Revista médica del
Hospital General de México

PERMANYER

Check for updates

REVIEW ARTICLE

Genomic studies in epilepsy

*Diana E. Guzmán-Jiménez[1,2], Erika L. Flores-Ramírez[2,3] and Ana L. Velasco-Monroy[2]**

[1]Programa de Doctorado en Ciencias Biomédicas, UNAM, Mexico City; [2]Clinica de Epilepsia, Unidad de Neurocirugía Funcional y Estereotaxia, Unidad de Neurología y Neurocirugía, Hospital General de México, Mexico City; [3]Estudiante de Servivio Social en Investigación, Universidad Nacional Autónoma de Guadalajara, Jalisco. Mexico

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 condition[1].

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 habitants[2].

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 affected[3].

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 factors[5].

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,

Correspondence:
Ana Luisa Velasco-Monroy
E-mail: analuisav@yahoo.com

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

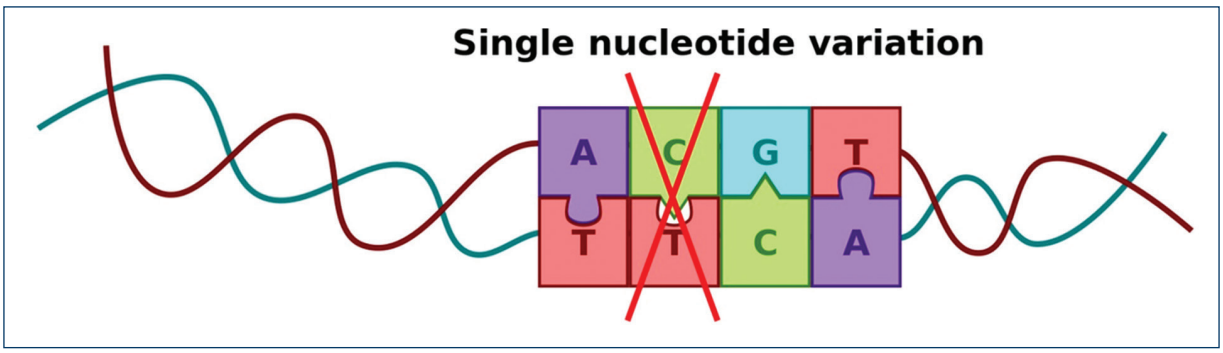

Figure 1. Variations in the genome of a single base. Variants of a single nucleotide within a DNA sequence can be classified as SNP> 1% or as a point mutation <1% according to their frequency in the study population.

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 twins[6]. Later, Watson and Crick (1953) propose the helical structure, antiparallel, and complementary to DNA[7], 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 disease[9].

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=8.71×10−10) that involves the gene SCN1A and in the loci 4p15.1 (p=5 44×10−9) that involves the PCDH7 gene in patients with focal and generalized epilepsy. For patients with generalized epilepsy at the 2p16.1 loci (p=9.99×10−9), which implicate the VRK2 or FANCL genes, they could not determine an SNP with statistical significance related to focal epilepsy[10]. 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=5.9×10−12 and p=1.2×10−9) involving the gene IFI44L and rs1318653 (p=9.6×10−11 and p=1.6×10−9) 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).

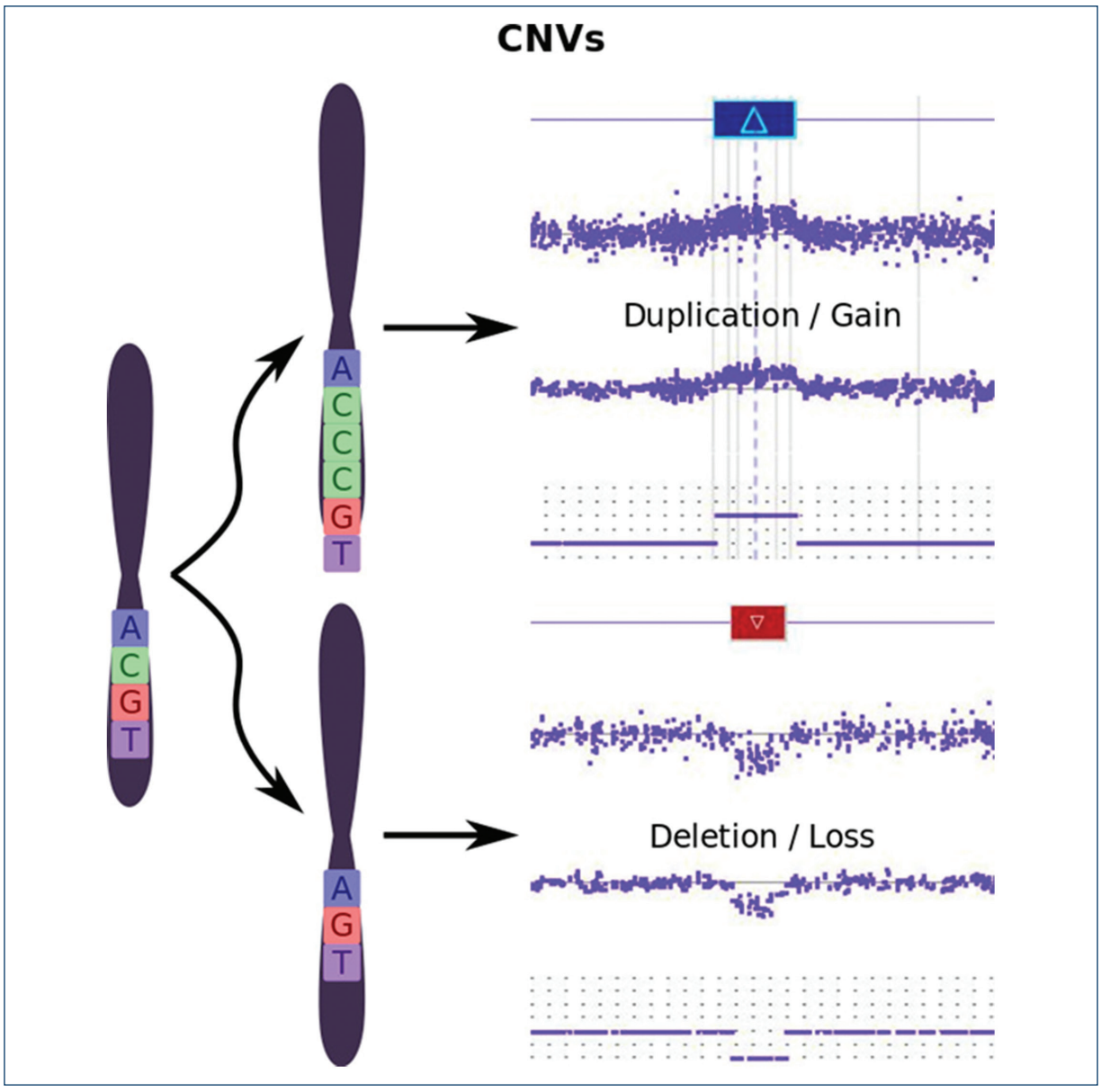

Figure 2. Copy number variations (CNVs). Variation in the number of copies, by loss (deletion) or gain (duplication) of a DNA segment greater than one kilobase with respect to a reference genome.

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 disease[15].

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 time[18].

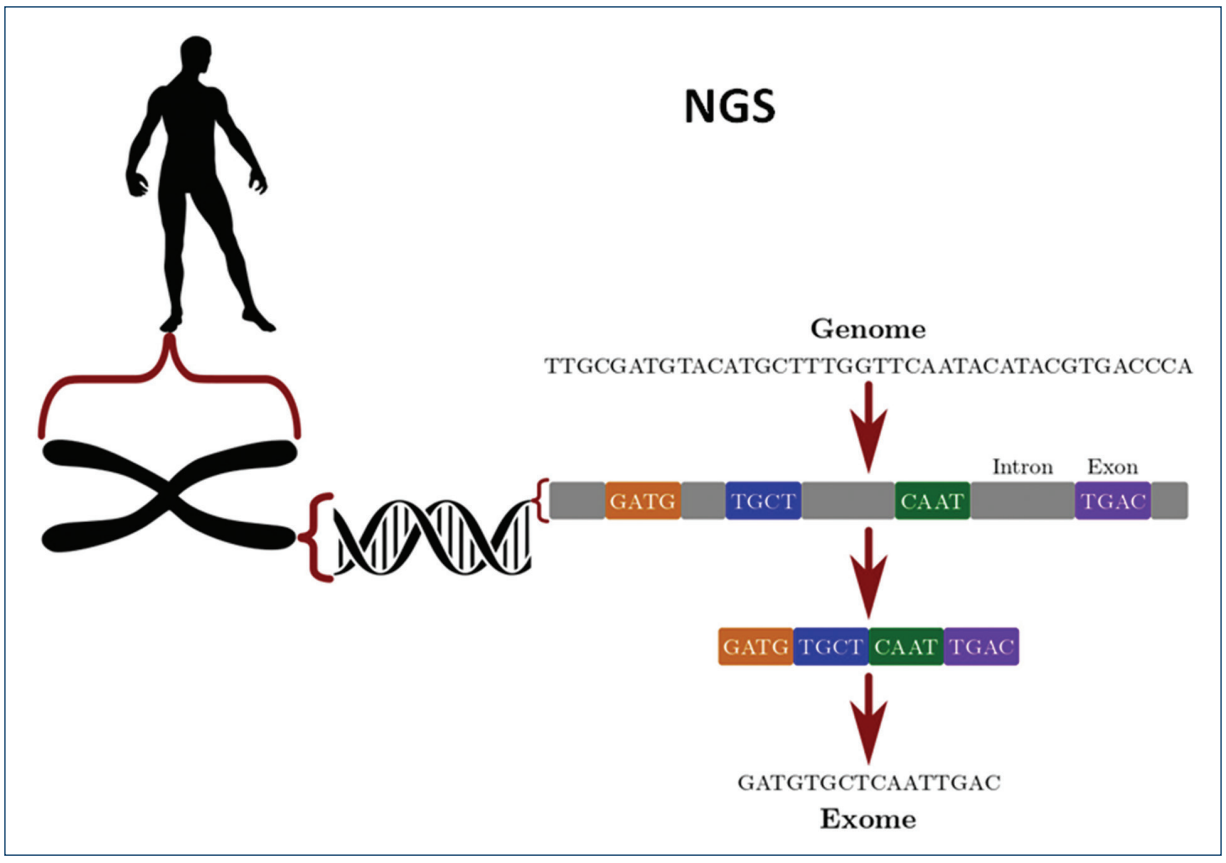

Figure 3. Next-generation sequencing (NGS) determines the order of the nucleotides of a specific sequence. It can be used to determine only the coding part of a sequence (exome) or the whole sequence (genome).

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 bp[19].

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 genome[20], it is estimated that 85% of the variations related to hereditary diseases are found in the exome[18].

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 onset[21].

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 quinidine[27]. 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 gene[28].

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 mentioned[29].

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) inheritance[32]. 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.

References

1. Fisher RS, Acevedo C, Arzimanoglou A, et al. ILAE official report: a practical clinical definition of epilepsy. Epilepsia. 2014;55:475-82.
2. OMS, Organización Mundial de la Salud. Available from: http://www.who.int/mediacentre/factsheets/fs999/en/. [Last accessed on 2016 Jul 17].
3. Programa Prioritario de Epilepsia. Frecuencia en México. Available from: http://www.epilepsiamexico.gob.mx/info-pacientes/frecuencia.htm. [Last accessed on 2016 Jul 17].
4. Epilpsy Society. Available from: https://www.epilepsysociety.org.uk/causes-epilepsy#.V8MuCSYoDtQ. [Last accessed on 2016 Jul 17].
5. Myers CT, Mefford HC. Advancing epilepsy genetics in the genomic era. Genome Med. 2015;7:91.
6. Lennox WG. The heredity of epilepsy as told by relatives and twins. J Am Med Assoc. 1951;146:529-36.
7. Watson JD, Crick FH. Molecular structure of nucleic acids; A structure for deoxyribose nucleic acid. Nature. 1953;171:737-8.
8. Genomics and World Health: report of the Advisory Committee on Health Research. Geneva: WHO; 2002. Available from: http://www.who.int/genomics/geneticsVSgenomics/en/. [Last accessed on 2016 Jul 17].
9. Wan X, Yang C, Yang Q, et al. Predictive rule inference for epistatic interaction detection in genome-wide association studies. Bioinformatics. 2010;26:30-7.
10. International League Against Epilepsy Consortium on Complex Epilepsies. Electronic address: epilepsy-austin@unimelb.edu.au. Genetic determinants of common epilepsies: a meta-analysis of genome-wide association studies. Lancet Neurol. 2014;13:893-903.
11. Feenstra B, Pasternak B, Geller F, et al. Common variants associated with general and MMR vaccine-related febrile seizures. Nat Genet. 2014;46:1274-82.
12. Hastings PJ, Lupski JR, Rosenberg SM, Ira G. Mechanisms of change in gene copy number. Nat Rev Genet. 2009;10:551-64.
13. Olson H, Shen Y, Avallone J, et al. Copy number variation plays an important role in clinical epilepsy. Ann Neurol. 2014;75:943-58.
14. Mefford HC, Yendle SC, Hsu C, et al. Rare copy number variants are an important cause of epileptic encephalopathies. Ann Neurol. 2011;70:974-85.
15. Helbig I, Swinkels ME, Aten E, et al. Structural genomic variation in childhood epilepsies with complex phenotypes. Eur J Hum Genet. 2014;22:896-901.
16. Mefford HC, Muhle H, Ostertag P, et al. Genome-wide copy number variation in epilepsy: novel susceptibility loci in idiopathic generalized and focal epilepsies. PLoS Genet. 2010;6:e1000962.
17. Heinzen EL, Radtke RA, Urban TJ, et al. Rare deletions at 16p13.11 predispose to a diverse spectrum of sporadic epilepsy syndromes. Am J Hum Genet. 2010;86:707-18.
18. Jiménez-Escrig A, Gobernado I, Sánchez-Herranz A. Secuenciación de genoma completo: un salto cualitativo en los estudios genéticos. Rev Neurol. 2012;54:692-8.
19. Martin HC, Kim GE, Pagnamenta AT, et al. Clinical whole-genome sequencing in severe early-onset epilepsy reveals new genes and improves molecular diagnosis. Hum Mol Genet. 2014;23:3200-11.
20. Kumar A, Turner E, Shendure J. Targeted capture and massively parallel sequencing of the human exome. J Investig Med. 2010;58:123.
21. Helbig KL, Farwell Hagman KD, Shinde DN, et al. Diagnostic exome sequencing provides a molecular diagnosis for a significant proportion of patients with epilepsy. Genet Med. 2016;18:898-905.
22. Møller RS, Dahl HA, Helbig I. The contribution of next generation sequencing to epilepsy genetics. Expert Rev Mol Diagn. 2015;15:1531-8.
23. The ILAE Genetics Commission Blog. Beyond the Ion Channel. Available from: http://www.epilepsygenetics.net/the-epilepsiome/scn1a-this-is-what-you-need-to-know/. [Last accessed on 2016 Mar 17].
24. Gene Cards. Available from: http://www.genecards.org/, 2016. [Last accessed on 2016 Mar 04].
25. Baulac S. Genetics advances in autosomal dominant focal epilepsies: focus on DEPDC5. Prog Brain Res. 2014;213:123-39.
26. Labate A, Gambardella A, Andermann E, et al. Benign mesial temporal lobe epilepsy. Nat Rev Neurol. 2011;7:237-40.
27. Milligan CJ, Li M, Gazina EV, et al. KCNT1 gain of function in 2 epilepsy phenotypes is reversed by quinidine. Ann Neurol. 2014;75:581-90.
28. Pierson TM, Yuan H, Marsh ED, et al. GRIN2A mutation and early-onset epileptic encephalopathy: personalized therapy with memantine. Ann Clin Transl Neurol. 2014;1:190-8.
29. Skjei KL, Church EW, Harding BN, et al. Clinical and histopathological outcomes in patients with SCN1A mutations undergoing surgery for epilepsy. J Neurosurg Pediatr. 2015;16:668-74.
30. Kovac S, Walker MC. Recent advances in epilepsy. J Neurol. 2014; 261:837-41.
31. Ortiz-Vilchis CM. Modelos experimentales en optogenética y su aplicación en enfermedades neurodegenerativas motoras. Rev Med Inv. 2015;3:107-68.
32. Lopes-Cendes I, Ribeiro PA. Aspectos genéticos de las epilepsias: una visión actualizada. Rev Méd Clín Las Condes. 3013;24:909-14.

Revista médica del
Hospital General de México

Check for updates

REVIEW ARTICLE

Genomic studies in epilepsy

Diana E. Guzmán-Jiménez[1,2], Erika L. Flores-Ramírez[2,3] and Ana L. Velasco-Monroy[2]*

[1]Programa de Doctorado en Ciencias Biomédicas, UNAM, Mexico City, Mexico; [2]Clinica de Epilepsia, Unidad de Neurocirugía Funcional y Estereotaxia, Unidad de Neurología y Neurocirugía, Hospital General de México, México; [3]Estudiante de Servivio Social en Investigación, Universidad Nacional Autónoma de Guadalajara, Ciudad de México, México

Supplementary Table 1. Epilepsy related genes

Gen	Proteina	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] Møller, 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] Shimojima et al., 2011[10]
ARX	Aristaless-related homeobox, X-Linked	Xp21.3	Dup Del SNP	- 24-BP DUP, NT428 - PRO353LEU - 1,517-BP DEL - 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] Strømme 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] Chioza et al., 2001[24] Holtmann et al., 2002[25] Jouvenceau 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 - ALA876THR	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 - VS6AS, G-T, -1 - ALA40VAL - ILE72THR - THR288ILE - CYS291TYR - 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[36] Erez et al., 2009[38] Møller, 2015[5] Mefford et al., 2011[33] Kalscheuer et al., 2003[39] Nectoux et al., 2006[40] Nemos et al., 2009[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] Peñagarikan et al., 2011[61] Strauss et al., 2006[62]
CSTB	Cystatin-B	21q22.3	Del SNP	- IVS1, G-C, -1 - ARG68TER - (CCCCGCCCCGCG) n EXPANSION, -12-MER EXPANSION, -PROMOTER REGION - GLY4ARG - 2-BP DEL, 2404TC - GLN71PRO	Epilepsia mioclónica progresiva (Síndrome de Unverricht-Lundborg)	Complete sequencing of the gene	Alakurtti et al., 2005[63] Bespalova et al., 1997[64] de Haan et al., 2004[65] Di Giaimo et al., 2002[66] Lafrenière et al., 1997[67] Lalioti et al., 1997[68] Mazarib et al., 2001[69] Pennacchio et al., 1996[70] Virtaneva et al., 1997[71]
DEPDC5	Dominio DEP 5	22q12.3	Del SNP	- TYR7TER - ARG555TER - 3-BP DEL, 488TGT - TRP1369TER - 1-BP DEL, 1122A - ARG239TER - 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., 2000[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, 201[55] 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] Maljevik 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 MET1THR THR531MET IVS5AS, A-G, -2 ARG518HIS PHE652VAL ARG681TER TYR943TER	SEA, EF	WES	Møller, 2015[5] Carvill et al., 2013[109] Endele et al., 2010[110] Lesca et al., 2013[111] Lemke 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[5]
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 MET546VAL GLY290ASP ALA265VAL	EEIT, ENFB	CGH WES	Lesca, 2015[9] Bassi et al., 2005[115] Berkovic et al., 1994[116] Biervert et al., 1998[117] Bievert and Steinlein, 1999[118] Borgatti et al., 2004[119] Dedek et al., 2003[120] del Giudice et al., 2000[121] Heron et al., 2007[122] Saitsu 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 ARG398GLN 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[5] 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 ARG136TRP ILE122LYS 81-KB DEL	ELTMF	Direct sequencing CNV analysis	Chabrol et al., 2007[135] Fanciulli 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] Sirerol-Piquer et al., 2006[141] Striano et al., 2008[142]
PCDH19	Protocadherin 19	Xq22.1	SNP Ins Dup	1-BP INS, 1091C VAL441GLU GLN85TER SER671TER 1-BP INS, 2030T GLU48TER 5-BP DUP, NT1036 ASN557LYS	EEIT en mujeres (Ohtahara, Dravet)	Microarrays, Systematic resequencing	Depienne 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, CICA	WES	Møller, 2015[5] 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[5]
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 THR1709ILE VAL1611PHE MET145THR IVS5N + 5G-A 1-BP DEL, 2528G DEL EX21-26 6.5-Kb DEL 1-BP DEL, 3608A ALA1669GLU ARG862GLY	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] Depienne et al., 2009[143] Dichgans et al., 2005[164] Escayg et al., 2000[165] Freilich et al., 2011[165] Mantegazza et al., 2005[167] McArdle et al., 2008[168] Moulard et al., 1999[169] Mulley et al., 2005[170] Ohmori et al., 2002[171] Orrico 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 ARG223GLN ARG1319GLN LEU1003ILE ARG102TER GLU1211LYS ILE1473MET ALA263VAL MET252VAL	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., 2010[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[50] De Kobel et al., 2014[185] Ohba et al., 2014[133] 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	PRO206LEU 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, NT6923 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] Saitsu et al., 2010[194]
STXBP1	Syntaxin-binding protein 1	9q34.11	SNP	GLY544ASP CYS180TYR MET443ARG VAL84ASP ARG388TER IVS3DS, G-A, +1 GLU283LYS	EIEE	WES	Møller, 2015[5] Carvill et al., 2014[195] Hamdan et al., 2009[190] Saitsu et al., 2008[196]
STX1B	Syntaxin 1B	16p11.2			Síndromes asociados con epilepsia febril	WES	Møller, 2015[5]
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 ARG143TER c. 321_324del c. 427C > T/p.Arg143	EEIT, mioclónicas, Aus	WES	Barryer et al., 2013[198] Carvill et al., 2013[199] Mignot et al., 2016[50]
SZT2	Seizure threshold 2, mouse homolog	1p34.2	SNP	ARG25TER 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 2-BP DEL, 969GT PHE229SER CYS156TER	EEIT, EMIF	CGH Candidate gene sequencing	Lesca, 2015[9] Corbett et al., 2010[201] Duru et al., 2010[202] Falace et al., 2010[203] Guven and Tolun, 2013[204] Milh 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 Microsatellite; DES: Direct Exon Sequencing; SSCA: Single-Stranded Conformation Analysis; EF: Epilepsia Focal; TCG: Crisis Tónico Clónicas Generalizadas; T: Crisi Tónicas; CF: Crisis Febriles; aA: Ausencias Atípicas; SE: Status Epiléptico; Aus: Ausencias; EMA: Epilepsia Mioclónica-Atónica; SEA: Síndrome Epilepsia-Afasia; ESG: Epilepsia Sintomática Generalizada; EMJ: Epilepsia Mioclónica Juvenil; EEIT: Encefalopatía Epiléptica Infantil Temprana; EGG: Epilepsia Generalizada Genética; EI: Espasmos Infantiles;; EGI: 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; EFFFM: Epilepsia Focal Familiar de Focos Múltiples; ELFNAD: Epilepsia del Lóbulo Frontal Nocturna Autosómica Dominante; ELTMF: Epilepsia del Lóbulo Temporal Mesial Familiar; ENFB: Epilepsia Neonatal Familiar Benigna; CIF: Crisis Infantiles Familares; SUDEP: Suden Unexpected Death of someone with Epilepsy; EMIF: Epilepsia Mioclónica Infantil Familiar

REFERENCES

1. de Ligt J, Willemsen MH, van Bon BW, et al. Diagnostic exome sequencing in persons with severe intellectual disability. N Engl J Med. 2012;367:1921-9.
2. Dimassi S, Labalme A, Ville D, et al. Whole-exome sequencing improves the diagnosis yield in sporadic infantile spasm syndrome. Clin Genet. 2016;89:198-204.
3. Epi4K Consortium, Epilepsy Phenome/Genome Project, Allen AS, et al. De novo mutations in epileptic encephalopathies. Nature. 2013;501:217-21.
4. Michaud JL, Lachance M, Hamdan FF, et al. The genetic landscape of infantile spasms. Hum Mol Genet. 2014;23:4846-58.
5. Møller RS, Dahl HA, Helbig I. The contribution of next generation sequencing to epilepsy genetics. Expert Rev Mol Diagn 2015;15:1531-8.
6. Timal S, Hoischen A, Lehle L, et al. Gene identification in the congenital disorders of glycosylation Type I by whole-exome sequencing. Hum Mol Genet. 2012;21:4151-61.
7. Harvey K, Duguid IC, Alldred MJ, et al. The GDP-GTP exchange factor collybistin: an essential determinant of neuronal gephyrin clustering. J Neurosci. 2004;24:5816-26.
8. Lesca G, Till M, Labalme A, Vallee D, et al. De novo xq11.11 microdeletion including ARHGEF9 in a boy with mental retardation, epilepsy, macrosomia, and dysmorphic features. Am J Med Genet A. 2011;155A: 1706-11.
9. Lesca G, Depienne C. Epilepsy genetics: the ongoing revolution. Rev Neurol. 2015;171:539-57.
10. Shimojima K, Sugawara M, Shichiji M, et al. Loss-of-function mutation of collybistin is responsible for X-linked mental retardation associated with epilepsy. J Hum Genet. 2011;56:561-5.
11. Bruyere H, Lewis S, Wood S, MacLeod PJ, Langlois S. Confirmation of linkage in X-linked infantile spasms (West syndrome) and refinement of the disease locus to xp21.3-xp22.1. Clin Genet. 1999;55:173-81.
12. Claes S, Devriendt K, Lagae L, et al. The X-linked infantile spasms syndrome (MIM 308350) maps to xp11.4-xpter in two pedigrees. Ann Neurol. 1997;42:360-4.
13. Feinberg AP, Leahy WR. Infantile spasms: case report of sex-linked inheritance. Dev Med Child Neurol. 1977;19:524-6.
14. Fullston T, Brueton L, Willis T, et al. Ohtahara syndrome in a family with an ARX protein truncation mutation (c.81C>G/p.Y27X). Eur J Hum Genet. 2010;18:157-62.
15. Giordano L, Sartori S, Russo S, et al. Familial ohtahara syndrome due to a novel ARX gene mutation. Am J Med Genet A. 2010;152A:3133-7.
16. Kato M, Das S, Petras K, et al. Mutations of ARX are associated with striking pleiotropy and consistent genotype-phenotype correlation. Hum Mutat. 2004;23:147-59.
17. Kato M, Saitoh S, Kamei A, et al. A longer polyalanine expansion mutation in the ARX gene causes early infantile epileptic encephalopathy with suppression-burst pattern (Ohtahara syndrome). Am J Hum Genet. 2007;81:361-6.
18. Poeta L, Fusco F, Drongitis D, et al. A regulatory path associated with X-linked intellectual disability and epilepsy links KDM5C to the polyalanine expansions in ARX. Am J Hum Genet. 2013;92:114-25.
19. Proud VK, Levine C, Carpenter NJ. New X-linked syndrome with seizures, acquired micrencephaly, and agenesis of the corpus callosum. Am J Med Genet. 1992;43:458-66.
20. Strømme P, Mangelsdorf ME, Shaw MA, et al. Mutations in the human ortholog of aristaless cause X-linked mental retardation and epilepsy. Nat Genet. 2002;30:441-5.
21. Strømme P, Sundet K, Mørk C, et al. X linked mental retardation and infantile spasms in a family: new clinical data and linkage to xp11.4-xp22.11. J Med Genet. 1999;36:374-8.
22. Turner G, Partington M, Kerr B, Mangelsdorf M, Gecz J. Variable expression of mental retardation, autism, seizures, and dystonic hand movements in two families with an identical ARX gene mutation. Am J Med Genet. 2002;112:405-11.
23. Chan YC, Burgunder JM, Wilder-Smith E, et al. Electroencephalographic changes and seizures in familial hemiplegic migraine patients with the CACNA1A gene S218L mutation. J Clin Neurosci. 2008;15:891-4.
24. Chioza B, Wilkie H, Nashef L, et al. Association between the alpha(1a) calcium channel gene CACNA1A and idiopathic generalized epilepsy. Neurology. 2001;56:1245-6.
25. Holtmann M, Opp J, Tokarzewski M, Korn-Merker E. Human epilepsy, episodic ataxia Type 2, and migraine. Lancet. 2002;359:170-1.
26. Jouvenceau A, Eunson LH, Spauschus A, et al. Human epilepsy associated with dysfunction of the brain P/Q-type calcium channel. Lancet. 2001;358:801-7.
27. Kors EE, Melberg A, Vanmolkot KR, et al. Childhood epilepsy, familial hemiplegic migraine, cerebellar ataxia, and a new CACNA1A mutation. Neurology. 2004;63:1136-7.
28. Chen Y, Lu J, Pan H, et al. Association between genetic variation of CACNA1H and childhood absence epilepsy. Ann Neurol. 2003;54:239-43.
29. Heron SE, Khosravani H, Varela D, et al. Extended spectrum of idiopathic generalized epilepsies associated with CACNA1H functional variants. Ann Neurol. 2007;62:560-8.
30. Khosravani H, Altier C, Simms B, et al. Gating effects of mutations in the cav3.2 T-type calcium channel associated with childhood absence epilepsy. J Biol Chem. 2004;279:9681-4.
31. Khosravani H, Bladen C, Parker DB, et al. Effects of cav3.2 channel mutations linked to idiopathic generalized epilepsy. Ann Neurol. 2005;57:745-9.
32. Vitko I, Chen Y, Arias JM, et al. Functional characterization and neuronal modeling of the effects of childhood absence epilepsy variants of CACNA1H, a T-type calcium channel. J Neurosci. 2005;25:4844-55.
33. Mefford HC, Yendle SC, Hsu C, et al. Rare copy number variants are an important cause of epileptic encephalopathies. Ann Neurol. 2011;70:974-85.
34. Vergult S, Dheedene A, Meurs A, et al. Genomic aberrations of the CACNA2D1 gene in three patients with epilepsy and intellectual disability. Eur J Hum Genet. 2015;23:628-32.
35. Archer HL, Evans J, Edwards S, et al. CDKL5 mutations cause infantile spasms, early onset seizures, and severe mental retardation in female patients. J Med Genet. 2006;43:729-34.
36. Elia M, Falco M, Ferri R, et al. CDKL5 mutations in boys with severe encephalopathy and early-onset intractable epilepsy. Neurology. 2008;71:997-9.
37. Bartnik M, Derwińska K, Gos M, et al. Early-onset seizures due to mosaic exonic deletions of CDKL5 in a male and two females. Genet Med. 2011;13:447-52.
38. Erez A, Patel AJ, Wang X, et al. Alu-specific microhomology-mediated deletions in CDKL5 in females with early-onset seizure disorder. Neurogenetics. 2009;10:363-9.
39. Kalscheuer VM, Tao J, Donnelly A, et al. Disruption of the serine/threonine kinase 9 gene causes severe X-linked infantile spasms and mental retardation. Am J Hum Genet. 2003;72:1401-11.
40. Nectoux J, Heron D, Tallot M, Chelly J, Bienvenu T. Maternal origin of a novel C-terminal truncation mutation in CDKL5 causing a severe atypical form of rett syndrome. Clin Genet. 2006;70:29-33.
41. Nemos C, Lambert L, Giuliano F, et al. Mutational spectrum of CDKL5 in early-onset encephalopathies: a study of a large collection of French patients and review of the literature. Clin Genet. 2009;76:357-71.
42. Rademacher N, Hambrock M, Fischer U, et al. Identification of a novel CDKL5 exon and pathogenic mutations in patients with severe mental retardation, early-onset seizures and rett-like features. Neurogenetics. 2011;12:165-7.
43. Rosas-Vargas H, Bahi-Buisson N, Philippe C, et al. Impairment of CDKL5 nuclear localisation as a cause for severe infantile encephalopathy. J Med Genet. 2008;45:172-8.
44. Russo S, Marchi M, Cogliati F, et al. Novel mutations in the CDKL5 gene, predicted effects and associated phenotypes. Neurogenetics. 2009;10:241-50.
45. Saletti V, Canafoglia L, Cambiaso P, et al. A CDKL5 mutated child with precocious puberty. Am J Med Genet A. 2009;149A:1046-51.
46. Scala E, Ariani F, Mari F, et al. CDKL5/STK9 is mutated in rett syndrome variant with infantile spasms. J Med Genet. 2005;42:103-7.
47. Tao J, Van Esch H, Hagedorn-Greiwe M, et al. Mutations in the X-linked cyclin-dependent kinase-like 5 (CDKL5/STK9) gene are associated with severe neurodevelopmental retardation. Am J Hum Genet. 2004;75:1149-54.
48. Van Esch H, Jansen A, Bauters M, Froyen G, Fryns JP. Encephalopathy and bilateral cataract in a boy with an interstitial deletion of xp22 comprising the CDKL5 and NHS genes. Am J Med Genet A. 2007;143:364-9.
49. Weaving LS, Christodoulou J, Williamson SL, et al. Mutations of CDKL5 cause a severe neurodevelopmental disorder with infantile spasms and mental retardation. Am J Hum Genet. 2004;75:1079-93.
50. Carvill GL, Heavin SB, Yendle SC, et al. Targeted resequencing in epileptic encephalopathies identifies de novo mutations in CHD2 and SYNGAP1. Nat Genet. 2013;45:825-30.
51. Chénier S, Yoon G, Argiropoulos B, et al. CHD2 haploinsufficiency is associated with developmental delay, intellectual disability, epilepsy and neurobehavioural problems. J Neurodev Disord. 2014;6:9.
52. Galizia EC, Myers CT, Leu C, et al. CHD2 variants are a risk factor for photosensitivity in epilepsy. Brain. 2015;138:1198-207.
53. Liu JC, Ferreira CG, Yusufzai T. Human CHD2 is a chromatin assembly ATPase regulated by its chromo-and DNA-binding domains. J Biol Chem. 2015;290:25-34.
54. Lund C, Brodtkorb E, Øye AM, Røsby O, Selmer KK. CHD2 mutations in lennox-gastaut syndrome. Epilepsy Behav. 2014;33:18-21.
55. Rauch A, Wieczorek D, Graf E, et al. Range of genetic mutations associated with severe non-syndromic sporadic intellectual disability: an exome sequencing study. Lancet. 2012;380:1674-82.
56. Suls A, Jaehn JA, Kecskés A, et al. De novo loss-of-function mutations in CHD2 cause a fever-sensitive myoclonic epileptic encephalopathy sharing features with dravet syndrome. Am J Hum Genet. 2013;93:967-75.
57. Thomas RH, Zhang LM, Carvill GL, et al. CHD2 myoclonic encephalopathy is frequently associated with self-induced seizures. Neurology. 2015;84:951-8.
58. Trivisano M, Striano P, Sartorelli J, et al. CHD2 mutations are a rare cause of generalized epilepsy with myoclonic-atonic seizures. Epilepsy Behav. 2015;51:53-6.
59. Dibbens LM, Mullen S, Helbig I, et al. Familial and sporadic 15q13.3 microdeletions in idiopathic generalized epilepsy: precedent for disorders with complex inheritance. Hum Mol Genet. 2009;18:3626-31.
60. Helbig I, Mefford HC, Sharp AJ, et al. 15q13.3 microdeletions increase risk of idiopathic generalized epilepsy. Nat Genet. 2009;41:160-2.
61. Peñagarikano O, Abrahams BS, Herman EI, et al. Absence of CNTNAP2 leads to epilepsy, neuronal migration abnormalities, and core autism-related deficits. Cell. 2011;147:235-46.
62. Strauss KA, Puffenberger EG, Huentelman MJ, et al. Recessive symptomatic focal epilepsy and mutant contactin-associated protein-like 2. N Engl J Med. 2006;354:1370-7.
63. Alakurtti K, Weber E, Rinne R, et al. Loss of lysosomal association of cystatin B proteins representing progressive myoclonus epilepsy, EPM1, mutations. Eur J Hum Genet. 2005;13:208-15.
64. Bespalova IN, Adkins S, Pranzatelli M, Burmeister M. Novel cystatin B mutation and diagnostic PCR assay in an unverricht-lundborg progressive myoclonus epilepsy patient. Am J Med Genet. 1997;74:467-71.
65. de Haan GJ, Halley DJ, Doelman JC, et al. Univerricht-lundborg (sic) disease: underdiagnosed in the Netherlands. Epilepsia. 2004;45:1061-3.
66. Di Giaimo R, Riccio M, Santi S, et al. New insights into the molecular basis of progressive myoclonus epilepsy: a multiprotein complex with cystatin B. Hum Mol Genet. 2002;11:2941-50.
67. Lafrenière RG, Rochefort DL, Chrétien N, et al. Unstable insertion in the 5' flanking region of the cystatin B gene is the most common mutation in progressive myoclonus epilepsy Type 1, EPM1. Nat Genet. 1997;15: 298-302.
68. Lalioti MD, Mirotsou M, Buresi C, et al. Identification of mutations in cystatin B, the gene responsible for the unverricht-lundborg type of progressive myoclonus epilepsy (EPM1). Am J Hum Genet. 1997;60:342-51.
69. Mazarib A, Xiong L, Neufeld MY, et al. Unverricht-lundborg disease in a five-generation arab family: instability of dodecamer repeats. Neurology. 2001;57:1050-4.
70. Pennacchio LA, Lehesjoki AE, Stone NE, et al. Mutations in the gene encoding cystatin B in progressive myoclonus epilepsy (EPM1) Science. 1996;271:1731-4.
71. Virtaneva K, D'Amato E, Miao J, et al. Unstable minisatellite expansion causing recessively inherited myoclonus epilepsy, EPM1. Nat Genet. 1997;15:393-6.
72. Baulac S, Ishida S, Marsan E, et al. Familial focal epilepsy with focal cortical dysplasia due to DEPDC5 mutations. Ann Neurol. 2015;77:675-83.
73. Berkovic SF, Serratosa JM, Phillips HA, et al. Familial partial epilepsy with variable foci: clinical features and linkage to chromosome 22q12. Epilepsia. 2004;45:1054-60.
74. Callenbach PM, van den Maagdenberg AM, Hottenga JJ, et al. Familial partial epilepsy with variable foci in a dutch family: clinical characteristics and confirmation of linkage to chromosome 22q. Epilepsia. 2003;44: 1298-305.
75. Dibbens LM, de Vries B, Donatello S, et al. Mutations in DEPDC5 cause familial focal epilepsy with variable foci. Nat Genet. 2013;45:546-51.
76. Ishida S, Picard F, Rudolf G, et al. Mutations of DEPDC5 cause autosomal dominant focal epilepsies. Nat Genet. 2013;45:552-5.
77. Klein KM, O'Brien TJ, Praveen K, et al. Familial focal epilepsy with variable foci mapped to chromosome 22q12: expansion of the phenotypic spectrum. Epilepsia. 2012;53:e151-5.
78. Martin C, Meloche C, Rioux MF, et al. A recurrent mutation in DEPDC5 predisposes to focal epilepsies in the french-canadian population. Clin Genet. 2014;86:570-4.
79. Picard F, Baulac S, Kahane P, et al. Dominant partial epilepsies. A clinical, electrophysiological and genetic study of 19 European families. Brain. 2000;123 (Pt 6):1247-62.
80. Picard F, Makrythanasis P, Navarro V, et al. DEPDC5 mutations in families presenting as autosomal dominant nocturnal frontal lobe epilepsy. Neurology. 2014;82:2101-6.
81. Scheffer IE, Heron SE, Regan BM, et al. Mutations in mammalian target of rapamycin regulator DEPDC5 cause focal epilepsy with brain malformations. Ann Neurol. 2014;75:782-7.
82. Scheffer IE, Phillips HA, O'Brien CE, et al. Familial partial epilepsy with variable foci: a new partial epilepsy syndrome with suggestion of linkage to chromosome 2. Ann Neurol. 1998;44:890-9.
83. Xiong L, Labuda M, Li DS, et al. Mapping of a gene determining familial partial epilepsy with variable foci to chromosome 22q11-q12. Am J Hum Genet. 1999;65:1698-710.
84. Epilepsy Phenome/Genome Project Epi4K Consortium. Copy number variant analysis from exome data in 349 patients with epileptic encephalopathy. Ann Neurol. 2015;78:323-8.
85. Boumil RM, Letts VA, Roberts MC, et al. A missense mutation in a highly conserved alternate exon of dynamin-1 causes epilepsy in fitful mice. PLoS Genet. 2010;6:e1001046.
86. Deciphering Developmental Disorders Study. Large-scale discovery of novel genetic causes of developmental disorders. Nature. 2015;519:223-8.
87. Dhindsa RS, Bradrick SS, Yao X, et al. Epileptic encephalopathy-causing mutations in DNM1 impair synaptic vesicle endocytosis. Neurol Genet. 2015;1:e4.
88. EuroEPINOMICS-RES Consortium, Epilepsy Phenome/Genome Project, Epi4K Consortium. De novo mutations in synaptic transmission genes including DNM1 cause epileptic encephalopathies. Am J Hum Genet. 2014;95:360-70.
89. Perrault I, Hamdan FF, Rio M, et al. Mutations in DOCK7 in individuals with epileptic encephalopathy and cortical blindness. Am J Hum Genet. 2014;94:891-7.
90. Carvill GL, Weckhuysen S, McMahon JM, et al. GABRA1 and STXBP1: novel genetic causes of dravet syndrome. Neurology. 2014;82:1245-53.
91. Cossette P, Liu L, Brisebois K, et al. Mutation of GABRA1 in an autosomal dominant form of juvenile myoclonic epilepsy. Nat Genet. 2002;31:184-9.
92. Ding L, Feng HJ, Macdonald RL, et al. GABA(A) receptor alpha1 subunit mutation A322D associated with autosomal dominant juvenile myoclonic epilepsy reduces the expression and alters the composition of wild type GABA(A) receptors. J Biol Chem. 2010;285:26390-405.
93. Lachance-Touchette P, Brown P, Meloche C, et al. Novel α1 and γ2 GABAA receptor subunit mutations in families with idiopathic generalized epilepsy. Eur J Neurosci. 2011;34:237-49.
94. Maljevic S, Krampfl K, Cobilanschi J, et al. A mutation in the GABA(A) receptor alpha(1)-subunit is associated with absence epilepsy. Ann Neurol. 2006;59:983-7.
95. Tanaka M, Olsen RW, Medina MT, et al. Hyperglycosylation and reduced GABA currents of mutated GABRB3 polypeptide in remitting childhood absence epilepsy. Am J Hum Genet. 2008;82:1249-61.
96. Urak L, Feucht M, Fathi N, Hornik K, Fuchs K. A GABRB3 promoter haplotype associated with childhood absence epilepsy impairs transcriptional activity. Hum Mol Genet. 2006;15:2533-41.
97. Audenaert D, Schwartz E, Claeys KG, et al. A novel GABRG2 mutation associated with febrile seizures. Neurology. 2006;67:687-90.
98. Baulac S, Huberfeld G, Gourfinkel-An I, et al. First genetic evidence of GABA(A) receptor dysfunction in epilepsy: a mutation in the gamma2-subunit gene. Nat Genet. 2001;28:46-8.
99. Chaumont S, André C, Perrais D, Boué-Grabot E, et al. Agonist-dependent endocytosis of γ-aminobutyric acid Type A (GABAA) receptors revealed by a γ2(R43Q) epilepsy mutation. J Biol Chem. 2013;288: 28254-65.
100. Chiu C, Reid CA, Tan HO, et al. Developmental impact of a familial GABAA receptor epilepsy mutation. Ann Neurol. 2008;64:284-93.
101. Frugier G, Coussen F, Giraud MF, et al. A gamma 2(R43Q) mutation, linked to epilepsy in humans, alters GABAA receptor assembly and modifies subunit composition on the cell surface. J Biol Chem. 2007;282: 3819-28.
102. Harkin LA, Bowser DN, Dibbens LM, et al. Truncation of the GABA(A)-receptor gamma2 subunit in a family with generalized epilepsy with febrile seizures plus. Am J Hum Genet. 2002;70:530-6.
103. Kananura C, Haug K, Sander T, et al. A splice-site mutation in GABRG2 associated with childhood absence epilepsy and febrile convulsions. Arch Neurol. 2002;59:1137-41.
104. Kang JQ, Shen W, Macdonald RL. Why does fever trigger febrile seizures? GABAA receptor gamma2 subunit mutations associated with idiopathic generalized epilepsies have temperature-dependent trafficking deficiencies. J Neurosci. 2006;26:2590-7.
105. Sancar F, Czajkowski C. A GABAA receptor mutation linked to human epilepsy (gamma2R43Q) impairs cell surface expression of alphabetagamma receptors. J Biol Chem. 2004;279:47034-9.
106. Tan HO, Reid CA, Single FN, et al. Reduced cortical inhibition in a mouse model of familial childhood absence epilepsy. Proc Natl Acad Sci U S A. 2007;104:17536-41.
107. Wallace RH, Marini C, Petrou S, et al. Mutant GABA(A) receptor gamma2-subunit in childhood absence epilepsy and febrile seizures. Nat Genet. 2001;28:49-52.
108. Nakamura K, Kodera H, Akita T, et al. De novo mutations in GNAO1, encoding a gαo subunit of heterotrimeric G proteins, cause epileptic encephalopathy. Am J Hum Genet. 2013;93:496-505.
109. Carvill GL, Regan BM, Yendle SC, et al. GRIN2A mutations cause epilepsy-aphasia spectrum disorders. Nat Genet. 2013;45:1073-6.
110. Endele S, Rosenberger G, Geider K, et al. Mutations in GRIN2A and GRIN2B encoding regulatory subunits of NMDA receptors cause variable neurodevelopmental phenotypes. Nat Genet. 2010;42:1021-6.
111. Lesca G, Rudolf G, Bruneau N, et al. GRIN2A mutations in acquired epileptic aphasia and related childhood focal epilepsies and encephalopathies with speech and language dysfunction. Nat Genet. 2013;45:1061-6.
112. Lemke JR, Lal D, Reinthaler EM, et al. Mutations in GRIN2A cause idiopathic focal epilepsy with rolandic spikes. Nat Genet. 2013;45:1067-72.
113. Scheffer IE, Jones L, Pozzebon M, et al. Autosomal dominant rolandic epilepsy and speech dyspraxia: a new syndrome with anticipation. Ann Neurol. 1995;38:633-42.
114. Nava C, Dalle C, Rastetter A, et al. De novo mutations in HCN1 cause early infantile epileptic encephalopathy. Nat Genet. 2014;46:640-5.
115. Bassi MT, Balottin U, Panzeri C, et al. Functional analysis of novel KCNQ2 and KCNQ3 gene variants found in a large pedigree with benign familial neonatal convulsions (BFNC). Neurogenetics. 2005;6:185-93.
116. Berkovic SF, Kennerson ML, Howell RA, et al. Phenotypic expression of benign familial neonatal convulsions linked to chromosome 20. Arch Neurol. 1994;51:1125-8.
117. Biervert C, Schroeder BC, Kubisch C, et al. A potassium channel mutation in neonatal human epilepsy. Science. 1998;279:403-6.
118. Biervert C, Steinlein OK. Structural and mutational analysis of KCNQ2, the major gene locus for benign familial neonatal convulsions. Hum Genet. 1999;104:234-40.
119. Borgatti R, Zucca C, Cavallini A, et al. A novel mutation in KCNQ2 associated with BFNC, drug resistant epilepsy, and mental retardation. Neurology. 2004;63:57-65.
120. Dedek K, Fusco L, Teloy N, Steinlein OK. Neonatal convulsions and epileptic encephalopathy in an italian family with a missense mutation in the fifth transmembrane region of KCNQ2. Epilepsy Res. 2003;54:21-7.
121. del Giudice EM, Coppola G, Scuccimarra G, et al. Benign familial neonatal convulsions (BFNC) resulting from mutation of the KCNQ2 voltage sensor. Eur J Hum Genet. 2000;8:994-7.
122. Heron SE, Cox K, Grinton BE, et al. Deletions or duplications in KCNQ2 can cause benign familial neonatal seizures. J Med Genet. 2007;44:791-6.
123. Saitsu H, Kato M, Koide A, et al. Whole exome sequencing identifies KCNQ2 mutations in ohtahara syndrome. Ann Neurol. 2012;72:298-300.
124. Singh NA, Charlier C, Stauffer D, et al. A novel potassium channel gene, KCNQ2, is mutated in an inherited epilepsy of newborns. Nat Genet. 1998;18:25-9.
125. Weckhuysen S, Mandelstam S, Suls A, et al. KCNQ2 encephalopathy: emerging phenotype of a neonatal epileptic encephalopathy. Ann Neurol. 2012;71:15-25.
126. Wuttke TV, Jurkat-Rott K, Paulus W, et al. Peripheral nerve hyperexcitability due to dominant-negative KCNQ2 mutations. Neurology. 2007;69:2045-53.
127. Yang WP, Levesque PC, Little WA, et al. Functional expression of two kvLQT1-related potassium channels responsible for an inherited idiopathic epilepsy. J Biol Chem. 1998;273:19419-23.
128. Zimprich F, Ronen GM, Stögmann W, et al. Andreas rett and benign familial neonatal convulsions revisited. Neurology. 2006;67:864-6.
129. Barcia G, Fleming MR, Deligniere A, et al. De novo gain-of-function KCNT1 channel mutations cause malignant migrating partial seizures of infancy. Nat Genet. 2012;44:1255-9.
130. Derry CP, Heron SE, Phillips F, et al. Severe autosomal dominant nocturnal frontal lobe epilepsy associated with psychiatric disorders and intellectual disability. Epilepsia. 2008;49:2125-9.
131. Heron SE, Smith KR, Bahlo M, et al. Missense mutations in the sodium-gated potassium channel gene KCNT1 cause severe autosomal dominant nocturnal frontal lobe epilepsy. Nat Genet. 2012;44:1188-90.
132. Ishii A, Shioda M, Okumura A, et al. A recurrent KCNT1 mutation in two sporadic cases with malignant migrating partial seizures in infancy. Gene. 2013;531:467-71.
133. Ohba C, Kato M, Takahashi S, et al. Early onset epileptic encephalopathy caused by de novo SCN8A mutations. Epilepsia. 2014;55:994-1000.
134. Vanderver A, Simons C, Schmidt JL, et al. Identification of a novel de novo p.Phe932Ile KCNT1 mutation in a patient with leukoencephalopathy and severe epilepsy. Pediatr Neurol. 2014;50:112-4.
135. Chabrol E, Popescu C, Gourfinkel-An I, et al. Two novel epilepsy-linked mutations leading to a loss of function of LGI1. Arch Neurol. 2007;64:217-22.
136. Fanciulli M, Santulli L, Errichiello L, et al. LGI1 microdeletion in autosomal dominant lateral temporal epilepsy. Neurology. 2012;78:1299-303.
137. Fertig E, Lincoln A, Martinuzzi A, Mattson RH, Hisama FM. Novel LGI1 mutation in a family with autosomal dominant partial epilepsy with auditory features. Neurology. 2003;60:1687-90.
138. Kalachikov S, Evgrafov O, Ross B, et al. Mutations in LGI1 cause autosomal-dominant partial epilepsy with auditory features. Nat Genet. 2002;30:335-41.
139. Morante-Redolat JM, Gorostidi-Pagola A, Piquer-Sirerol S, et al. Mutations in the LGI1/Epitempin gene on 10q24 cause autosomal dominant lateral temporal epilepsy. Hum Mol Genet. 2002;11:1119-28.
140. Nobile C, Michelucci R, Andreazza S, et al. LGI1 mutations in autosomal dominant and sporadic lateral temporal epilepsy. Hum Mutat. 2009;30:530-6.
141. Sirerol-Piquer MS, Ayerdi-Izquierdo A, Morante-Redolat JM, et al. The epilepsy gene LGI1 encodes a secreted glycoprotein that binds to the cell surface. Hum Mol Genet. 2006;15:3436-45.
142. Striano P, de Falco A, Diani E, et al. A novel loss-of-function LGI1 mutation linked to autosomal dominant lateral temporal epilepsy. Arch Neurol. 2008;65:939-42.
143. Depienne C, Bouteiller D, Keren B, et al. Sporadic infantile epileptic encephalopathy caused by mutations in PCDH19 resembles dravet syndrome but mainly affects females. PLoS Genet. 2009;5:e1000381.
144. Dibbens LM, Tarpey PS, Hynes K, et al. X-linked protocadherin 19 mutations cause female-limited epilepsy and cognitive impairment. Nat Genet. 2008;40:776-81.
145. Hynes K, Tarpey P, Dibbens LM, et al. Epilepsy and mental retardation limited to females with PCDH19 mutations can present de novo or in single generation families. J Med Genet. 2010;47:211-6.
146. Kurian MA, Meyer E, Vassallo G, et al. Phospholipase C beta 1 deficiency is associated with early-onset epileptic encephalopathy. Brain. 2010;133:2964-70.
147. Poduri A, Chopra SS, Neilan EG, et al. Homozygous PLCB1 deletion associated with malignant migrating partial seizures in infancy. Epilepsia. 2012;53:e146-50.
148. Shen J, Gilmore EC, Marshall CA, et al. Mutations in PNKP cause microcephaly, seizures and defects in DNA repair. Nat Genet. 2010;42:245-9.
149. Chen WJ, Lin Y, Xiong ZQ, et al. Exome sequencing identifies truncating mutations in PRRT2 that cause paroxysmal kinesigenic dyskinesia. Nat Genet. 2011;43:1252-5.
150. Heron SE, Grinton BE, Kivity S, et al. PRRT2 mutations cause benign familial infantile epilepsy and infantile convulsions with choreoathetosis syndrome. Am J Hum Genet. 2012;90:152-60.
151. Lee HY, Huang Y, Bruneau N, et al. Mutations in the gene PRRT2 cause paroxysmal kinesigenic dyskinesia with infantile convulsions. Cell Rep. 2012;1:2-12.
152. Méneret A, Grabli D, Depienne C, et al. PRRT2 mutations: a major cause of paroxysmal kinesigenic dyskinesia in the European population. Neurology. 2012;79:170-4.
153. Ono S, Yoshiura K, Kinoshita A, et al. Mutations in PRRT2 responsible for paroxysmal kinesigenic dyskinesias also cause benign familial infantile convulsions. J Hum Genet. 2012;57:338-41.
154. Pelzer N, de Vries B, Kamphorst JT, et al. PRRT2 and hemiplegic migraine: a complex association. Neurology. 2014;83:288-90.
155. Schubert J, Paravidino R, Becker F, et al. PRRT2 mutations are the major cause of benign familial infantile seizures. Hum Mutat. 2012;33:1439-43.
156. Striano P, Lispi ML, Gennaro E, et al. Linkage analysis and disease models in benign familial infantile seizures: a study of 16 families. Epilepsia. 2006;47:1029-34.
157. Wang JL, Cao L, Li XH, Hu ZM, Li JD, Zhang JG, et al. Identification of PRRT2 as the causative gene of paroxysmal kinesigenic dyskinesias. Brain. 2011;134:3493-501.
158. Weber YG, Berger A, Bebek N, et al. Benign familial infantile convulsions: linkage to chromosome 16p12-q12 in 14 families. Epilepsia. 2004;45:601-9.
159. Abou-Khalil B, Ge Q, Desai R, et al. Partial and generalized epilepsy with febrile seizures plus and a novel SCN1A mutation. Neurology. 2001;57:2265-72.
160. Baulac S, Gourfinkel-An I, Picard F, et al. A second locus for familial generalized epilepsy with febrile seizures plus maps to chromosome 2q21-q33. Am J Hum Genet. 1999;65:1078-85.
161. Buoni S, Orrico A, Galli L, et al. SCN1A (2528delG) novel truncating mutation with benign outcome of severe myoclonic epilepsy of infancy. Neurology. 2006;66:606-7.
162. Rojo DC, Hamiwka L, McMahon JM, et al. De novo SCN1A mutations in migrating partial seizures of infancy. Neurology. 2011;77:380-3.
163. Claes L, Del-Favero J, Ceulemans B, et al. De novo mutations in the sodium-channel gene SCN1A cause severe myoclonic epilepsy of infancy. Am J Hum Genet. 2001;68:1327-32.
164. Dichgans M, Freilinger T, Eckstein G, et al. Mutation in the neuronal voltage-gated sodium channel SCN1A in familial hemiplegic migraine. Lancet. 2005;366:371-7.
165. Escayg A, MacDonald BT, Meisler MH, et al. Mutations of SCN1A, encoding a neuronal sodium channel, in two families with GEFS+2. Nat Genet. 2000;24:343-5.
166. Freilich ER, Jones JM, Gaillard WD, et al. Novel SCN1A mutation in a proband with malignant migrating partial seizures of infancy. Arch Neurol. 2011;68:665-71.
167. Mantegazza M, Gambardella A, Rusconi R, et al. Identification of an nav1.1 sodium channel (SCN1A) loss-of-function mutation associated with familial simple febrile seizures. Proc Natl Acad Sci U S A. 2005;102: 18177-82.
168. McArdle EJ, Kunic JD, George AL Jr. Novel SCN1A frameshift mutation with absence of truncated nav1.1 protein in severe myoclonic epilepsy of infancy. Am J Med Genet A. 2008;146A:2421-3.
169. Moulard B, Buresi C, Malafosse A. Study of the voltage-gated sodium channel beta 1 subunit gene (SCN1B) in the benign familial infantile convulsions syndrome (BFIC). Hum Mutat. 2000;16:139-42.
170. Mulley JC, Scheffer IE, Petrou S, et al. SCN1A mutations and epilepsy. Hum Mutat. 2005;25:535-42.
171. Ohmori I, Ouchida M, Ohtsuka Y, Oka E, Shimizu K. Significant correlation of the SCN1A mutations and severe myoclonic epilepsy in infancy. Biochem Biophys Res Commun. 2002;295:17-23.
172. Orrico A, Galli L, Grosso S, et al. Mutational analysis of the SCN1A, SCN1B and GABRG2 genes in 150 italian patients with idiopathic childhood epilepsies. Clin Genet. 2009;75:579-81.
173. Petrovski S, Scheffer IE, Sisodiya SM, et al. Lack of replication of association between scn1a SNP and febrile seizures. Neurology. 2009;73:1928-30.
174. Schlachter K, Gruber-Sedlmayr U, Stogmann E, et al. A splice site variant in the sodium channel gene SCN1A confers risk of febrile seizures. Neurology. 2009;72:974-8.
175. Vahedi K, Depienne C, Le Fort D, et al. Elicited repetitive daily blindness: a new phenotype associated with hemiplegic migraine and SCN1A mutations. Neurology. 2009;72:1178-83.
176. Zucca C, Redaelli F, Epifanio R, et al. Cryptogenic epileptic syndromes related to SCN1A: twelve novel mutations identified. Arch Neurol. 2008;65:489-94.
177. Berkovic SF, Heron SE, Giordano L, et al. Benign familial neonatal-infantile seizures: characterization of a new sodium channelopathy. Ann Neurol. 2004;55:550-7.
178. Heron SE, Crossland KM, Andermann E, et al. Sodium-channel defects in benign familial neonatal-infantile seizures. Lancet. 2002;360:851-2.
179. Kamiya K, Kaneda M, Sugawara T, et al. A nonsense mutation of the sodium channel gene SCN2A in a patient with intractable epilepsy and mental decline. J Neurosci. 2004;24:2690-8.
180. Liao Y, Anttonen AK, Liukkonen E, et al. SCN2A mutation associated with neonatal epilepsy, late-onset episodic ataxia, myoclonus, and pain. Neurology. 2010;75:1454-8.
181. Malacarne M, Gennaro E, Madia F, et al. Benign familial infantile convulsions: mapping of a novel locus on chromosome 2q24 and evidence for genetic heterogeneity. Am J Hum Genet. 2001;68:1521-6.
182. Ogiwara I, Ito K, Sawaishi Y, et al. De novo mutations of voltage-gated sodium channel alphaII gene SCN2A in intractable epilepsies. Neurology. 2009;73:1046-53.
183. Sugawara T, Tsurubuchi Y, Agarwala KL, et al. A missense mutation of the na+ channel alpha II subunit gene na(v)1.2 in a patient with febrile and afebrile seizures causes channel dysfunction. Proc Natl Acad Sci U S A. 2001;98:6384-9.
184. Blanchard MG, Willemsen MH, Walker JB, et al. De novo gain-of-function and loss-of-function mutations of SCN8A in patients with intellectual disabilities and epilepsy. J Med Genet. 2015;52:330-7.
185. de Kovel CG, Meisler MH, Brilstra EH, et al. Characterization of a de novo SCN8A mutation in a patient with epileptic encephalopathy. Epilepsy Res. 2014;108:1511-8.
186. Veeramah KR, O'Brien JE, Meisler MH, et al. De novo pathogenic SCN8A mutation identified by whole-genome sequencing of a family quartet affected by infantile epileptic encephalopathy and SUDEP. Am J Hum Genet. 2012;90:502-10.
187. Arsov T, Mullen SA, Rogers S, et al. Glucose transporter 1 deficiency in the idiopathic generalized epilepsies. Ann Neurol. 2012;72:807-15.
188. Striano P, Weber YG, Toliat MR, et al. GLUT1 muations are a rare cause of familial idiopathic generalized epilepsy. Neurology. 2012;78:557-62.
189. Suls A, Mullen SA, Weber YG, et al. Early-onset absence epilepsy caused by mutations in the glucose transporter GLUT1. Ann Neurol. 2009;66:415-9.
190. Molinari F, Raas-Rothschild A, Rio M, et al. Impaired mitochondrial glutamate transport in autosomal recessive neonatal myoclonic epilepsy. Am J Hum Genet. 2005;76:334-9.
191. Poduri A, Heinzen EL, Chitsazzadeh V, et al. SLC25A22 is a novel gene for migrating partial seizures in infancy. Ann Neurol. 2013;74:873-82.
192. Hamdan FF, Saitsu H, Nishiyama K, et al. Identification of a novel in-frame de novo mutation in SPTAN1 in intellectual disability and pontocerebellar atrophy. Eur J Hum Genet. 2012;20:796-800.
193. Nonoda Y, Saito Y, Nagai S, et al. Progressive diffuse brain atrophy in west syndrome with marked hypomyelination due to SPTAN1 gene mutation. Brain Dev. 2013;35:280-3.
194. Saitsu H, Tohyama J, Kumada T, et al. Dominant-negative mutations in alpha-II spectrin cause west syndrome with severe cerebral hypomyelination, spastic quadriplegia, and developmental delay. Am J Hum Genet. 2010;86:881-91.
195. Hamdan FF, Piton A, Gauthier J, et al. De novo STXBP1 mutations in mental retardation and nonsyndromic epilepsy. Ann Neurol. 2009;65:748-53.
196. Saitsu H, Kato M, Mizuguchi T, et al. De novo mutations in the gene encoding STXBP1 (MUNC18-1) cause early infantile epileptic encephalopathy. Nat Genet. 2008;40:782-8.
197. Edvardson S, Baumann AM, Mühlenhoff M, et al. West syndrome caused by ST3Gal-III deficiency. Epilepsia. 2013;54:e24-7.
198. Berryer MH, Hamdan FF, Klitten LL, et al. Mutations in SYNGAP1 cause intellectual disability, autism, and a specific form of epilepsy by inducing haploinsufficiency. Hum Mutat. 2013;34:385-94.
199. Mignot C, von Stülpnagel C, Nava C, et al. Genetic and neurodevelopmental spectrum of SYNGAP1-associated intellectual disability and epilepsy. J Med Genet. 2016;53:511-22.
200. Basel-Vanagaite L, Hershkovitz T, Heyman E, et al. Biallelic SZT2 mutations cause infantile encephalopathy with epilepsy and dysmorphic corpus callosum. Am J Hum Genet. 2013;93:524-9.
201. Corbett MA, Bahlo M, Jolly L, et al. A focal epilepsy and intellectual disability syndrome is due to a mutation in TBC1D24. Am J Hum Genet. 2010;87:371-5.
202. Duru N, Iseri SA, Selçuk N, Tolun A. Early-onset progressive myoclonic epilepsy with dystonia mapping to 16pter-p13.3. J Neurogenet. 2010;24:207-15.
203. Falace A, Filipello F, La Padula V, et al. TBC1D24, an ARF6-interacting protein, is mutated in familial infantile myoclonic epilepsy. Am J Hum Genet. 2010;87:365-70.
204. Guven A, Tolun A. TBC1D24 truncating mutation resulting in severe neurodegeneration. J Med Genet. 2013;50:199-202.
205. Milh M, Falace A, Villeneuve N, et al. Novel compound heterozygous mutations in TBC1D24 cause familial malignant migrating partial seizures of infancy. Hum Mutat. 2013;34:869-72.
206. Zara F, Gennaro E, Stabile M, et al. Mapping of a locus for a familial autosomal recessive idiopathic myoclonic epilepsy of infancy to chromosome 16p13. Am J Hum Genet. 2000;66:1552-7.