Acta Biomed 2020; Vol. 91, Supplement 13: e2020005 DOI: 10.23750/abm.v91i13-S.10596

Review

Genetic analysis of genes associated with epilepsy

Giulia Guerri,[1] Marco Castori,[2] Leonardo D'Agruma,[2] Antonio Petracca,[2] Danjela Kurti,[3] Matteo Bertelli[1,3,4]

[1] MAGI'S LAB, Rovereto (TN), Italy; [2] Division of Medical Genetics, Fondazione IRCCS-Casa Sollievo della Sofferenza, San Giovanni Rotondo (FG), Italy; [3] EBTNA-LAB, Rovereto (TN), Italy; [4] MAGI EUREGIO, Bolzano, Italy

Abstract. *Background and aim:* Epilepsy is a neurological disorder in which the altered activity of neurons causes convulsions, periods of unusual behavior and, sometimes, loss of consciousness. The aim of this mini-review is to summarize all the syndromes characterized by epilepsy and for which the associated gene is known. *Methods:* We searched those syndromes in PubMed and OMIM database. *Results:* Genetic causes underlie epilepsy in about 40% of individuals. Epilepsies are phenotypically and genetically heterogeneous. Inheritance can be autosomal dominant or recessive or X-linked recessive/dominant. *Conclusion:* Since epilepsy has high genetic heterogeneity, in diagnostics, the parallel sequencing of a panel of genes may speed up the determination of the molecular etiology and/or establish a risk of recurrence in family members for the purpose of planning appropriate preventive and/or therapeutic measures. (www.actabiomedica.it)

Key words: epilepsy, genetic test, molecular diagnosis

Epilepsy is a neurological disorder in which the altered activity of neurons causes convulsions, periods of unusual behavior and, sometimes, loss of consciousness. The International League against Epilepsy (ILAE) classifies seizures in two main categories: "Idiopathic generalized epileptic seizures" involving both cerebral hemispheres and which can manifest with typical absences, myoclonus and generalized tonic-clonic seizures, alone or in various combinations and severity, and "Focal seizures" that arise in neural networks of a single hemisphere, and are in turn distinguished into simple partial seizures that do not involve an alteration of consciousness, and complex partial seizures that cause a change in behavior or loss of consciousness. Some types of seizures, such as infantile spasms, do not fall into either category (1). Epilepsy may be an isolated neurological symptom or may be associated with other neurological symptoms or diseases (2). Anti-convulsant drugs are the main treatment for epilepsy and often have to be taken throughout life (3). About 1% of the world's population suffers from epilepsy (4). A diagnosis of epilepsy is based on clinical observation, family history and clinical investigations, such as electroencephalogram, computed tomography and magnetic resonance imaging (5). Syncope, hyperventilation, migraines, narcolepsy, panic attacks and non-epileptic psychogenic seizures can be confused with seizures. In children, some behaviors, such as emotional spasms, bed-wetting, night terrors, tics and myoclonus, can easily be mistaken for epileptic seizures; gastroesophageal reflux can cause arching of the back and sideways head twisting in infants, and this can be confused with tonic-clonic seizures (6). Genetic causes underlie epilepsy in about 40% of individuals (7). Epilepsies are phenotypically and genetically heterogeneous. Inheritance can be autosomal dominant or recessive or X-linked recessive or dominant (Table 1).

Pathogenic variants may be missense, nonsense, splice-site and small intragenic deletions/insertions. The test guidelines can be found in "Genetics Home Reference" (ghr.nlm.nih.gov). The test is useful for confirming diagnosis, differential diagnosis and recurrence risk evaluation.

Table 1. Syndromes characterized by epilepsy for which the genetic basis is known.
AD = Autosomal dominant; AR = Autosomal recessive; ADSLD = Adenyl succinase deficiency; AHC = Alternating hemiplegia of childhood; AS = Angelman syndrome; BFIS = Benign familial infantile seizures; BFNS = Benign familial neonatal seizures; CAD-EDS = Cerebellar atrophy, developmental delay, seizures; CCDS = Cerebral creatine deficiency syndrome; CLN = neuronal ceroid lipofuscinosis; DOORS = Deafness, onychodystrophy, osteodystrophy, mental retardation, seizures syndrome; EA = Episodic ataxia; EEOC = childhood-onset epileptic encephalopathy; EIEE = Early infantile epileptic encephalopathy; EKD = Episodic kinesigenic dyskinesia; ENFL = Nocturnal frontal lobe epilepsy; EPD = Pyridoxine-dependent epilepsy; EPM = Progressive myoclonic epilepsy; EPRPDC = Rolandic epilepsy with paroxysmal exercise-induced dystonia and writer's cramp; ETL = Familial temporal lobe epilepsy; FCORD = Focal cortical dysplasia; FEB = Familial febrile seizures; FESD = Focal epilepsy with speech disorder with/without mental retardation; FHM = Familial hemiplegic migraine; FIME = Familial infantile myoclonic epilepsy; GEFSP = Generalized epilepsy with febrile seizures plus; GLUT1DS = GLUT1 deficiency syndrome; HPMRS = Hyperphosphatasia with mental retardation syndrome; ICCA = Familial infantile convulsions with paroxysmal choreoathetosis; KDVS = Koolen-De Vries syndrome; KLEFS = Kleefstra syndrome; MAE = Myoclonic-atonic epilepsy; MCAHS = Multiple congenital anomalies-hypotonia-seizures syndrome; MCSZ = Microcephaly, seizures, developmental delay; MEDS = Microcephaly, epilepsy, diabetes syndrome; MICPCH = Mental retardation and microcephaly with pontine and cerebellar hypoplasia; MOWS = Mowat-Wilson syndrome; MRD = Mental retardation; MRX = X-linked mental retardation; MRXSCH = Syndromic X-linked mental retardation, Christianson type; MRXSH = Syndromic X-linked mental retardation, Hedera type; MTDPS = Mitochondrial DNA depletion syndrome; MYOCL = Familial myoclonus; NDHMSD/R = autosomal dominant/recessive neurodevelopmental disorder with or without hyperkinetic movements and seizures; NEDCAS = Neurodevelopmental disorder with cerebellar atrophy with/without seizures; NBIA = Neurodegeneration with brain iron accumulation; PMSE = Polyhydramnios, megalencephaly, symptomatic epilepsy; PNKD = Paroxysmal nonkinesigenic dyskinesia with/without generalized epilepsy; PNPOD = Pyridoxamine 5-prime-phosphate oxidase deficiency; PTHS/L = Pitt-Hopkins syndrome/-like; PVNH = Periventricular nodular heterotopia; RESDX = X-linked Rolandic epilepsy, mental retardation, speech dyspraxia; RMFSL = Lethal neonatal rigidity and multifocal seizure syndrome; RTT = Rett syndrome; SANDO = Sensory ataxic neuropathy, dysarthria, ophthalmoparesis; SESAMES = Seizures, sensorineural deafness, ataxia, mental retardation, electrolyte imbalance; SMAPME = Spinal muscle atrophy with progressive myoclonic epilepsy; THMD = Thiamine metabolism dysfunction syndrome; XLD/R = X-linked, dominant/recessive.

Gene	OMIM gene	Disease	OMIM disease	Inheritance	**Protein function** (https://www.genecards.org/)
ATP1A2	182340	AHC1, FHM2	104290, 602481	AD	Catalytic subunit of the pump that maintains an essential electrochemical gradient in cells through active transport of Na^+ and K^+ ions
ATP1A3	182350	AHC2	614820	AD	Catalytic subunit of the pump that maintains an essential electrochemical gradient in cells through active transport of Na^+ and K^+ ions
CACNA1A	601011	EIEE42	617106	AD	Mediation of Ca^{2+} influx in response to depolarization. Regulation of neurotransmission
CHD2	602119	EEOC	615369	AD	Chromatin remodeling
CHRNA2	118502	ENFL4	610353	AD	Alpha subunit of the nicotinic acetylcholine receptor involved in fast synaptic transmission
CHRNA4	118504	ENFL1	600513	AD	Integral membrane receptor subunit of the nicotinic acetylcholine receptor
CHRNB2	118507	ENFL3	605375	AD	Beta subunit of the neuronal acetylcholine receptor
CPA6	609562	ETL5, FEB11	614417, 614418	AD, AR	Proteolytic inactivation of enkephalins and neurotensin. Conversion of inactive angiotensin I into active angiotensin II
DNAJC5	611203	CLN4B	162350	AD	Calcium-dependent neurotransmitter release at nerve endings
DNM1	602377	EIEE31	616346	AD	Vesicle trafficking and receptor-mediated endocytosis
DYRK1A	600855	MRD7	614104	AD	Regulation of cell proliferation. Brain development
EHMT1	607001	KLEFS1	610253	AD	G0/G1 cell cycle transition

(continued on next page)

Table 1 *(continued)***.** Syndromes characterized by epilepsy for which the genetic basis is known.

Gene	OMIM gene	Disease	OMIM disease	Inheritance	**Protein function** (https://www.genecards.org/)
FOXG1	164874	RTT	613454	AD	Establishment of regional subdivision of the developing brain and telencephalon development
GABRA1	137160	EIEE19	615744	AD	Formation of functional GABAergic synapses, mediation of synaptic inhibition
GABRB3	137192	EIEE43	617113	AD	Formation of functional GABAergic synapses, mediation of synaptic inhibition
GRIN1	138249	NDHMSD/R	614254	AD, AR	Plasticity of synapses that underlies memory and learning
GRIN2A	138253	FESD	245570	AD	Higher sensitivity of glutamate and faster NMDA channel kinetics
GRIN2B	138252	EIEE27	616139	AD	Brain development, circuit formation, synaptic plasticity, cell migration and differentiation
HNRNPU	602869	EIEE54	617391	AD	Formation of ribonucleoprotein complexes in the nucleus with heterogeneous nuclear RNA
KANSL1	612452	KDVS	610443	AD	Acetylation of nucleosomal histone H4 on lysine residues involved in transcription regulation
KCNMA1	600150	PNKD3, CADEDS	609446, 617643	AD, AR	Control of excitability for the regulation of smooth muscle contraction, tuning of cochlear hair cells, regulation of transmitter release, innate immunity
KCNA1	176260	EA1	160120	AD	Regulation of neuron excitability in the hippocampus, downstream effector for G protein-coupled receptors, inhibition of GABAergic inputs to basolateral amygdala neurons, regulation of neurotransmitter release, generation of action potentials and prevention of hyperexcitability in myelinated axons of the vagus nerve
KCNQ2	602235	EIEE7, BFNS1	613720, 121200	AD	Regulation of neuron excitability
KCNQ3	602232	BFNS2	121201	AD	Regulation of neuron excitability
LGI1	604619	ETL1	600512	AD	Regulation of voltage-gated potassium channel activity, neuron growth regulation, cell survival
MBD5	611472	MRD1	156200	AD	Heterochromatin binding
MEF2C	600662	MRD20	613443	AD	Role in hippocampal-dependent learning and memory through regulation of basal and evoked synaptic transmission. Normal neuron development and distribution, neocortical electrical activity
PRRT2	614386	ICCA, EKD1, BFIS2	602066, 128200, 605751	AD	Synaptic transmission in the central nervous system Neurotransmitter release in presynaptic terminals of hippocampal neurons
SCN1A	182389	GEFSP2, EIEE6	604403, 607208	AD	Regulation of neurotransmitter release
SCN2A	182390	EIEE11, BFIS3	613721, 607745	AD	Regulation of hippocampal replay, important for memory
SCN8A	600702	MYOCL2, EIEE13, BFIS5	618364, 614558, 617080	AD	Ion pore region of voltage-gated sodium channel. Essential for rapid membrane depolarization during action potential formation in excitable neurons

(continued on next page)

Table 1 *(continued)***.** Syndromes characterized by epilepsy for which the genetic basis is known.

Gene	OMIM gene	Disease	OMIM disease	Inheritance	**Protein function** (https://www.genecards.org/)
SCN9A	603415	GEFSP7	613863	AD	Mediation of voltage-dependent sodium ion permeability of excitable membranes
SLC2A1	138140	GLUT1DS1/2	606777, 612126	AD, AR	Expressed at the blood-brain barrier, facilitation of glucose transport into the brain
SLC6A1	137165	MAE	616421	AD	GABA reuptake into presynaptic terminals
SPTAN1	182810	EIEE5	613477	AD	Ca^{2+}-dependent interaction with calmodulin, Ca^{2+}-dependent movement of the cytoskeleton at plasma membrane
STXBP1	602926	EIEE4	612164	AD	Release of neurotransmitters via regulation of syntaxin
SYNGAP1	603384	MRD5	612621	AD	Regulation of synaptic plasticity and neuron homeostasis
TCF4	602272	PTHS	610954	AD	Initiation of neuron differentiation
TSC1	605284	FCORD2	607341	AD (somatic)	Negative regulation of anabolic cell growth
TSC2	191092				Tumor suppressor
MTOR	601231				Central regulator of cell metabolism, growth and survival in response to hormones, growth factors, nutrients, energy and stress signals
ZEB2	605802	MOWS	235730	AD	Transcriptional inhibitor. Represses transcription of E-cadherin
UBE3A	601623	AS	105830	AD	Regulator of synaptic development
ABAT	137150	GABA-transaminase deficiency	613163	AR	Catabolism of gamma-aminobutyric acid
ADSL	608222	ADSLD	103050	AR	*De novo* AMP synthesis
ALDH7A1	107323	EPD	266100	AR	Catabolism of betaine aldehyde, lipid peroxidation-derived aldehydes, lysine
ASAH1	613468	SMAPME	159950	AR	Catabolism of ceramide into sphingosine and free fatty acids
BRAT1	614506	NEDCAS, RMFSL	618056, 614498	AR	Regulation of mitochondrial function and cell proliferation
CLN3	607042	CLN3	204200	AR	Microtubule-dependent, anterograde transport of late endosomes and lysosomes
CLN5	608102	CLN5	256731	AR	Retrograde trafficking of lysosomal sorting
CLN6	606725	CLN4A, CLN6	601780, 204300	AR	Degradation of post-translationally modified proteins in lysosomes
CLN8	607837	CLN8, neuronal ceroid lipofuscinosis 8 Northern epilepsy variant	600143, 610003	AR	Cell proliferation during neuronal differentiation and protection against cell death
CNTNAP2	604569	PTHSL1	610042	AR	Radial and longitudinal organization of myelinated axons. Formation of functionally distinct domains critical for saltatory conduction of nerve impulses in myelinated nerve fibers. Demarcation of the juxtaparanodal region of the axo-glial junction

(continued on next page)

Table 1 *(continued)***.** Syndromes characterized by epilepsy for which the genetic basis is known.

Gene	OMIM gene	Disease	OMIM disease	Inheritance	**Protein function** (https://www.genecards.org/)
CSTB	601145	Myoclonic epilepsy of Unverricht and Lundborg	254800	AR	Protection against proteases leaking from lysosomes
CTSD	116840	CLN10	610127	AR	Protein turnover, and proteolytic activation of hormones and growth factors
EPM2A	607566	Myoclonic epilepsy of Lafora	254780	AR	Prevention of formation of glycogen-insoluble aggregates
FOLR1	136430	Neurodegeneration due to cerebral folate transport deficiency	613068	AR	Required for normal embryo development and normal cell proliferation
GAMT	601240	CCDS2	612736	AR	Important in nervous system development
GATM	602360	CCDS3	612718	AR	Embryo and central nervous system development
GOSR2	604027	EPM6	614018	AR	Transport of proteins from the cis/medial-Golgi to the trans-Golgi network
IER3IP1	609382	MEDS	614231	AR	Regulation of apoptosis. Involved in protein transport between endoplasmic reticulum and Golgi apparatus
KCNJ10	602208	SESAMES	612780	AR	Responsible for potassium buffering action of glial cells in the brain
KCTD7	611725	EPM3	611726	AR	Control of excitability of cortical neurons
MFSD8	611124	CLN7	610951	AR	Transport of small solutes via chemiosmotic ion gradients
NHLRC1	608072	Myoclonic epilepsy of Lafora	254780	AR	Misfolded protein degradation via the ubiquitin-proteasome system
PIGN	606097	MCAHS1	614080	AR	Glycosylphosphatidylinositol-anchor biosynthesis
PIGO	614730	HPMRS2	614749	AR	Glycosylphosphatidylinositol-anchor biosynthesis
PLCB1	607120	EIEE12	613722	AR	Synthesis of inositol 1,4,5-trisphosphate and diacylglycerol from phosphatidylinositol 4,5-bisphosphate
PNPO	603287	PNPOD	610090	AR	Catalysis of the terminal rate-limiting step of vitamin B6 synthesis
POLG	174763	MTDPS4A/4B, SANDO	203700, 613662, 607459	AR	Replication of mitochondrial DNA
PPT1	600722	CLN1	256730	AR	Catabolism of lipid-modified proteins during lysosomal degradation
PRICKLE1	608500	EPM1B	612437	AR	Involved in the planar cell polarity pathway that controls convergent extension during gastrulation and neural tube closure
PNKP	605610	MCSZ	613402	AR	Repair of DNA damage
SCARB2	602257	EPM4	254900	AR	Membrane transport and reorganization of the endosomal/lysosomal compartment
SLC19A3	606152	THMD2	607483	AR	High affinity thiamine uptake
SLC25A22	609302	EIEE3	609304	AR	Transport of glutamate across the inner mitochondrial membrane
STRADA	608626	PMSE	611087	AR	G1 cell cycle arrest

(continued on next page)

Table 1 *(continued)***.** Syndromes characterized by epilepsy for which the genetic basis is known.

Gene	OMIM gene	Disease	OMIM disease	Inheritance	**Protein function** (https://www.genecards.org/)
TBC1D24	613577	DOORS, EPRPDC, EIEE16, FIME	220500, 608105, 615338, 605021	AR	Neuronal projection development
TPP1	607998	CLN2	204500	AR	Non-specific lysosomal peptidase which generates tripeptides from lysosomal proteinase breakdown products
WWOX	605131	EIEE28	616211	AR	Tumor suppressor gene
ALG13	300776	EIEE36	300884	XLD	Protein N-glycosylation
ARHGEF9	300429	EIEE8	300607	XLR	Receptor recruitment in GABAergic and glycinergic synapses
ARX	300382	EIEE1	308350	XLR	Maintenance of neuron subtypes in the cerebral cortex, axonal guidance in the floor plate
ATP6AP2	300556	MRXSH	300423	XLR	Control of V-ATPase pump assembly and acidification of lysosomes. Role in synapse morphology, synaptic transmission
CASK	300172	MICPCH	300749	XLD	Regulation of mitochondrial function and cell proliferation
CDKL5	300203	EIEE2	300672	XLR	Ciliogenesis
FLNA	300017	PVNH1	300049	XLD	Neuroblast migration from ventricular zone into cortical plate. Ciliogenesis. Cell-cell contacts and adherens junctions during brain development. Required for growth cone collapse during axon guidance
IQSEC2	300522	MRX1	309530	XLD	Component of postsynaptic density at excitatory synapses. Critical role in cytoskeletal and synapse organization
MECP2	300005	RTT	312750	XLD	Essential for embryo development
PCDH19	300460	EIEE9	300086	XL, female restricted	Ca^{2+}-dependent cell-adhesion protein primarily expressed in the brain
PIGA	311770	MCAHS2	300868	XLR	Necessary for synthesis of N-acetylglucosaminyl-phosphatidylinositol, early intermediate in GPI-anchor biosynthesis
SLC6A8	300036	CCDS1	300352	XLR	Required for uptake of creatine by muscles and brain
SLC9A6	300231	MRXSCH	300243	XLD	Exchange of protons for Na^+ and K^+ across endosome membranes. Ca^{2+} homeostasis
SMC1A	300040	EIEE85	301044	XLD	Part of functional kinetochores
SRPX2	300642	RESDX	300643	XLR	Promotion of synapse formation
WDR45	300526	NBIA5	300894	XLD	Autophagosome assembly

The search for pathogenic variants in the genes listed in Table 1 is based on analysis of a multi-gene panel by next generation sequencing of the coding regions and their intron-exon junctions. The test has an analytic sensitivity of 96-100% and an analytic specificity of ≥99%, compared with a diagnostic sensitivity of ≥37% deduced from the literature (8,9). Since epilepsy has high genetic heterogeneity (10), the use in diagnostics of a large panel of genes may speed up the determination of the molecular etiology and/or establish a risk of recurrence in family members for the purpose of planning appropriate preventive and/or therapeutic measures.

Conflict of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

References

1. Berg AT, Berkovic SF, Brodie MJ, et al. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on classification and terminology, 2005-2009. Epilepsia 2010; 51: 676-85.
2. Pellock JM. The challenge of neuropsychiatric issues in pediatric epilepsy. J Child Neurol 2004; 19: S1-5.
3. Diagnosis and management of epilepsy in adults. A national clinical guideline, 2015. Available at: https://www.guidelinecentral.com/share/summary/56a775bf791d0#section-society
4. Thurman DJ, Beghi E, Begley CE, et al. Standards for epidemiologic studies and surveillance of epilepsy. Epilepsia 2011; 52: 2-26.
5. National Clinical Guideline Centre (UK). The epilepsies: the diagnosis and management of the epilepsies in adults and children in primary and secondary care. London: Royal College of Physicians (UK), 2012.
6. Walls R, Hockberger R, Gausche-Hill M. Rosen's emergency medicine: concepts and clinical practice. Mosby/Elsevier, Philadelphia. 2010.
7. Pong AW, Pal DK, Chung WK. Developments in molecular genetic diagnostics: an update for the pediatric epilepsy specialist. Pediatr Neurol 2011; 44: 317-27.
8. Wang J, Gotway G, Pascual JM, Park JY. Diagnostic yield of clinical next-generation sequencing panels for epilepsy. JAMA Neurol 2014; 71: 650-1.
9. Della Mina E, Ciccone R, Brustia F, et al. Improving molecular diagnosis in epilepsy by a dedicated high-throughput sequencing platform. Eur J Hum Genet 2015; 23: 354-62.
10. https://www.lice.it/pdf/Percorso_diagnostico_Epilessie_Genetiche_web.pdf

Received: 3 September 2020
Accepted: 14 October 2020
Correspondence:
Stefano Paolacci
Via delle Maioliche, 57/D, Rovereto (TN), Italy
E-mail: stefano.paolacci@assomagi.org