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Review

Epilepsy-associated genes

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ABSTRACT

Development in genetic technology has led to the identification of an increasing number of genes associated with epilepsy. These discoveries will both provide the basis for including genetic tests in clinical practice and improve diagnosis and treatment of epilepsy. By searching through several databases (OMIM, HGMD, and EpilepsyGene) and recent publications on PubMed, we found 977 genes that are associated with epilepsy. We classified these genes into 4 categories according to the manifestation of epilepsy in phenotypes. We found 84 genes that are considered as epilepsy genes: genes that cause epilepsies or syndromes with epilepsy as the core symptom. 73 genes were listed as neurodevelopment-associated genes: genes associated with both brain-development malformations and epilepsy. Several genes (536) were epilepsy-related: genes associated with both physical or other systemic abnormalities and epilepsy or seizures. We found 284 additional genes putatively associated with epilepsy; this requires further verification. These integrated data will provide new insights useful for both including genetic tests in the clinical practice and evaluating the results of genetic tests. We also summarized the epilepsy-associated genes according to their function, with the goal to better characterize the association between genes and epilepsies and to further understand the mechanisms underlying epilepsy.

1. Introduction

Advances in genomics techniques, especially the development of next-generation sequencing, have greatly increased our knowledge on the genetic changes occurring across the entire human genome, allowing for rapid and efficient discovery of genes involved in many diseases. Epilepsies may result from primary genetic abnormalities or secondary to well-defined structural or metabolic disorders, of which, some also have genetic causes. It is estimated that more than half of epilepsies have a genetic basis [1]. The application of genomic technologies has a tremendous impact on the discovery of the genetic basis of epilepsy, and it is expected to play a pivotal role in the diagnosis and treatment of epilepsy. However, epilepsies associated with genetic abnormalities display large heterogeneity. Mutations in some genes may selectively cause epilepsies or syndromes with epilepsy as the core symptom (e.g., *SCN1A* mutations cause epilepsies with febrile seizures plus [2]), while other genes may be associated with gross brain developmental malformations and epilepsies (e.g., mutations in *TSC1* and *TSC2* genes cause tuberous sclerosis [3,4]). Seizures may also occur in other genetic disorders affecting the central nervous system, such as Fragile X Syndrome [5] and myoclonus-dystonia [6]. Therefore, it is a challenge to decide which gene, or group of genes, should be characterized in a specific target patient population before designing an efficient and cost-effective genetic-testing strategy. In this review, we present a summary of the genes associated with epilepsy. We grouped the genes according to the manifestation of epilepsy in the phenotype, i.e., whether epilepsy is the exclusive outcome of the mutation or part of a group of unrelated symptoms. The aim of the present review is to offer an insight into the genes that should be included in the genetic testing of patients with a distinct phenotype. The association between genes and epilepsy will further our

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Table 1
Epilepsy genes.

Phenotype (in order of the onset age)	Inheritance	Gene
Neonatal		
Pyridoxamine 5'-phosphate oxidase deficiency (PNPOD)	AR	*PNPO*
Pyridoxine-dependent epilepsy (EPD)	AR	*ALDH7A1*
Benign familial neonatal seizures (BFNS)	AD	***KCNQ2***,*KCNQ3*
Infantile and childhood		
Familial infantile myoclonic epilepsy (FIME)	AR	***TBC1D24***
Benign familial infantile seizures (BFIS)	AD	*PRRT2*, ***SCN2A***, ***SCN8A***
Amish infantile epilepsy syndrome (AIES)	AR	*ST3GAL5*
Early infantile epileptic encephalopathy (EIEE)	AD	*CACNA1A*, ***GABRA1***, ***GABRB3***, ***KCNQ2***, ***KCNT1***, ***SCN2A***, ***SCN8A***
	AR	*AARS*, *ARV1*, *DOCK7*, *FRRS1L*, *GUF1*, *ITPA*, *NECAP1*, *PLCB1*, ***SLC12A5***, *SLC13A5*, *SLC25A12*, *SLC25A22*, *ST3GAL3*, *SZT2*, ***TBC1D24***, *WWOX*
	XLD	*CDKL5*
	XLR	*ARHGEF9*
	XL	*ALG13, PCDH19*
	UN	*DNM1, EEF1A2, FGF12, GABRB1, GNAO1, GRIN2B, GRIN2D, HCN1, KCNA2, KCNB1, SIK1, SLC1A2, SPTAN1, STXBP1, UBA5*
Dravet syndrome (DS)	AD	***SCN1A***, ***SCN9A***[b]
Familial febrile seizures (FFS)	AD	***GABRG2***, *GPR98*, ***SCN1A***, ***SCN9A***
	AR	***CPA6***
Generalized epilepsy with febrile seizures plus (GEFS +)	AD	***GABRD***, ***GABRG2***, ***SCN1A***, *SCN1B*, ***SCN9A***, *STX1B*
Generalized epilepsy and paroxysmal dyskinesia (GEPD)	AD	*KCNMA1*
Myoclonic-atonic epilepsy (MAE)	AD	*SLC6A1*
Childhood-onset epileptic encephalopathy (COEE)	AD	*CHD2*
Focal epilepsy and speech disorder (FESD) with or without mental retardation	AD	*GRIN2A*
Childhood absence epilepsy (CAE)	AD	***GABRG2***
	UN	***CACNA1H***, ***GABRA1***, ***GABRB3***
Juvenile and later		
Juvenile absence epilepsy (JAE)	AD	***CLCN2***[a], ***EFHC1***
Juvenile myoclonic epilepsy (JME)	AD	***CACNB4***, ***CLCN2***[a], ***EFHC1***, ***GABRD***
	UN	***GABRA1***
Idiopathic generalized epilepsy (IGE)	AD	***CACNB4***, ***CLCN2***[a], ***GABRD***, ***SLC12A5***, *SLC2A1*
	UN	***CACNA1H***, *CASR*
Familial adult myoclonic epilepsy (FAME)	AD	*ADRA2B*
	AR	*CNTN2*
Familial temporal lobe epilepsy (FTLE)	AD	***CPA6***, *GAL*, *LGI1*
Not specific		
Progressive myoclonic epilepsy (PME)	AD	*KCNC1*
	AR	*CERS1*, *CSTB*, *EPM2A*, *GOSR2*, *KCTD7*, *LMNB2*, *NHLRC1*, *PRDM8*, *PRICKLE1*, *SCARB2*
Nocturnal frontal lobe epilepsy (NFLE)	AD	*CHRNA2*, *CHRNA4*, ***KCNT1***
	UN	*CHRNB2*
Familial focal epilepsy with variable foci (FFEVF)	AD	*DEPDC5*

Bold italics, with multiple epilepsy phenotypes.
AD, autosomal dominant; AR, autosomal recessive; UN, unknown; XL, X-linked; XLD, X-linked dominant; XLR, X-linked recessive.
AARS, alanyl-tRNA synthetase; *ADRA2B*, alpha-2B-adrenergic receptor; *ALDH7A1*, aldehyde dehydrogenase 7 family, member A1; *ALG13*, asparagine-linked glycosylation 13, S. cerevisiae, homolog of; *ARHGEF9*, RHO guanine nucleotide exchange factor 9; *ARV1*, ARV1, S. cerevisiae, homolog of; *CACNA1A*, calcium channel, voltage-dependent, P/Q type, alpha-1A subunit; *CACNA1H*, calcium channel, voltage-dependent, T type, alpha-1H subunit; *CACNB4*, calcium channel, voltage-dependent, beta-4 subunit; *CASR*, calcium-sensing receptor; *CDKL5*, cyclin-dependent kinase-like 5; *CERS1*, ceramide synthase 1; *CHD2*, chromodomain helicase DNA-binding protein 2; *CHRNA2*, cholinergic receptor, neuronal nicotinic, alpha polypeptide 2; *CHRNA4*, cholinergic receptor, neuronal nicotinic, alpha polypeptide 4; *CHRNB2*, cholinergic receptor, neuronal nicotinic, beta polypeptide 2; *CLCN2*, chloride channel 2; *CNTN2*, contactin 2; *CPA6*, carboxypeptidase A6; *CSTB*, cystatin B; *DEPDC5*, DEP domain-containing protein 5; *DNM1*, dynamin 1; *DOCK7*, dedicator of cytokinesis 7; *EEF1A2*, eukaryotic translation elongation factor 1, alpha-2; *EFHC1*, EF-hand domain (C-terminal)-containing protein 1; *EPM2A*, EPM2A gene, encodes laforin; *FGF12*, fibroblast growth factor 12; *FRRS1L*, ferric chelate reductase 1-like; *GABRA1*, gamma-aminobutyric acid receptor, alpha-1; *GABRB1*, gamma-aminobutyric acid receptor, beta-1; *GABRB3*, gamma-aminobutyric acid receptor, beta-3; *GABRD*, gamma-aminobutyric acid receptor, delta; *GABRG2*, gamma-aminobutyric acid receptor, gamma-2; *GAL*, galanin; *GNAO1*, guanine nucleotide-binding protein, alpha-activating activity polypeptide O; *GOSR2*, golgi snap receptor complex member 2; *GPR98*, G protein-coupled receptor 98; *GRIN2A*, glutamate receptor, ionotropic, N-methyl-D-aspartate, subunit 2A; *GRIN2B*, glutamate receptor, ionotropic, N-methyl-D-aspartate, subunit 2B; *GRIN2D*, glutamate receptor, ionotropic, N-methyl-D-aspartate, subunit 2D; *GUF1*, GUF1 GTPase, S. cerevisiae, homolog of; *HCN1*, hyperpolarization-activated cyclic nucleotide-gated potassium channel 1; *ITPA*, inosine triphosphatase; *KCNA2*, potassium channel, voltage-gated, shaker-related subfamily, member 2; *KCNB1*, potassium channel, voltage-gated, shab-related subfamily, member 1; *KCNC1*, potassium channel, voltage-gated, shaw-related subfamily, member 1; *KCNMA1*, potassium channel, calcium-activated, large conductance, subfamily M, alpha member 1; *KCNQ2*, potassium channel, voltage-gated, KQT-like subfamily, member 2; *KCNQ3*, potassium channel, voltage-gated, KQT-like subfamily, member 3; *KCNT1*, potassium channel, subfamily T, member 1; *KCTD7*, potassium channel tetramerization domain-containing protein 7; *LGI1*, leucine-rich gene, glioma-inactivated, 1; *LMNB2*, lamin B2; *NECAP1*, NECAP endocytosis-associated protein 1; *NHLRC1*, NHL repeat-containing 1 gene; *PCDH19*, protocadherin 19; *PLCB1*, phospholipase C, beta-1; *PNPO*, pyridoxamine 5-prime-phosphate oxidase; *PRDM8*, PR domain-containing protein 8; *PRICKLE1*, prickle, drosophila, homolog of, 1; *PRRT2*, proline-rich transmembrane protein 2; *SCARB2*, scavenger receptor class B, member 2; *SCN1A*, sodium channel, neuronal type I, alpha subunit; *SCN1B*, sodium channel, voltage-gated, type I, beta subunit; *SCN2A*, sodium channel, voltage-gated, type II, alpha subunit; *SCN8A*, sodium channel, voltage-gated, type VIII, alpha subunit; *SCN9A*, sodium channel, voltage-gated, type IX, alpha subunit; *SIK1*, salt-inducible kinase 1; *SLC1A2*, solute carrier family 1 (glial high affinity glutamate transporter), member 2; *SLC12A5*, solute carrier family 12 (potassium/chloride transporter), member 5; *SLC13A5*, solute carrier family 13 (sodium-dependent citrate transporter), member 5; *SLC25A12*, solute carrier family 25 (mitochondrial carrier, aralar), member 12; *SLC25A22*, solute carrier family 25 (mitochondrial carrier, glutamate), member 22; *SLC2A1*, solute carrier family 2 (facilitated glucose transporter), member 1; *SLC6A1*, solute carrier family 6 (neurotransmitter transporter, gaba), member 1; *SPTAN1*, spectrin, alpha, nonerythrocytic 1; *ST3GAL3*, ST3 beta-galactoside alpha-2,3-sialyltransferase 3; *ST3GAL5*, ST3 beta-galactoside alpha-2,3-sialyltransferase 5; *STX1B*, syntaxin 1B; *STXBP1*, syntaxin-binding protein 1; *SZT2*, seizure threshold 2, mouse, homolog of; *TBC1D24*, Tre2-Bub2-Cdc16/TBC1 domain family, member 24; *UBA5*, ubiquitin-like modifier activating enzyme 5; *WWOX*, WW domain-containing oxidoreductase.
[a] Description on phenotype was modified after retraction of the initial report.
[b] Potential modifier gene.