for a member of the IML1 family of proteins involved in G-protein signaling pathways (mTORC1) and regulates cell growth by detecting nutrient availability; inhibition of mTOR can cause cortical dysplasia at variable sites. Mutations in this gene have been related to focal epilepsy of variable foci, nocturnal frontal lobe dominant epilepsy, and temporal mesial lobe family epilepsy^{23,24}.

LGI1 gene codes for a member of the superfamily of proteins rich in leucine (glioma rich in inactivated leucine), can regulate the activity of voltage-dependent potassium channels, and is involved in the regulation

of neuronal growth and cell survival. This gene is rearranged as the result of translocations in glioblastoma cell lines. Mutations in this gene are related to lateral temporal epilepsy^{23,24}.

The discovery of mutations in specific genes (encoders for ion channels expressed in brain neurons, neurotransmitter receptors, or molecules with assumed functions in intercellular communication) has allowed to corroborate the suspicions that the physiopathological bases of this disease seem to be related with alterations in the electrical type processes, especially those that cause alterations in the stability of the membranes^{25,26}.

The table summarizes some of the candidate genes related to epilepsy, discovered by sequencing, association studies, DNA microarrays, etc. ([Supplementary Table 1](#)).

One of the main goals in the molecular research of epilepsy is to provide personalized treatment, and some data are beginning to emerge that this may be possible, in 2014, the abnormal gain of the function of the KCNQ1 gene that codes for member 1 of the Q subfamily of potassium channels dependent on filtration and reverts with quinidine²⁷. On the other hand, personalized therapy with memantine or topiramate was also proposed in two patients with early-onset epileptic encephalopathy with mutation in the GRIN2A gene²⁸.

It is important to take into account the genetic factors related to the disease when deciding the treatment of the patient, especially if the treatment is a surgical procedure. Skjei et al. published a series of cases in which they describe the clinical and histopathological characteristics in six patients with refractory epilepsy and mutations in the SCN1A gene undergoing focal cortical resection. In all cases, patients were refractory to the surgical procedure; it was observed mild diffuse malformations of cortical development in four of six patients concluding that cortical resection may not be effective in patients with this mutation and with the neuropathological changes mentioned²⁹.

New approaches for the treatment of epilepsy are under development, experimental research based on viral vectors, genetic opto tools involving the use of light at wavelengths of 280-570 nm, to control the activity of ion channels in rhodopsin and halorhodopsin in hippocampal neurons, dentate gyrus, and cerebellum, which activate or inhibit a neuron and even several conglomerates of neuronal networks that allow a control of neuronal electrical activity and cell graft techniques in animal models; all of them are new techniques used for a future to prevent the disease or to provide the best treatment to this type of patients^{30,31}.

Conclusion

Epilepsy is considered a disease of complex inheritance, the main difficulties associated with the study of complex diseases are incomplete penetrance, genetic heterogeneity, and polygenic (or multifactorial) inheritance³². Therefore, it is not yet clear what is the role of inheritance and other genetic factors in epileptogenesis. There is currently a project called Phenotype/Epilepsy Genotype EPGP: the Epilepsy Phenome/Genome Project; it is a large-scale project involving 27 centers in the United States, Australia, Argentina and Canada with the aims of analyzing the detailed phenotype of patients, determining the genotype and discovering new genes. Genetics and genomics in epilepsy is an open field of research that has had a great break in the last 15 years, which has solved many of the cases that were previously classified as of unknown cause, however, there is still a long way to go.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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Supplementary Table 1. Epilepsy related genes

Gen	Proteína	Localización	Tipo	Alteración	Fenotipo	Técnica	Fuentes
ALG13	Asparagine-linked glycosylation 13, S. cerevisiae, homolog of glycosyltransferase 28 domain-containing 1	Xq23	SNP	- LYS94GLU - ASN107SER	EETI, EI	WES	De Ligt et al., 2012 ¹ Dimassi et al., 2016 ² Allen et al., 2013 ³ Michaud et al., 2014 ⁴ Muller, 2015 ⁵ Timal et al., 2012 ⁶
ARHGEF9	Rho guanine nucleotide exchange factor 9 (Collybistin)	Xq11	SNP	- GLY55ALA - GLN2TER	EIEE	Array CGH	Harvey et al., 2004 ⁷ Lesca et al., 2011 ⁸ Lesca et al., 2015 ⁹ Shimajima et al., 2011 ¹⁰
ARX	Aristaless-related homeobox, X-Linked	Xp21.3	Dup Del SNP	- 24-BP DUP, NT428 - PRO353LEU - 1,517-BP DUP - 33-BP DUP - 1-BP DEL, 1465G - 27-BP DUP, NT430 - TYR27TER (c. 81C-G/p.Y27X) - LEU535GLN (c. 1604T > A)	EEIT	CGH WES mRNA (ratas, Poeta et al.) HPM	Bruyere et al., 1999 ¹¹ Claes et al., 1997 ¹² Feinberg and Leahy, 1977 ¹³ Fullston et al., 2010 ¹⁴ Giordano et al., 2010 ¹⁵ Kato et al., 2004 ¹⁶ Kato et al., 2007 ¹⁷ Lesca, 2015 ⁹ Poeta et al., 2013 ¹⁸ Proud et al., 1992 ¹⁹ Stromme et al., 2002 ²⁰ Strømme et al., 1999 ²¹ Turner et al., 2002 ²²
CACNA1A	Subunidad alpha-1-a de canal P/Q de calcio dependiente de voltaje	19p13.13	SNP	- ARG1820TER	Aus, EGI	WES DES	Chan et al., 2008 ²³ Chiozza et al., 2001 ²⁴ Holman et al., 2002 ²⁵ Jouveneau et al., 2001 ²⁶ Kors et al., 2004 ²⁷
CACNA1H	Calcium channel, voltage-dependent, T type, alpha 1H subunit	16p13.3	SNP	- PHE161LEU - GLU282LYS - VAL831MET - GLY773ASP - ARG788CYS - PRO618LEU - ALA867THR	Aus, EGI	DES SSCA	Chen et al., 2003 ²⁸ Heron et al., 2007 ²⁹ Khosravani et al., 2004 ³⁰ Khosravani et al., 2005 ³¹ Vitko et al., 2005 ³²
CACNA2D1	Calcium channel, voltage-dependent. alpha2/delta subunit 1	7q11-q21	Del	- 7.5-MB deletion 7q21.11-q21.12 - 2.72-MB del en 7q21.11	ESG	GWEF Array CGH	Mefford et al., 2011 ³³ Vergult et al., 2015 ³⁴
CDKL5	Cyclin-dependent kinase-like 5	Xp22.13	Del SNP	- 1-BP DEL, 183T - IVSAS13, G-A, -1 - CYS152PHE - 4-BP DEL, 166GAAA - 2-BP DEL, 2636CT - ARG175SER - GLN834TER - VSGAS, G-T, -1 - ALA40VAL - ILE727THR - THR280LE - CYS291TYR - IVS15AS, A-C, -2 - 2-BP INS, 903GA - ARG178PRO	EEIT, EI, EMT	WES GWEF Array CGH	Archer et al., 2006 ³⁵ Elia et al., 2008 ³⁶ Bartnik et al., 2011 ³⁷ Elia et al., 2008 ³⁸ Erez et al., 2009 ³⁸ Møller, 2015 ⁹ Mefford et al., 2011 ³³ Kalscheuer et al., 2003 ³⁹ Nectoux et al., 2006 ⁴⁰ Nemos et al., 2005 ⁴¹ Rademacher et al., 2011 ⁴² Rosas-Vargas et al., 2008 ⁴³ Russo et al., 2009 ⁴⁴ Saletti et al., 2009 ⁴⁵ Scala et al., 2005 ⁴⁶ Tao et al., 2004 ⁴⁷ Van Esch et al., 2007 ⁴⁸ Weaving et al., 2004 ⁴⁹
CHD2	Chromodomain helicase DNA-binding protein 2	15q26.1	Del SNP	- 1-BP DEL, 1809G GLU1412GLYFSTER64 - ARG121TER GLY491VALFSTER13 ARG1644LYSFSTER22 - TRP548ARG - TRP1657TER - IVS15AS, A-C, -2 - ARG466TER	Síndrome de Dravet, Lennox-Gastaut y Doose. (Fotosensible) EMA, Aus	WES, Targeted sequencing	Carvill et al., 2013, ⁵⁰ Chenier et al., 2014 ⁵¹ Galizia et al., 2015 ⁵² Liu et al., 2015 ⁵³ Lund et al., 2014 ⁵⁴ Rauch et al., 2012 ⁵⁵ Suls et al., 2013 ⁵⁶ Thomas et al., 2015 ⁵⁷ Trivisano et al., 2015 ⁵⁸
CHRNA7	Cholinergic receptor, nicotinic, alpha 7	15q13.3	Del		EGG	GWAS CGH	Dibbens et al., 2009 ⁵⁹ Helbig et al., 2009 ⁶⁰ Mefford et al., 2011 ³³
CNTNAP2	Contactin-associated protein-like 2	7q35	Del	1-BP DEL, 3709G	EF con regresión. Síndrome Epilepsia Focal-Displasia Cortical	GWEF array CGH Targeted sequencing	Mefford et al., 2011 ³³ Peñagarikán et al., 2011 ⁶¹ Strauss et al., 2006 ⁶²
CSTB	Cystatin-B	21q22.3	Del SNP	- IVS1, G-C, -1 - ARG58TER - (CCCCGCCCGCCG) n EXPANSION, -12-MER EXPANSION, -PROMOTER REGION - GLY4ARG - 2-BP DEL, 2404TC - GLN71PRO	Epilepsia mioclónica progresiva (Síndrome de Haan et al., 2004 ⁶³ Unverricht-Lundborg)	Complete sequencing of the gene	Alakurti et al., 2005 ⁶⁴ Bespalova et al., 1997 ⁶⁴ de Haan et al., 2004 ⁶³ Di Giaino et al., 2002 ⁶⁶ Lafrenière et al., 1997 ⁶⁷ Laloti et al., 1997 ⁶⁸ Mazarib et al., 2001 ⁶⁹ Pennacchio et al., 1996 ⁷⁰ Virtanen et al., 1997 ⁷¹
DEPDC5	Dominio DEP 5	22q12.3	Del SNP	- TYR7TER - ARG555TER - 3-BP DEL, 488TGT - TRP1389TER - 1-BP DEL, 1122A - ARG228TER - ARG328TER - ARG1087TER - ARG487TER - ARG843TER - THR864MET - GLN140TER	EFFFM, ELFNAD, ELTMF	WES, Direct sequencing	Baulac et al., 2015 ⁷² Berkovic et al., 2004 ⁷³ Callenbach et al., 2003 ⁷⁴ Dibbens et al., 2013 ⁷⁵ Ishida et al., 2013 ⁷⁶ Klein et al., 2014 ⁷⁷ Martin et al., 2014 ⁷⁸ Picard et al., 2009 ⁷⁹ Picard et al., 2014 ⁸⁰ Scheffer et al., 2014 ⁸¹ Scheffer et al., 1998 ⁸² Xiong et al., 1999 ⁸³
DMRT2, DMRT3	Doublesex- and Mab-3-related transcription factor 2 and factor 3	9p24.3	Del		EI	Array - CGH	Epi4K Consortium and Epilepsy Phenome/Genome Project, 2015 ⁸⁴
DNM1	Dynamin 1	9q34.11	SNP	ALA177PRO LYS206ASN GLY359ALA 130982480C-T 130984491A-T	EEIT (Lennox-Gastaut), EI	WES	Møller, 2015 ⁹ Boumil et al., 2010 ⁸⁵ Deciphering Developmental Disorders Study, 2015 ⁸⁶ Dhindsa et al., 2015 ⁸⁷ EuroEPINOMICS-RES Consortium et al., 2014 ⁸⁸
DOCK7	Dedicator for cytokinesis 7	1p31.3	Del SNP	- 1-BP DEL, 2510A - ARG1237TER - SER328TER - GLU2078TER	EEIT	WES	Perrault et al., 2014 ⁸⁹
GABRA1	Gamma-aminobutyric acid (GABA) A receptor, alpha 1	5q34	SNP Del Ins	- ALA322ASP - 1-BP DEL, 975C - GLY251SER - ARG112GLN - LYS306THR - 25-BP INS - ASP219ASN	EEIT, EMJ, Aus	Array - CGH WES	Carvill et al., 2014 ⁹⁰ Cossette et al., 2002 ⁹¹ Ding et al., 2010 ⁹² Epi4K Consortium and Epilepsy Phenome/Genome Project, 2015 ⁸⁴ Lachance-Touchette et al., 2011 ⁹³ Maljevic et al., 2006 ⁹⁴
GABRB3	Gamma-aminobutyric acid A receptor, beta 3	15q11	SNP	- PRO11SER - SER15PHE - GLY32ARG	EI, TCG, T, atonicas, Aus	Array - CGH WES	Epi4K Consortium and Epilepsy Phenome/Genome Project, 2015 ⁸⁴ Tanaka et al., 2008 ⁹⁵ Urak et al., 2006 ⁹⁶
GABRG2	Receptor GABA-A, Polipéptido gamma-2	5q34	SNP	- LYS289MET - ARG43GLN - GLN351TER - ARG139GLY - ARG323GLN	EGI, CF, Aus	Candidate gene sequencing	Audenaert et al., 2006 ⁹⁷ Baulac et al., 2011 ⁹⁸ Chaumont et al., 2013 ⁹⁹ Chiu et al., 2008 ¹⁰⁰ Frugier et al., 2007 ¹⁰¹ Harkin et al., 2002 ¹⁰² Kananura et al., 2002 ¹⁰³ Kang et al., 2006 ¹⁰⁴ Lachance-Touchette et al., 2011 ⁹³ Sancar and Czajkowski, 2004 ¹⁰⁵ Tan et al., 2007 ¹⁰⁶ Wallace et al., 2001 ¹⁰⁷
GNAO1	Guanine nucleotide-binding protein alpha activating	16q12.2	SNP Del	- ILE279ASN - ASP174GLY - 21-BP DEL, NT572 - GLY203ARG	EEIT	CGH WES	Lesca, 2015 ⁹ Nakamura et al., 2013 ¹⁰⁸
GRIN2A	Glutamate receptor, ionotropic, N-methyl D-aspartate 2A	16p13.2	SNP	GLN218TER IVS4DS, G-A, +1 ASN615LYS LEU649VAL PRO522ARG MET11THR THR531MET IVS5AS, A-G, -2 ARG518HIS PHE652VAL ARG681TER TYR943TER	SEA, EF	WES	Møller, 2015 ⁹ Carvill et al., 2013 ¹⁰⁹ Endele et al., 2010 ¹¹⁰ Lesca et al., 2013 ¹¹¹ Schme et al., 2013 ¹¹² Scheffer et al., 1995 ¹¹³
HCN1	Hyperpolarization-activated cyclic nucleotide-gated potassium channel 1	5p12	SNP	ASP401HIS SER100PHE SER272PRO ARG297THR HIS279TYR	EEIT	CGH WES	Lesca, 2015 ⁹ Nava et al., 2014 ¹¹⁴
HDAC4	Histone deacetylase 4	2q37.3			EEIT	WES	Møller, 2015 ⁹
HIP1	Huntingtin interacting Protein 1	7q11			EI	Array - CGH	Epi4K Consortium and Epilepsy Phenome/Genome Project, 2015 ⁸⁴
KCNQ2	Potassium channel, voltage-gated, KQT-like subfamily, member 2	20q13.3	SNP Ins Del	TYR284CYS ALA306THR 5-BP INS 1-BP DEL, 1846T ARG214TRP ARG207TRP LYS526ASN SER247TRP 10-BP DEL/1-BP INS, NT761 1-BP DEL, 2127T ARG207GLN ARG213GLN MET549VAL GLY290ASP ALA265VAL	EEIT, ENFB	CGH WES	Lesca, 2015 ⁹ Bassi et al., 2005 ¹¹⁵ Berkovic et al., 1994 ¹¹⁶ Biervert et al., 1998 ¹¹⁷ Biever and Steinlein, 1999 ¹¹⁸ Borgatti et al., 2004 ¹¹⁹ Dedeck et al., 2003 ¹²⁰ del Giudice et al., 2000 ¹²¹ Heron et al., 2007 ¹²² Saitou et al., 2012 ¹²³ Singh et al., 1998 ¹²⁴ Weckhuysen et al., 2012 ¹²⁵ Wuttke et al., 2007 ¹²⁶ Yang et al., 1998 ¹²⁷ Zimprich et al., 2006 ¹²⁸
KCNT1	Potassium channel, sodium-activated subfamily T, member 1	9q34.4	SNP	ARG428GLN ALA934THR ARG474HIS ILE760MET ARG928CYS TYR796HIS ARG396GLN MET896ILE PHE932ILE GLY288SER	ELFNAD, EICFM	WES	Barcia et al., 2012 ¹²⁹ Derry et al., 2008 ¹³⁰ Heron et al., 2012 ¹³¹ Ishii et al., 2013 ¹³² Møller et al., 2015 ⁹ Ohba et al., ¹³³ Vanderver et al., 2014 ¹³⁴
LGI1	Leucine-rich gene, glioma inactivated 1	10q23.33	SNP Del	GLU383ALA 1-BP DEL, 835C IVS3AS, C-A, -3 CYS46ARG 1320C-T PHE318CYS IVS5DS, G-A, +1 LEU232PRO ARG1385TRP ILE122LYS 81-KB DEL	ELTMF	Direct sequencing CNV analysis	Chabrol et al., 2007 ¹³⁵ Fioravanti et al., 2012 ¹³⁶ Fertig et al., 2003 ¹³⁷ Kalachikov et al., 2002 ¹³⁸ Morante-Redolat et al., 2002 ¹³⁹ Nobile et al., 2009 ¹⁴⁰ Strieder-Piquier et al., 2006 ¹⁴¹ Striano et al., 2008 ¹⁴²
PCDH19	Protocadherin 19	Xq22.1	SNP Ins Dup	1-BP INS, 1091C VAL441GLU GLN65TER SER671TER 1-BP INS, 2030T GLU48TER 5-BP DUP, NT1036 ASN557LYS	EEIT en mujeres (Ohtahara, Dravet)	Microarrays, Systematic resequencing	Deplienne et al., 2009 ¹⁴³ Dibbens et al., 2008 ¹⁴⁴ Hynes et al., 2010 ¹⁴⁵
PLCB1	Phospholipase C, beta-1	20p12.3	Del	0.5-MB DEL	EEIT, CPMMI	CGH Genome-wide scan	Lesca, 2015 ⁹ Kurian et al., 2010 ¹⁴⁶ Poduri et al., 2012 ¹⁴⁷
PNKP	Polynucleotide kinase 3 phosphatase	19q13.33	SNP Dup Del	GLU326LYS 17-BP DUP, NT1250 LEU176PHE 17-BP DEL	EEIT, Microcefalia-Crisis y Retraso Mental	CGH Genome-wide scan	Lesca, 2015 ⁹ Shen et al., 2010 ¹⁴⁸
PRRT2	Proline-rich transmembrane protein 2	16p11.2	Dup Ins SNP Del	1-BP DUP, 649C 1-BP INS, 629C SER317ASN IVS2DS, G-A, +5 ARG240TER 1-BP INS, 516T GLN163TER GLN188TER 1-BP DEL, 629C 1-BP DEL, 291C GLN250TER 1-BP DEL, 650G	CIF, CERA	WES	Møller, 2015 ⁹ Chen et al., 2011 ¹⁴⁹ Heron et al., 2012 ¹⁵⁰ Lee et al., 2012 ¹⁵¹ Meneret et al., 2012 ¹⁵² Ono et al., 2012 ¹⁵³ Pelzer et al., 2014 ¹⁵⁴ Schubert et al., 2012 ¹⁵⁵ Striano et al., 2006 ¹⁵⁶ Wang et al., 2011 ¹⁵⁷ Weber et al., 2004 ¹⁵⁸
RYR3	Ryanodine receptor 3	15q13.3			EEIT	WES	Møller, 2015 ⁹
SCN1A	Sodium voltage-gated channel alpha subunit 1	2q24.3	SNP Del	ARG1648HIS THR875MET ASP188VAL VAL1353LEU ILE1656MET TRP1204ARG 2-BP DEL, 657AG ARG222TER LEU986PHE LYS1270THR VAL1428ALA THR1708ILE VAL1611PHE MET1455THR IVS5N + 5G-A 1-BP DEL, 2528G DEL EX21-26 6.5-Kb DEL 1-BP DEL, 3608A ALA1699GLU ARG962GLY	Síndrome de Dravet, CF familiares, EEIT	WES SSCA Multiplex ligation-dependent probe amplification	Abou-Khalil et al., 2001 ¹⁵⁹ Baulac et al., 1999 ¹⁶⁰ Buoni et al., 2006 ¹⁶¹ Carranza Rojo et al., 2011 ¹⁶² Claes et al., 2001 ¹⁶³ Deplienne et al., 2009 ¹⁴³ Escayg et al., 2000 ¹⁶⁵ Freilich et al., 2011 ¹⁶⁵ Mantegazza et al., 2005 ¹⁶⁷ McArdle et al., 2008 ¹⁶⁸ Moultard et al., 1999 ¹⁶⁹ Mulley et al., 2005 ¹⁷⁰ Ohmori et al., 2002 ¹⁷¹ Orriero et al., 2009 ¹⁷² Petrovsky et al., 2009 ¹⁷³ Schlachter et al., 2009 ¹⁷⁴ Vahedi et al., 2009 ¹⁷⁵ Zucca et al., 2008 ¹⁷⁶
SCN2A	Sodium channel, voltage-gated, type II, alpha subunit	2q24.3		ARG188TRP LEU1330PHE LEU1563VAL VAL892ILE ARG232GLN ARG1319GLN LEU1003ILE ARG102TER GLU1211LYS ILE1473MET ALA263VAL MET253VAL	EEIT	Direct sequencing, WES, Genome-wide analysis.	Berkovic et al., 2004 ¹⁷⁷ Heron et al., 2002 ¹⁷⁸ Kamiya et al., 2004 ¹⁷⁹ Liao et al., 2014 ¹⁸⁰ Malacarne et al., 2001 ¹⁸¹ Ogiwara et al., 2009 ¹⁸² Sugawara et al., 2001 ¹⁸³
SCN8A	Sodium channel, voltage-gated, type VIII, alpha subunit	12q13.13	SNP	ASN1768ASP LEU1290VAL ARG1617GLN ASN1466LYS ASN1466THR ARG223GLY ASN984LYS GLY1451SER	EEIT SUDEP	WES Targeted capture sequencing	Blanchard et al., 2015 ¹⁸⁴ Carvill et al., 2013 ⁹⁰ De Kobel et al., 2014 ¹⁸⁵ Ohba et al., 2014 ¹⁸⁶ Veeramah et al., 2012 ¹⁸⁶
SLC2A1	Solute carrier family 2 (facilitated glucose transporter), member 1	1p34.2	SNP	ARG232CYS ARG223PRO ARG458TRP ASN411SER	EGI	Direct sequencing, PCR sequencing	Arsov et al., 2012 ¹⁸⁷ Striano et al., 2012 ¹⁸⁸ Suls et al., 2009 ¹⁸⁹
SLC25A22	Solute carrier family 25 (mitochondrial carrier, glutamate) member 22	11p15.5	SNP	PRO208LEU GLY236TRP GLY110ARG	EEIT	CGH WES	Lesca, 2015 ⁹ Molinari et al., 2005 ¹⁹⁰ Poduri et al., 2013 ¹⁹¹
SLC26A1	Solute carrier family 26, (anion exchanger), member 1	4p16			SEA	GWEF array CGH	Mefford et al., 2011 ³⁰
SLC35A2	Solute carrier family 35 (UDP-galactose transporter) member 2	Xp11.23	Del SNP	2-BP DEL, 433TA 1-BP DEL, 972T SER213PHE	EEIT	CGH WES	Lesca, 2015 ⁹ Nakamura et al., 2013 ¹⁰⁸
SPTAN1	Alpha, non-erythrocytic, spectrin 1	9q34.11	Del Dup	3-BP DEL, 6619GAG 6-BP DUP, NT5923 3-BP DEL, NT6605 9-BP DUP, NT6908	EEIT	CGH Direct sequencing.	Lesca, 2015 ⁹ Hamdan et al., 2012 ¹⁹² Nonoda et al., 2013 ¹⁹³ Saitou et al., 2010 ¹⁹⁴
STXBP1	Syntaxin-binding protein 1	9q34.11	SNP	GLY544ASP CYS180TYR MET442ARG VAL84ASP ARG388TER IVS3DS, G-A, +1 GLU283LYS	EIEE	WES	Møller, 2015 ⁹ Carvill et al., 2014 ¹⁹⁵ Hamdan et al., 2009 ¹⁹⁶ Saitou et al., 2008 ¹⁹⁶
STX1B	Syntaxin 1B	16p11.2			Síndromes asociados con epilepsia febril	WES	Møller, 2015 ⁹
ST3GAL3	ST3 beta-galactoside alpha-2,3-sialyltransferase 3	1p34.1	SNP	ALA320PRO	EEIT	CGH WES	Lesca, 2015 ⁹ Edvarson et al., 2013 ¹⁹⁷
SYNGAP1	Synaptic RAS-GTPase-activating protein 1	6p21.32	SNP	PRO562LEU TRP267TER ARG1433TER c. 321_324del c. 427C > T/p.Arg143	EEIT, mioclónicas, Aus	WES	Barry et al., 2013 ¹⁹⁸ Carvill et al., 2013 ¹⁹⁹ Mignot et al., 2016 ²⁰⁰
SZT2	Seizure threshold 2, mouse homolog	1p34.2	SNP	ARG26TER GLN698TER c. 1496G-T -	EEIT	CGH WES	Basel-Vanagaite et al., 2013 ²⁰⁰ Lesca, 2015 ⁹
TAS2R1, FAM173B, CCT5, MTRR	Taste receptor, type 2, member 1/family with sequence similarity 173, member B/chemokine receptor 5/5-methyltetrahydrofolate-homocysteine methyltransferase reductase	5p15			FS, focal, TCG, aA, SE	Array - CGH	Epi4K Consortium and Epilepsy Phenome/Genome Project, 2015 ⁸⁴
TBC1D24	TBC1 domain family, member 24	16p13.3	SNP Del	ASP147HIS ALA509VAL PHE251LEU PHE229SER CYS156TER	EEIT, EMIF	CGH Candidate gene sequencing	Lesca, 2015 ⁹ Corbett et al., 2010 ²⁰¹ Duru et al., 2012 ²⁰² Falace et al., 2010 ²⁰³ Guven and Tolun, 2013 ²⁰⁴ Mih et al., 2013 ²⁰⁵ Zara et al., 2000 ²⁰⁶
UBE3A	Ubiquitin protein ligase E3A	15q11	Del		EMA	GWEF array CGH	Mefford et al., 2011 ³³

GWAS: Genome Wide Association Study; WES: Whole Exome Sequencing; Array-CGH: Array Comparative Genome Hybridization; NGS: Next Generation Sequencing; HPM: Highly Polymorphic Microsatellites; DES: Direct Exon Sequencing; SSCA: Single-Stranded Conformation Analysis; EF: Epilepsia Focal; TCG: Crisis Tónico Clónica Generalizada; T: Crisis Tónicas; CF: Crisis Febriles; aA: Ausencias Atípicas; SE: Status Epiléptico; Aus: Ausencias; EMA: Epilepsia Mioclónica Atónica; SEA: Síndrome Epilepsia Atípica; ESG: Epilepsia Sintomática Generalizada; EMJ: Epilepsia Mioclónica Juvenil; EET: Encéfalo Epilepsia Infantil Temprana; EGG: Epilepsia Generalizada Genética; EII: Espasmos Infantiles; ESI: Epilepsia Generalizada Idiopática; CICA: Convulsiones Infantiles y Coreo-Atetosis; EICFM: Epilepsia Infantil con Crisis Focales Migratorias; CPMMI: Crisis Parciales Malignas Migratorias de la Infancia; EMT: Epilepsia Mioclónica Tardía; EFFF: Epilepsia Focal Familiar de Focos Múltiples; ELFNAD: Epilepsia del Lóbulo Frontal Nocturno Autosómica Dominante; ELTMF: Epilepsia del Lóbulo Temporal Mesial Familiar; ENFB: Epilepsia Neonatal Familiar Benigna; CIF: Crisis Infantiles Familiares; SUDEP: Sudden Unexpected Death of someone with Epilepsy; EMIF: Epilepsia Mioclónica Infantil Familiar

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