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Epilepsy-associated genes: an update

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ABSTRACT

Purpose: To provide an updated list of epilepsy-associated genes based on clinical-genetic evidence.
Methods: Epilepsy-associated genes were systematically searched and cross-checked from the OMIM, HGMD, and PubMed databases up to July 2023. To facilitate the reference for the epilepsy-associated genes that are potentially common in clinical practice, the epilepsy-associated genes were ranked by the mutation number in the HGMD database and by case number in the China Epilepsy Gene 1.0 project, which targeted common epilepsy.
Results: Based on the OMIM database, 1506 genes were identified to be associated with epilepsy and were classified into three categories according to their potential association with epilepsy or other abnormal phenotypes, including 168 epilepsy genes that were associated with epilepsies as pure or core symptoms, 364 genes that were associated with neurodevelopmental disorders as the main symptom and epilepsy, and 974 epilepsy-related genes that were associated with gross physical/systemic abnormalities accompanied by epilepsy/seizures. Among the epilepsy genes, 115 genes (68.5%) were associated with epileptic encephalopathy. After cross-checking with the HGMD and PubMed databases, an additional 1440 genes were listed as potential epilepsy-associated genes, of which 278 genes have been repeatedly identified variants in patients with epilepsy. The top 100 frequently reported/identified epilepsy-associated genes from the HGMD database and the China Epilepsy Gene 1.0 project were listed, among which 40 genes were identical in both sources.
Significance: Recognition of epilepsy-associated genes will facilitate genetic screening strategies and be helpful for precise molecular diagnosis and treatment of epilepsy in clinical practice.

1. Introduction

The widespread applications of next-generation sequencing technologies have accelerated the discovery of genes associated with epilepsy. Genetic factors are believed to be the major contributors to the cause of epilepsy in up to 80% of people with epilepsy [1–3]. In 2017, we summarized 977 genes that are associated with epilepsy based on clinical-genetic evidence [4]. Over the past six years, a great number of novel epilepsy-associated genes have been reported, which has led to encouraging progress in the field of epilepsy genetics. Recently, two genetic databases for epilepsy have been established: the Seizure-Associated Genes Across Species (SAGAS) database (www.sagas.ac), which included 2876 epilepsy-associated genes by gathering the genes potentially associated with seizures or epilepsies in multiple species [5], and the Gene4epilepsy database (https://github.com/bahlolab/genes4epilepsy), which contained 926 genes by comparing genes included on the epilepsy panels of four clinical diagnostic providers and two research resources, in which genes were mostly associated with developmental and epileptic encephalopathies [6]. From the perspective of clinical practice, it is important to know which genes are clinically associated with epilepsy and the relationships between epilepsy and the other abnormal phenotypes. As the pace of epilepsy-associated gene discovery accelerates, we now update the list of epilepsy-associated genes based on the genes that are currently reported to be related to

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epilepsy clinically. We searched for epilepsy-associated genes by reviewing the literature in the Online Mendelian Inheritance in Man (OMIM) database, Human Gene Mutation Database (HGMD), and PubMed. The purpose of the present study is to provide a list of epilepsy-associated genes that is potentially useful for facilitating the application of genetic tests in the clinical genetic diagnosis and precise treatment of epilepsy.

2. Methods

To update the list of genes associated with epilepsy, a systematic review was conducted based on data from online databases until July 2023. Following the methods described in the first version [4], genes were first searched in the OMIM database (https://www.omim.org/) using the following terms: "epilepsy/epilepsies/epileptic", "seizure/seizures", and "convulsion/convulsions". The OMIM database is the primary repository of comprehensive and curated information on genes and genetic phenotypes and the relationships between them [7]. Over 4000 items were retrieved from the OMIM database, among which those related to epilepsy with well-characterized genetic mutations in humans were included. The excluded items were (1) that in clinical genetic reports (studies) without definite molecular genetic confirmation; (2) that from linkage studies without identification of specific genes; (3) that were associated genomic rearrangement without definite causative genes; (4) the studies in which the patients with epilepsy had not been subjected to genetic tests; and (5) genes related to epilepsy in animal models but not in humans yet. The 977 genes in the first version were rereviewed and reclassified. Some genes have been upgraded with novel epilepsy-related evidence, whereas some were removed from the list of epilepsy-associated genes. Finally, 1506 genes were identified to be associated with epilepsy, including 680 previously reported in the first version and 826 newly obtained genes. According to the phenotype described currently in the OMIM database, these genes were classified into three categories: (1) epilepsy genes, i.e., genes that were potentially associated with epilepsies as pure or core symptoms, including genes that may be associated with multiple phenotypes other than epilepsy or seizures but have also been reported in cases presented pure epilepsy or seizures; (2) neurodevelopment-associated epilepsy genes, i.e., genes that were associated with gross brain developmental malformations or neurodevelopmental disorders that were accompanied by epilepsy or seizures; and (3) epilepsy-related genes, i.e., genes associated with gross physical or other systemic abnormalities and accompanied by epilepsy or seizures.

Then, genes with mutations in the epilepsy-related phenotypes were comprehensively searched in the HGMD (http://www.hgmd.cf.ac.uk/ac/index.php, version: HGMD Professional 2022.4). The HGMD constitutes a comprehensive collection of published germline mutations in nuclear genes that are thought to underlie or are closely associated with human inherited disease [8]. Furthermore, epilepsy-related publications from January 2017 to July 2023 were searched in the PubMed database. The terms "epilepsy/epilepsies/epileptic", "seizure/seizures", and "convulsion/convulsions" were used for the search. The results from these databases were cross-checked. The genes that were reported to be associated with epileptic phenotypes in the HGMD and/or PubMed databases but were not yet included in the OMIM database were listed as potential epilepsy-associated genes, which included 1367 genes from HGMD and an additional 73 genes that appeared only in PubMed. Compared with the previous version from 2017, we excluded 46 potential epilepsy-associated genes from the EpilepsyGene databases (http://61.152.91.49/EpilepsyGene/) due to insufficient evidence.

Genes from the two online databases for epilepsy, the SAGAS database and the Genes4Epilepsy database, were reviewed and checked by gene ID. There was duplicate recruitment of synonymous genes in the SAGAS database, including *ADGRV1/ADRV1, AKAP5/AKAP150, CDKL5/CDLK5, COX2/MTCO2, DNAJC21/DNAJA5, DNM1/DMN1, IFIH1/IFIHI1, MIR128/MIR128-1, MTTK/MT-TK, MTTW/MT-TW, MTOR/MTORC, MECP/MECP2, OCRL/OCRL1, PIK3CA/PI3KCA, SRP54/SCN8, SLC35A2/SCL35A2, SIK1/SIK1B*, and *SAMD12/FCMTE1*. The duplicate recruiting of synonymous genes in the Genes4Epilepsy database were *ADPRHL2/ADPRS, H3-3A/H3F3A, H3-3B/H3F3B*, and *PLPBP/PROSC*. After excluding duplicates, the epilepsy-associated genes were confirmed to be 2858 in the SAGAS database (2876 genes in the previous report) and 922 in the Genes4Epilepsy database (926 genes in the previous report), which were compared with the updated epilepsy-associated genes in the present study ($n = 2946$).

To facilitate the reference for the epilepsy-associated genes that are potentially common in clinical practice, we ranked the epilepsy-associated genes by the number of mutations associated with epileptic phenotypes in the HGMD database. Similarly, we ranked the causative genes by case number using data from the China Epilepsy Gene 1.0 project, which were obtained from trio-based whole-exome sequencing (WES) analysis of 2757 unrelated cases with common epilepsies, reflecting the scenery of the real world. Trio-based WES was performed in all cases. The included variants met the criteria in two aspects. First, the variants were *de novo*, recessive from the two asymptomatic parents each, hemizygous, or cosegregated variants, which highlights the genetic difference between the affected child and the parents and thus explains the occurrence of phenotype in a given family (trio). Second, the variants met the following criteria on the minor allele frequency (MAF): (1) the MAF for *de novo* variants is < 0.0001, according to gnomAD in the general population or East Asian population; (2) homozygotes/hemizygotes are not present in the controls, according to gnomAD; (3) the MAF of biallelic variants of compound heterozygotes is < 0.005 for each heterozygous variant; and (4) the MAF of cosegregated variants is < 0.005 and at least two affected individuals in a family. The top 100 epilepsy-associated genes from the HGMD database and the China Epilepsy Gene 1.0 project were listed.

3. Results

The present study established a list of 2946 epilepsy-associated genes (Fig. 1A) and grouped the genes according to their potential association with epilepsy and the relationship between epilepsy and other clinical abnormalities. These genes included 168 epilepsy genes, 364 neurodevelopment-associated epilepsy genes, and 974 epilepsy-related genes, which were recruited in OMIM (Fig. 1B, 1506 in total). An additional 1440 genes were retrieved from HGMD and PubMed and were listed as potential epilepsy-associated genes, among which variants in 278 genes have been repetitively identified in patients with epilepsy. Therefore, based on clinical-genetic evidence currently available, a total of 1784 (1506 + 278) genes are potentially significant in practice.

Compared with the SAGAS database and the Genes4Epilepsy database, 807 genes were common among the three databases. There were 62 genes from the Genes4Epilepsy database but were not enrolled in the present epilepsy-associated gene list, which were mostly genes involved in development but without clinical evidence on association with epilepsy, e.g., *AKT1*, which was associated with schizophrenia and development disorders [9,10], and *ZMYND8*, which was associated with autism spectrum disorder [11]. Almost 1000 genes from the SAGAS database were not included in the present list due to insufficient clinical evidence, such as *ADAM10* [12] and *HAS3* [13], which had only epilepsy-related evidence from animal studies. A total of 1025 genes uniquely appeared in the present list of epilepsy-associated genes (Fig. 1C).

3.1. Epilepsy genes

Overall, 168 genes were classified as epilepsy genes, including 82 genes from the previous version and 86 newly reported genes. Two epilepsy genes in the previous list, *ADRA2B* and *SCN9A*, were downgraded to potential epilepsy-associated genes due to the lack of definite evidence, such as a lack of cosegregation studies, high frequencies of

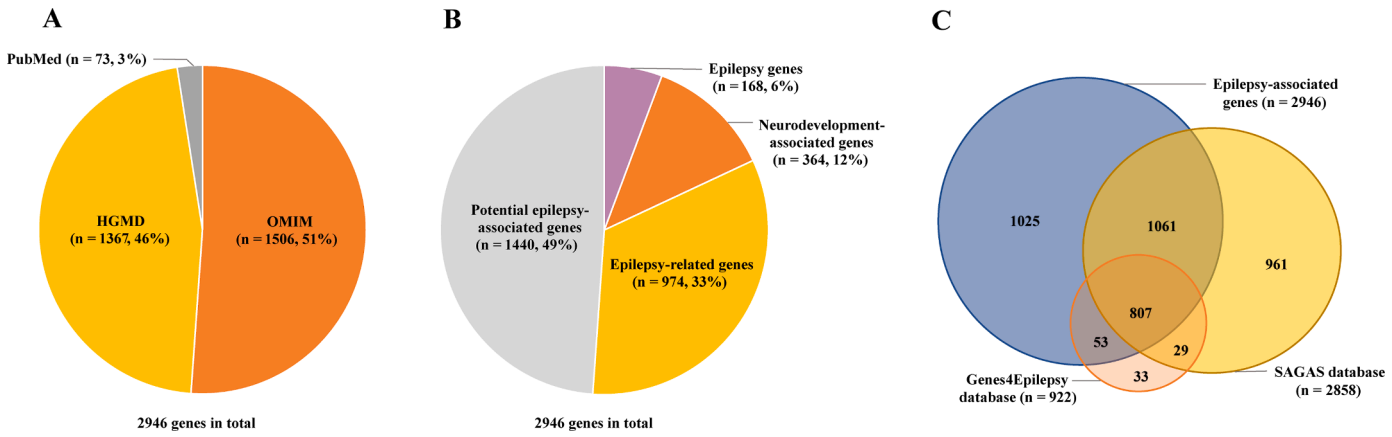

Fig. 1. The overall illustration of epilepsy-associated genes.
(A) Epilepsy-associated genes identified in the OMIM, HGMD, and PubMed databases.
(B) The epilepsy-associated genes were classified into four categories according to their potential association with epilepsy.
(C) Comparison of genes in the SAGAS database, the Genes4Epilepsy database, and the updated epilepsy-associated genes of the present study.

variants in the general population, and additional causative factors in the cases [14,15].

These 168 genes were listed according to the clinical features of epileptic phenotypes (Table 1). The majority of epilepsy genes (90, 53.6%) were of autosomal dominant inheritance; 62 genes were of autosomal recessive inheritance; 4 genes were of both autosomal dominant and recessive inheritance; 9 genes were of X-linked inheritance; and 3 genes had undefined inheritance pattern. Among these genes, 68.5% (115/168) were causative genes of epileptic encephalopathy, and 13 genes (7.7%) were causative genes of progressive myoclonic epilepsy. Heterogeneity in phenotypes and inheritance patterns has been observed in several genes, such as the *SLC12A5* variants that were associated with epileptic encephalopathy in autosomal recessive inheritance but with idiopathic generalized epilepsy in autosomal dominant inheritance [16–18].

3.2. Neurodevelopment-associated epilepsy genes

A total of 364 genes were categorized as neurodevelopment-associated epilepsy genes, which was 291 more than that in the first version. These genes were listed according to phenotype features (Table 2), which cover a wide range of brain abnormalities from focal brain malformations (e.g., cortical dysplasia) to general brain malformations (e.g., microcephaly) and others.

The neurodevelopment-associated genes presented recessive inheritance in the majority (214/364, 58.8%), including 206 genes with autosomal recessive inheritance and 8 genes with X-linked recessive inheritance. Four genes were associated with the inheritance of both autosomal dominant and recessive features, including *AP1G1, ATAD3A, CLCN3*, and *NARS1*.

An increasing number (211) of genes associated with general neurodevelopmental disorders have been identified, including 49 genes with multisystemic abnormalities (e.g., cardiac defects, renal anomalies, and gastrointestinal issues). For instance, variants in *ADNP* cause Helsmoortel-Van der Aa syndrome (HVDAS), which is a neurodevelopmental disorder characterized by impaired intellectual development/motor delay, autism spectrum disorder, facial dysmorphisms, hypotonia, congenital heart disease, visual difficulties, and gastrointestinal issues [19]. In contrast, 162 genes have not been associated with multisystemic abnormalities reported thus far.

3.3. Epilepsy-related genes

Up to 974 genes were categorized as epilepsy-related genes, which was 438 more than that in the first version. These genes are listed in Table 3, with the detailed epilepsy-related phenotypes in Table S1.

Genes with recessive inheritance accounted for the majority (665/974, 68.3%), which included 605 genes with autosomal recessive inheritance and 60 genes with X-linked recessive inheritance. Both autosomal dominant and recessive inheritance features were observed in 26 genes.

Variants in these genes result in diseases presenting gross physical or other systemic abnormalities that are accompanied by epilepsy or seizures, e.g., mitochondrial complex deficiency, cardiac disease, and metabolic disorders. Cardiac diseases, such as long QT syndrome, congenital heart defects, cardiomyopathy, and heart block, potentially present cardiac arrhythmias and subsequently recurrent syncope, seizures, and even sudden death [20]. Metabolic disorders, typically as combined oxidative phosphorylation deficiency and glycogen storage disease, are potentially associated with seizures due to the involvement of the central nervous system.

3.4. Potential epilepsy-associated genes

In total, 1440 genes were classified as potential epilepsy-associated genes, including 1367 genes from the HGMD database and an additional 73 genes from PubMed (Table 4). The reported epileptic phenotypes with the corresponding number of mutations in each gene are listed in Table S2. The majority of the genes (1162) had only a single variant identified in epileptic phenotypes and thus warrant further studies to validate their association with epilepsy. In contrast, variants of 278 genes have been repeatedly identified in patients with epilepsy, including 34 genes with 5 or more variants identified in epileptic phenotypes. Validating experimental evidence supporting the gene-disease association was also obtained for some genes, such as *PRICKLE2* [21], *KCNH5* [22], *GABRA6* [23], *KCND2* [24,25], and *UNC13B* [26], which are potential epilepsy genes but have not yet been included in OMIM.

3.5. Frequently reported/identified epilepsy-associated genes

The top 100 epilepsy-associated genes obtained from the HGMD and the China Epilepsy Gene 1.0 project are summarized in Table 5. *SCN1A* is the most frequent epilepsy gene in both databases. While 40 genes appeared identically, the epilepsy-associated genes differed in 60 genes in the two databases, potentially due to the study subjects and publication bias. For example, *STXBP1* has been associated with rare and severe epileptic encephalopathy and is ranked seventh among the top 100 epilepsy-associated genes from the HGMD database, potentially due to the severe phenotype that is commonly the subject of studies; however, *STXBP1* did not appear in the top 100 epilepsy-associated genes

Table 1
Epilepsy genes ($n = 168$).

Phenotype (in order of the onset age)	Inheritance	Genes by 2017	Genes updated
Neonatal			
Pyridoxine-dependent epilepsy	AR	*ALDH7A1, PNPO*	*PLPBP*
Benign familial neonatal seizures (BFNS)	AD	***KCNQ2***, *KCNQ3*	
Myoclonus, intractable, neonatal	AD		*KIF5A*
Rigidity and multifocal seizure syndrome, lethal neonatal	AR		*BRAT1*
Infantile and childhood			
Familial infantile myoclonic epilepsy (FTLE)	AR	***TBC1D24***	
Benign familial infantile seizures (BFIS)	AD	*PRRT2*, ***SCN2A, SCN8A***	
Epileptic encephalopathy	AD	*CACNA1A, CHD2, DNM1, EEF1A2, FGF12*, ***GABRA1***, *GABRB1*, ***GABRB3, GABRG2***, *GNAO1, GRIN2B, GRIN2D*, ***HCN1***, *KCNA2, KCNB1*, ***KCNQ2, KCNT1, SCN1A, SCN2A, SCN8A***, *SIK1, SLC1A2, SPTAN1*	*AP2M1, ATP1A2, ATP1A3, ATP6V0A1, ATP6V1A, ATP6V0C, CACNA1E, CDK19, CELF2, CUX2, CYFIP2, FBXO28, FZR1, GABBR2, GABRA2, GABRA5, GABRB2, HNRNPU, KCNC2, KCNT2, MAST3, NEUROD2, NSF, NTRK2, NUS1, PACS2, PHACTR1, PPP3CA, RHOBTB2, RNF13*, ***SCN3A***, *SETD1A, SETD1B, YWHAG*
	AR	*AARS1, ARV1, DOCK7, FRRS1L, GUF1, ITPA, NECAP1, PLCB1*, ***SCN1B, SLC12A5***, *SLC13A5, SLC25A12, SLC25A22, ST3GAL3, ST3GAL5, SZT2*, ***TBC1D24***, *UBA5, WWOX*	*ACTL6B, ADAM22, AP3B2, CACNA2D1, CAD, CNPY3, CPLX1, DALRD3, DENND5A, DMXL2, GAD1, GLS, GOT2, GRIN1, HID1, MDH1, MDH2, NAPB, NRROS, PARS2, PIGB, PIGP, PIGS, SLC38A3, SYNJ1, TRAK1, UFSP2, UGDH, UGP2*
	AD, AR	*STXBP1*	
	XLD	*CDKL5*	*SLC35A2, SMC1A*
	XLR		*ARX*
	XL	*ALG13, ARHGEF9, PCDH19*	*FGF13, GABRA3*
Dravet syndrome (DS)	AD	***SCN1A***	
Familial febrile seizures (FFS)	AD	*ADGRV1*, ***GABRG2, SCN1A***	***HCN2***
	AR	***CPA6***	
Generalized epilepsy with febrile seizures plus (GEFS+)	AD	***GABRD, GABRG2, SCN1A, HCN1, SCN1B***, *STX1B*	***HCN2***
Myoclonic-atonic epilepsy (MAE)	AD	*SLC6A1*	
Focal epilepsy and speech disorder	AD	*GRIN2A*	
(FESD) with or without impaired intellectual development			
Childhood absence epilepsy (CAE)	AD	***GABRG2***	
	UN	***CACNA1H, GABRA1, GABRB3***	
Juvenile and later			
Juvenile absence epilepsy (JAE)	AD	***CLCN2, EFHC1***	
Juvenile myoclonic epilepsy (JME)	AD	***CACNB4, CLCN2, EFHC1, GABRD***	*ICK*
	UN	***GABRA1***	
Idiopathic generalized epilepsy (IGE)	AD	***CACNB4, CLCN2, GABRD***, *KCNMA1*, ***SLC12A5***, *SLC2A1*	*RORB*, ***HCN2***, *HCN4*
	UN	***CACNA1H***, *CASR*	
Familial adult myoclonic epilepsy (FAME)	AD		*TNRC6A, RAPGEF2, YEATS2, SAMD12, STARD7, MARCH6*
	AR	*CNTN2*	
Familial temporal lobe epilepsy (FTLE)	AD	***CPA6***, *GAL, LGI1*	*RELN*
Not specific			
Progressive myoclonic epilepsy (PME)	AD	*KCNC1*	*SEMA6B*
	AR	*CERS1, CSTB, EPM2A, GOSR2, KCTD7, LMNB2, NHLRC1, PRDM8, PRICKLE1, SCARB2*	*SLC7A6OS*
Nocturnal frontal lobe epilepsy (NFLE)	AD	*CHRNA2, CHRNA4*, ***KCNT1***	
	UN	*CHRNB2*	
Familial focal epilepsy with variable foci (FFEVF)	AD	*DEPDC5*	*NPRL2, NPRL3*, ***SCN3A***

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.

from the China Epilepsy Gene 1.0 project, which targeted common epilepsies, including common epilepsy with favorable outcomes (e.g., *UNC13B*). This explains the appearance of several newly identified epilepsy genes, such as *HCFC1* [27], *BCOR* [28], *PKD1* [29], *AFF2* [30], *MED12* [31], *NEXMIF* [32], *BSN* [33], *CELSR1* [34], *FAT1* [35], *LAMA5* [36], *BRWD3* [37], *CELSR3* [38], *FRMPD4* [39], *RYR2* [40], *SHROOM4* [41], *UNC13B* [26], *APC2* [42], *CHD4* [43], *PGM3* [44], *MPDZ* [45], *ATP6V0C* [46] and *UNC79* [47], in the epilepsy-associated genes from the China Epilepsy Gene 1.0 project.

4. Discussion

The gene-disease association refers to three levels in general: (1) what phenotype a gene is associated with; (2) whether a gene is associated with the phenotype (pathogenic potential of a gene); and (3) how a gene is associated with the phenotype (pathogenic feature of a gene). Evaluating gene-disease associations is a complex task that involves multiple aspects of evidence. The present study focused on the first level of gene-disease association, i.e., which gene is potentially associated with epilepsy and the relationship between epilepsy and other clinical abnormalities. A list of epilepsy-associated genes was established based on clinical-genetic evidence, which provides an overview of the epilepsy-associated genes and is potentially helpful for gene screening in clinical practice. The epilepsy-associated genes were further classified into four categories, which are potentially useful for clinical genetic diagnosis and precise treatment.

Table 2
Neurodevelopment-associated epilepsy genes ($n = 364$).

Phenotype	Inheritance	Genes by 2017	Genes updated
Focal or multifocal brain malformation			
grey matter			
Holoprosencephaly	AD	*PTCH1*	*CNOT1*
	AR		*PLCH1*
Pseudo-TORCH syndrome	AR	*OCLN*	
Polymicrogyria	AR	***ADGRG1***, *FIG4*	*COL3A1, PI4KA*
	UN	***ADGRG1***	
CK syndrome	XLR	*NSDHL*	
Megalencephaly-polymicrogyria-polydactyly-hydrocephalus syndrome	AD	*PIK3R2*	*AKT3, CCND2*
Rolandic epilepsy, impaired intellectual development, and speech dyspraxia	UN	*SRPX2*	
Periventricular heterotopia	AD	*ERMARD*	*ARF1, MAP1B, NEDD4L*
	AR	*ARFGEF2*	
	XLD	*FLNA*	
Band heterotopia	AR		*EML1*
Subcortical laminar heterotopia	AD	***PAFAH1B1***	
	XL	***DCX***	
Focal cortical dysplasia, type II, somatic	UN		*MTOR*
Complex cortical dysplasia with other brain malformations	AD	*KIF2A, KIF5C, TUBB2A, TUBB2B, TUBB3, TUBG1*	
	AR		*APC2, CAMSAP1, CTNNA2*
Pitt-Hopkins like syndrome	AR	*CNTNAP2*	
Occipital cortical malformations	AR	*LAMC3*	
Pontocerebellar hypoplasia	AR	*AMPD2, CLP1, EXOSC3, PCLO, SEPSECS, TSEN2, TSEN15, TSEN54, VPS53*	***ATAD3A***, *CDC40, EXOSC9, MINPP1, PPIL1, PRDM13, RARS2, SLC25A46, TBC1D23, TOE1, VPS51*
Cerebellar hypoplasia/atrophy	AR		*CACNA2D2, EXOSC5, OXR1, VLDLR*
Diencephalic-mesencephalic junction dysplasia syndrome	AR		*PCDH12*
Dentatorubro-pallidoluysian atrophy	AD	***ATN1***	
Idiopathic basal ganglia calcification	AD	*SLC20A2, XPR1*	
	AR		*JAM2, MYORG*
White matter			
Agenesis of the corpus callosum	AD		*CDH2*
	AR	*SLC12A6*	
	XLR		*L1CAM*
Encephalopathy, progressive, early-onset, with brain atrophy and thin corpus callosum	AR		*TBCD*
Leukodystrophy/Leukoencephalopathy	AD		*ATP11A, CLDN11, CSF1R, EIF2AK2, FBP2, TMEM106B, TMEM163, TUBB4A*
	AR	*PLEKHG2*	*AIMP1, AIMP2, ARSA, CNP, DARS2, DEGS1, EIF2B1, EIF2B2, EIF2B3, EIF2B4, EIF2B5, EPRS,*

Table 2 (*continued*)

Phenotype	Inheritance	Genes by 2017	Genes updated
			HEPACAM, HSPD1, HYCC1, MLC1, KARS1, POLR3A, POLR3B, POLR3K, PYCR2, RARS1, RNASET2, SNORD118, UFM1, VPS11
	XLR		*PLP1*
General brain malformation & others			
Lissencephaly	AD	*TUBA1A*, ***PAFAH1B1***	*CEP85L, MACF1*
	AR	*CDK5, KATNB1, LAMB1, NDE1*	*TMTC3*
	XL	***DCX***	
Mega-corpus-callosum syndrome with cerebellar hypoplasia and cortical malformations	AD		*MAST1*
Microcephaly with variable abnormalities	AD	*KIF11*	
	AR	*DIAPH1, IER3IP1, MED17, PNKP, PPP1R15B, QARS1, RTTN, STAMBP, TRMT10A*	*DTYMK, SLC1A4, TUBGCP6, TUBGCP2, WDR4, YIPF5*
Primary microcephaly	AD		*LMNB1*
	AR	*ANKLE2, ASPM, CENPE, CENPJ, WDR62, SASS6*	*CIT, NCAPD3, PDCD6IP, STIL, ZNF335*
Macrocephaly, dysmorphic facies, and psychomotor retardation	AR	*HERC1*	
Polyhydramnios, megalencephaly, and symptomatic epilepsy	AR	*STRADA*	
Hypotonia with psychomotor retardation and characteristic facies	AR		*NALCN, TBCK, UNC80*
Hydrocephalus	AD		*SMARCC1, TRIM71*
	AR	*CCDC88C, MPDZ*	
Brain small vessel disease	AD	*COL4A2*	*COL4A1*
Schizencephaly	UN	*EMX2*	*SIX3*
Neurodevelopmental disorder	AD		*ADGRL1, AGO1, ARFGEF1, BAP1, BPTF, BRPF1, CACNA1C, CACNA1I, CDC42BPB, CHAMP1, CHD1, CHD3, CHD5, CSNK2B, DHDDS, DHX30, DLL1, DPYSL5, FBXW7, FOXG1, FOXP1, FRMD5, GNAI1, GRIA2, GRIA4, GRIK2, H3-3A, H3-3B, H4C3, H4C5, HDAC4, HECW2, HNRPH1, HNRPR, IRF2BPL, KAT8, KCNN2, KDM6B, KMT2C, KMT2E, LMBRD2, MAPK8IP3, MEF2C, NACC1, NBEA, NCDN,*

(*continued on next page*)

Table 2 (*continued*)

Phenotype	Inheritance	Genes by 2017	Genes updated
			NOVA2, NR4A2, PAK1, PHF21A, POGZ, POLR2A, POU3F3, PPP2CA, PRKAR1B, RAB11B, RALA, RFX7, RNF2, SOX5, TANC2, TCF20, TRIO, TRPM3, UBE3A, VAMP2, WASF1, WDR26, ZIC1, ZMIZ1, ZSWIM6
	AR	*MFSD2A, SNIP1*	*ADARB1, ATP9A, BCAS3, CACNA1B, CHKA, CPSF3, CRADD, DEAF1, DHPS, DOHH, DYNC1I2, EMC10, ESAM, EXOC2, EXOC7, EXOC8, EXT2, GPT2, GRM7, GTPBP2, HECTD4, HPDL, INTS8, INTS11,* LNP*K, MADD, MED11, MED27, MTHFS, NAE1, NFASC, NRCAM, NSRP1, NTNG2, OGDHL, P4HTM, PCDHGC4, PDZD8, PGAP1, PIDD1, PIGG, PIGK, PIGU, PLAA, PLXNA1, PPFIBP1, PRUNE1, PTPN23, PUS3, RALGAPA1, RBL2, SHQ1, SMPD4, SPATA5L1, SPTBN4, SVBP, TAF8, TBC1D2B, THUMPD1, TIAM1, TMEM222, TMX2, TRAPPC10, TRAPPC4, TRAPPC6B, TTC5, UBE3C, UBE4A, UFC1, VARS1, WARS1, WDR45B, YIF1B, ZNF142, ZNF526, ZNF668, ZNHIT3*
	AD, AR		*AP1G1,* ***ATAD3A****, CLCN3, NARS1*
	XLR	*OPHN1*	*HS6ST2, BCORL1, ZC4H2*
	XLD	*CASK*	*HNRNPH2*
	XL	*SYN1*	*SLITRK2*
Neurodevelopmental disorder with multisystemic abnormalities	AD	***ATN1****, TSC1, TSC2*	*ASXL2, ADNP, AGO2, CDK8, CREBBP, CSNK2A1, CUL3, DPH5, GATAD2B, GNB2, KAT5, MED12L, PSMD12, PURA,*
	AR	*SPATA5, WDR73*	*RAC3, SIAH1, SPEN, SUPT16H, TRRAP, USP7, WAC, ZMYM2, CAPN15, DHX37, FRA10AC1, GEMIN4, INTS1, KIAA1109, PGM2L1, PIGN, PIGQ, PIGT, SARS1,* SEC*31A, THOC6, TMEM147, TMEM94, UBR7, VPS50, WARS2*
	XLD		*TCEAL1*
	XLR		*PIGA*
	XL		*NAA10, HUWE1*

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.

In this study, 168 genes were classified as epilepsy genes, which was twice as many as in the first version in 2017 [4]. Variants in these genes cause pure or relatively pure epilepsies or syndromes with epilepsy as the core syndrome. These genes probably play a major role in patients with epilepsy as the primary clinical manifestation. It is noteworthy that genes associated with neurodevelopmental abnormalities or other systemic abnormalities are also potentially associated with pure epilepsies, such as *MED12* [31], *RYR2* [40], and *PKD1* [29], as shown in recent studies.

The present list included 364 neurodevelopment-associated epilepsy genes, which were associated with general or focal brain structural abnormalities. The etiology of epilepsy is currently classified into structural, genetic, infectious, metabolic, immune, and unknown [48]. However, the growing number of genes potentially associated with brain structure abnormalities suggests attention to the underlying genetic etiology of brain structure disorders, which implies significance in clinical practice, such as presurgical evaluation.

Up to 974 genes were considered as epilepsy-related genes. Variants in these genes result in diseases presenting gross physical or other systemic abnormalities that are accompanied by epilepsy or seizures. The typical clinical features of gross physical or systemic abnormalities provide useful evidence for clinical and genetic diagnosis. A comprehensive systemic examination is required to detect specific systemic involvement, such as cardiac examination, metabolic screening, and hormone blood tests, depending on the specific genetic etiology. Accurate and early genetic diagnosis is potentially helpful in the precise management of patients, such as riboflavin in patients with glutaric acidemia caused by *ETFDH* mutations [49].

In the present study, 1440 genes were considered as potential epilepsy-associated genes. The evidence supporting their gene-disease associations varies. Most of these genes had only a single case reported and thus warrant further studies to validate the gene-disease associations. In contrast, clinical and experimental evidence has been obtained supporting the gene-disease association in several genes, such as *UNC13B*. Variants in *UNC13B* have been recurrently identified in unrelated families with partial (focal) epilepsy and/or febrile seizures [26,50]; *Unc13b* knockdown in Drosophila increased seizure-like behavior and firing of neurons in electrophysiological recordings [26]; and other evidence, such as lethality by genetic knockout, high pRec (1.0), expression profile, and vesicle-release related function (https://gdap.org.cn/), also support the gene-disease association.

We listed the top 100 frequently reported/identified epilepsy-associated genes that were ranked by mutation number in the HGMD database and case number in the China Epilepsy Gene 1.0 project, which

Table 3
Epilepsy-related genes ($n = 974$).

Inheritance	Genes
AD	*ABCC8, ACTA2, ACTB, ACTG1, ACVR1, AFF3, AHDC1, AKAP9, AKT2, ALG10B, ANKH, ANKRD11, ANKRD17, APP, ARCN1, ARID1A, ARID1B, ARID2, ASH1L, ASXL1, ASXL3, ATP1A1, ATP2A2, ATP2B1, ATXN10, AUTS2, BCL11B, BICD2, BICRA, BMP4, BRAF, CACNA1D, CACNA1G, CALM2, CALM3, CAMK2B, CAMTA1, CAV3, CCM2, CDC42, CDK13, CELSR1, CERT1, CHD4, CHD8, CHN1, CIC, CLCN6, CLTC, CNOT2, CNOT3, COMT, CTLA4, DHX16, DIP2B, DLG4, DNAJC5, DNMT1, DNMT3A, DRD3, DYNC1H1, DYRK1A, EBF3, EED, EFTUD2, EHMT1, ELN, EZH2, FAM111A, FBXO11, FGF8, FGFR2, FGFR3, FXYD2, GARS1, GATA6, GCK, GFAP, GJA1, GLI2, GLI3, GLUD1, GNA11, GNB1, HIVEP2, HMBS, HNF1B, HTR2A, HTRA1, INSR, IRF3, ITPR1, KANSL1, KAT6A, KCNA1, KCNE1, KCNE2, KCNH1, KCNH2, KCNJ11, KCNJ5, KCNJ6, KCNK4, KCNQ1, KCNQ5, KDM1A, KDM3B, KDM4B, KIF1A, KMT2A, KMT2D, KMT5B, KRAS, KRIT1, LMX1B, LRRK2, MAF, MAGEL2, MAP2K1, MAPK1, MAPRE2, MAPT, MBD5, MED13, MED13L, MEN1, MN1, MSX2, MYRF, MYT1L, NAA15, NF1, NFE2L2, NFIA, NIPA1, NIPBL, NOD2, NONO, NOTCH1, NOTCH2, NOTCH2NLC, NOTCH3, NPTX1, NR2F1, NSD1, NSD2, OTX2, PACS1, PAK2, PDYN, PHOX2B, PKD1, POLG2, POMP, PPOX, PPP1R12A, PPP2R1A, PPP2R5D, PRKACB, PRNP, PROK2, PSEN1, PSEN2, PTEN, PUF60, PUM1, RAC1, RAD21, RAI1, RANBP2, RBP4, ROBO1, RORA, RRAGD, PROKR2, RNF125, RTN4R, RYR1, RYR2, SATB1, SATB2, SCN5A, SERPINI1, SET, SETBP1, SETD2, SGCE, SHANK3, SIN3A, SLC25A4, SMAD2, SMARCA2, SMARCA4, SMARCB1, SMARCC2, SMARCE1, SNORA31, SNTA1, SON, SOX2, SOX4, SPAST, SPECC1L, SPOP, SPTBN1, SPTLC2, SRCAP, SRP54, STAG1, STUB1, SYN2, SYNGAP1, TBK1, TBL1XR1, TBP, TBX1, TCF4, THRB, TLK2, TNPO2, TOP2B, TP53, TRAF3, TRAF7, TRIM8, TRIP12, TTR, UBTF, VPS4A, WDR37, ZBTB18, ZEB2, ZMYND11, ZNF292* ($n = 234$)
AR	*AASS, ABAT, ABCA2, ABHD12, ABHD16A, ACADM, ACADS, ACADSB, ACO2, ACOX1, ACY1, ADA2, ADAMTSL2, ADD3, ADK, ADPRHL2, ADSL, AFG3L2, AGA, AGL, AGPS, AHI1, ALDH18A1, ALDH3A2, ALDH4A1, ALDH5A1, ALDOB, ALG1, ALG11, ALG12, ALG14, ALG2, ALG3, ALG6, ALG8, ALG9, ALKBH8, ALPL, AMACR, AMFR, AMT, ANK3, ANO10, ANTXR1, AP3D1, AP4B1, AP4E1, AP4M1, AP4S1, APOPT1, ARG1, ARHGDIA, ARMC9, ARNT2, ASAH1, ASL, ASNS, ASPA, ASS1, ATAD1, ATG7, ATIC, ATM, ATP13A2, ATP5F1A, ATP5F1D, ATP5F1E, ATP5PO, ATP6V0A2, ATP7B, ATPAF2, AUH, B3GALNT2, B4GAT1, B9D2, BCKDHA, BCL10, BCS1L, BLOC1S6, BOLA3, BRCA2, BSCL2, BTD, BUB1B, C12orf57, C2orf69, CAMLG, CARD9, CARS2, CASQ2, CC2D2A, CCBE1, CCDC88A, CD59, CDK10, CEP164, CHKB, CKAP2L, CLDN16, CLN3, CLN5, CLN6, CLN8, CLPP, CNTNAP1, COG2, COG4, COG5, COG6, COG7, COL18A1, COLGALT1, COPB1, COQ2, COQ4, COQ5, COQ6, COQ8A, COQ9, CORO1A, COX10, COX11, COX15, COX4I1, COX6B1, COX8A, COXFA4, CPS1, CPT1A, CRB2, CRBN, CRIPT, CRLF1, CRLS1, CRYAB, CSPP1, CTC1, CTH, CTSA, CTSD, CTSF, CYB5R3, CYP27A1, CYP27B1, D2HGDH, DCAF17, DDX59, DHCR24, DHFR, DHTKD1, DLD, DNAJC12, DNAJC21, DNAJC6, DOCK6, DOCK8, DOLK, DPAGT1, DPH1, DPM1, DPM2, DPM3, DPP9, DPYD, DPYS, DSTYK, EARS2, ECHS1, ECM1, EGF, EIF3F, ELOVL4, ELP2, EMC1, EN1, ENTPD1, EPG5, ERCC6, ERLIN2, ESCO2, ETFDH, ETHE1, EXTL3, F2, FA2H, FADD, FAR1, FARS2, FARSB, FASTKD2, FAT4, FBXL4, FCHO1, FCSK, FDFT1, FH, FIT2, FKTN, FLVCR2, FMN2, FOLR1, FOXRED1, FTO, FUT8, GALC, GALNT2, GAMT, GBA, GCDH, GCH1, GCSH, GET4, GFER, GFM1, GFM2, GGT1, GJC2, GLB1, GLDC, GLE1, GLRB, GLUL, GLYCTK, GM2A, GMPPB, GNB5, GNPAT, GOLGA2, GPAA1, GPSM2, GPX4, GRM1, GRN, GSS, GTPBP3, GUCY1A3, GYS1, GYS2, HACE1, HADHSC, HAX1, HERC2, HEXA, HGSNAT, HHAT, HIBCH, HINT1, HLCS, HMGCL, HMGCS2, HMOX1, HPD, HSD17B4, HTRA2, IARS1, IARS2, IBA57, IFNAR1, IFNAR2, IFT140, IL6ST, INPP5K, IQSEC1, IREB2, ISCA1, ISCA2, ISG15, JAM3, KCNJ10, KIAA0753, KIF7, KLHL7, KPTN, L2HGDH, LAMA2, LAMA5, LARS1, LARS2, LCP2, LETM1, LGI3, LGI4, LIAS, LIG3, LINGO1, LIPT2, LMAN2L, LMBRD1, LRP2, LRPPRC, LSM11, LSS, MAGI2, MAN1B1, MANBA, MAPKAPK5, MBOAT7, MCCC1, MCCC2, MCM3AP, MCM8, MDM2, MED23, MED25, MEGF10, METTL23, METTL5, MFF, MFSD8, MGAT2, MGP, MICOS13, MICU1, MIPEP, MKS1, MLYCD, MMAA, MMACHC, MMADHC, MOCS1, MOCS2, MOGS, MPC1, MPDU1, MPI, MPV17, MRAP, MRM2, MRPL12, MRPS22, MTFMT, MTHFD1, MTHFR, MTO1, MTR, MTX2, MYMK, MYO1H, MYO5A, NADK2, NAGA, NAGLU, NANS, NARS2, NAXD, NAXE, NBAS, NDST1, NDUFA13, NDUFA2, NDUFA6, NDUFA8, NDUFAF2, NDUFAF3, NDUFAF4, NDUFAF5, NDUFAF6, NDUFAF8, NDUFB8, NDUFC2, NDUFS3, NDUFS4, NDUFS7, NDUFS8, NDUFV1, NDUFV2, NEU1, NFS1, NGLY1, NIN, NNT, NPC1, NPC2, NRXN1, NSUN2, NSUN3, NTRK1, NUBPL, NUP133, NUP214, OGDH, OPA3, ORAI1, OSGEP, OTUD6B, P4HTM, PAH, PANK2, PARN, PC, PCCA, PCCB, PCDH15, PCK1, PCNT, PCSK1, PCYT2, PDE10A, PDE2A, PDHB, PDHX, PDP1, PDSS2, PET100, PEX1, PEX10, PEX12, PEX13, PEX14, PEX19, PEX2, PEX26, PEX3, PEX5, PEX6, PEX7, PGAP2, PGAP3, PGM1, PGM3, PHGDH, PHKG2, PIBF1, PIGC, PIGF, PIGH, PIGL, PIGM, PIGO, PIGV, PIGW, PIGY, PITRM1, PLA2G6, PLVAP, PMM2, PMPCB, PNPLA8, PNPT1, POLE, POLG, POMC, POMGNT1, POMK, POMT1, POMT2, PPA2, PPCS, PPP2R3C, PPT1, PRDX1, PRF1, PRKDC, PRMT7, PRODH, PRORP, PROS1, PSAP, PSAT1, PSMB8, PSPH, PTRH2, PTS, QDPR, RAB18, RAB27A, RAB3GAP1, RAB3GAP2, RAPSN, RBCK1, RBM8A, RFT1, RMND1, RNASEH2A, RNU12, RNU7–1, ROGDI, RPIA, RRM2B, RSRC1, RTN4IP1, RUBCN, RUSC2, SACS, SARDH, SBF1, SCO2, SCYL1, SCYL2, SDHA, SDHB, SDHD, SELENOI, SERAC1, SGPL1, SGSH, SLC12A1, SLC12A3, SLC17A5, SLC19A2, SLC19A3, SLC25A1, SLC25A10, SLC25A13, SLC25A15, SLC25A19, SLC25A20, SLC25A3, SLC25A36, SLC25A42, SLC26A4, SLC28A1, SLC31A1, SLC33A1, SLC35A1, SLC35A3, SLC35C1, SLC39A8, SLC44A1, SLC45A1, SLC46A1, SLC5A6, SLC6A19, SLC9A1, SMARCAL1, SMC5, SMG9, SMO, SNAP29, SNX14, SOBP, SPTSSA, SQOR, STAR, STAT1, STAT2, STT3A, STT3B, STX11, STXBP2, SUCLA2, SUCLG1, SUMF1, SUOX, SURF1, SYT14, TAF13, TAF2, TANGO2, TARS2, TASP1, TBC1D20, TBCE, TBX19, TCIRG1, TDP1, TDP2, TECPR2, TELO2, TGFB1, THG1L, TIMM50, TIMMDC1, TMCO1, TMEM165, TMEM67, TMEM70, TP53RK, TPK1, TPP1, TRAPPC11, TRAPPC12, TRAPPC9, TRIP13, TRIT1, TRMT1, TRMT5, TRNT1, TRPM6, TSFM, TSPYL1, TWNK, TXN2, TYROBP, UCHL1, UGT1A1, UNC13D, UPB1, UQCC2, USP18, USP53, VARS2, VPS13A, VPS13B, VPS13D, VPS35L, VPS41, WASHC4, WFS1, WIPI2, XPNPEP3, YARS1, YRDC, ZBTB11, ZFYVE26, ZMPSTE24, ZNFX1* ($n = 605$)
AD, AR	*APOE, CAMK2A, CFH, CLPB, CNNM2, CPT2, DNM1L, FTL, GCM2, GLRA1, GRIA1, HESX1, HTT, IFIH1, OPLAH, POLRMT, PROC, PTH, RNF213, SLC16A1, SPR, TET3, TICAM1, TLR3, TREX1, ZFP57* ($n = 26$)
XLD	*AMER1, ATRX, BCOR, CLCN4, FMR1, GDI1, HCCS, HNRNPH2, HSD17B10, IQSEC2, KDM6A, MSL3, NDUFB11, NEXMIF, NHS, PDHA1, USP9X, WDR45* ($n = 17$)
XLR	*ABCD1, AFF2, AIFM1, ANOS1, AP1S2, ATP6AP1, ATP6AP2, ATP7A, AVPR2, BCAP31, BRWD3, CHRDL1, CLIC2, CUL4B, DKC1, DLG3, EBP, EIF2S3, FAM50A, FGD1, FTSJ1, GK, GRIA3, HCFC1, HPRT1, IDS, IKBKG, IL1RAPL1, KDM5C, KIF4A, KLHL15, LAGE3, MAOA, MBTPS2, MECP2, MED12, MID2, NDP, NDUFA1, OCRL, OFD1, OTUD5, PAK3, PGK1, PHF6, PHF8, PQBP1, RAB39B, RBM10, RPL10, SLC6A8, SMS, SSR4, STS, SYP, TAF1, THOC2, TMLHE, UBE2A, UPF3B* ($n = 60$)
XL	*CNKSR2, DDX3X, FRMPD4, GLRA2, NLGN3, OTC, RNF113A, SLC9A6, TFE3, XK, ZDHHC9* ($n = 11$)
DR	*KNSTRN+PIK3CD* ($n = 2$)
UN	*ACSF3, BCKDK, CACNG2, CEP290, COG8, FGFR1, GNAQ, GPHN, HADHA, HADHB, IDH2, KCNK9, MTSS2, NAT8L, NRAS, PIK3CA, SLC1A3, SLC9A9, ZFHX3* ($n = 19$)

AD, autosomal dominant; AR, autosomal recessive; DR, Digenic recessive; UN, unknown; XL, X-linked; XLD, X-linked dominant; XLR, X-linked recessive.

may be referred in clinical practice. While severe epilepsies such as epileptic encephalopathy are more commonly targeted in clinical and genetic studies, attention is advocated for genes associated with common epilepsies, which is potentially significant in the clinical management of patients, e.g., *UNC13B* [26] and *FAT1* [35]. The patient with the biallelic *UNC13B* variant presented with frequent daily seizures with abnormalities of the hippocampus but achieved seizure-free status without surgery [26]. The patients with *FAT1* variants showed relapse of epilepsy after long-term seizure-free status, which could potentially be explained by the genetic expression (dependent) stage of *FAT1* [35], offering an example of how to consider the optimal duration of therapies.

Regarding whether a gene is associated with a phenotype, two frameworks have been developed previously by Clinical Genome Resource (ClinGen) [51] and Ambry Genetics [52]. The two frameworks score publicly available clinical genetic and experimental evidence, and the scoring on clinical genetic evidence was generally based on the number of cases/variants or statistical data. ClinGen has curated 2265

Table 4
Potential epilepsy-associated genes ($n = 1440$).

Source	Genes
HGMD	*AACS, AARS2, AARSD1, AATK, ABCA10, ABCA5, ABCA6, ABCA7, ABCB1, ABCB11, ABCB9, ABCC12, ABCC2, ABCC4, ABCC6, ABCG8, ACADVL, ACAP3, ACCS, ACD, ACER2, ACMSD, ACOT7, ACP4, ACSM2A, ACSM5, ACTA1, ACTC1, ACY3, ADA, ADAM21, ADAMTS16, ADAMTS17, ADAMTS4, ADAR, ADCY1, ADCY7, ADCYAP1R1, ADGRE2, ADGRF4, ADPRM, ADRA1B, ADRA2B, AFAP1L1, AFAP1L2, AFF4, AGAP1, AGBL4, AGFG2, AGTR2, AKAP6, AKAP7, ALG10, ALK, ALKBH2, ALPG, ALX4, AMBRA1, AMHR2, AMZ1, ANK1, ANK2, ANKRD16, ANKRD30A, ANKRD33B, ANKRD36, ANKRD54, ANO3, ANO7, ANXA6, AOC1, AP1B1, AP5B1, AP5Z1, APBA2, APBA3, APC, APOB, APOC2, APRT, ARAP3, AREL1, ARF3, ARGLU1, ARHGAP21, ARHGAP24, ARHGAP32, ARHGAP35, ARHGEF10, ARHGEF15, ARHGEF18, ARHGEF7, ARNTL2, ARRB2, ARSH, ASB11, ASGR2, ASPH, ASTE1, ASTL, ASTN1,* ***ASTN2****, ATAD3B, ATAD3C, ATAT1, ATG12, ATG16L2, ATG2A, ATG3, ATP13A5, ATP2A1, ATP2B3, ATP6V0D1, ATP6V1B2, ATP8A2, ATP8B2, ATPAF1, ATRN, ATRNL1, AZI2, BAG2, BAIAP2, BAZ1A, BBS2, BCAM, BCL11A, BCL2L12, BCLAF1, BCR, BDNF, BEAN1, BEST2, BEX3, BHLHE40, BHLHE41, BIRC6, BMP10,* ***BMP5****, BMP6, BRD7,* ***BSN****, C11orf65, C1orf54, C1orf87, C1QTNF12, C1QTNF7, C20orf194, C2CD3, C3, C3orf20, C7orf50, C9orf72, CABP4, CADM3, CADPS2, CALN1, CAMK2G, CAMTA2, CAND1, CAPN1, CAPN10, CAPN11, CAPN3, CAPZA1, CAPZA2, CARD10, CARD14, CARNS1, CASP8AP2, CAVIN2, CBL, CC2D1A, CCDC121, CCDC127, CCDC141, CCDC15, CCDC17, CCDC178, CCDC186, CCDC96, CCKBR, CCN3, CD177, CD93, CDAN1, CDC123, CDC25C, CDC42EP1, CDC7, CDH11, CDH12, CDH13, CDH15, CDH22, CDH4, CDH6, CDH8, CDK20, CDK5R2, CDK5RAP1, CELF4,* ***CELSR3****, CENPQ, CEP120, CEP170, CEP170B, CEP68, CEP76, CEP89, CETP, CFAP69, CFAP91, CHADL, CHCHD1, CHCHD6, CHD1L, CHD7, CHGA, CHL1, CHMP4C, CHRFAM7A, CHRM1, CHRNA3,* ***CHRNA7****, CHRNB3, CHST2, CINP, CLCN1, CLDN23, CLIP1, CLOCK, CLRN3, CLSTN1, CLTCL1, CMYA5, CNBP, CNIH3, CNIH4, CNNM3, CNNM4, CNPY2, CNTD1, CNTN1, CNTN5, CNTN6, COASY, COL10A1, COL11A2, COL12A1, COL13A1, COL17A1, COL20A1, COL21A1, COL2A1, COL5A3, COL6A2, COL6A3, COL7A1, COL9A2, COLQ, COPB2, CORO7, COX6A1, CP, CPEB2, CPNE2, CPNE6, CPQ, CRH, CRHR1, CRIM1, CSAD, CSMD1, CSMD3, CSNK1E, CSNK1G1, CTBP2, CTDP1, CTNNA3, CTNNB1, CTNND2, CTR9, CTTNBP2, CUBN, CUX1, CWF19L1, CXCR4, CYB561A3, CYFIP1, CYP2A13, CYP51A1, CYREN, DAB2IP, DAG1,* ***DAGLA****, DAGLB, DAP3, DCAF13, DCAF15, DCC, DCHS1, DCLK2, DDX31, DDX43, DDX49, DDX60, DDX60L, DENND1A, DENND2B, DENND2C, DENR, DGAT1, DGKD, DGKE, DGKG, DGKZ, DHODH, DHRS3, DHRS9, DIAPH3, DIP2C, DLAT, DLG1, DLG2, DLGAP2, DLGAP4, DMBX1,* ***DMD****, DMXL1, DNA2, DNAH1, DNAH11, DNAH14, DNAH6, DNAH7, DNAJA1, DNAJB8, DNAJC15, DNM3, DOCK10, DOK7, DPP8, DRP2, DSCAM, DSP, DTWD2, DTX3, DUOX1, DUOX2, DUS1L, DUS2, DUS3L, DVL2, DYNC1I1, DYNC2H1, DYNC2I1, DYSF, DZIP1, ECRG4, ECT2, EDEM2, EDN3, EEF1AKMT3, EFCAB1, EFNA3, EFNB2, EIF2AK3, EIF3E, ELFN1, ELMO1, ELOA, EML4, EML5, EML6, ENPP7, ENTPD3, EP300, EP400, EPB41L3, EPHA2, EPHA5, EPHB1, EPHB2, EPHB6, ERAP2, ERBB4, ERMAP, ESF1, ESPNL, ESRP1, ESYT2, ETV1, ETV2, EVPL, EXD3, EXOC6, EXOC6B, EYA1, EYA3, F13A1, F5, FAAH2, FAAP20, FAHD2A, FAM114A1, FAM131C, FAM149A, FAM151A, FAM170A, FAM180B, FAM186A, FAM20C, FAM219A, FAM71B, FAM89A, FANCA, FANCC, FASN,* ***FAT1****, FAT2,* ***FAT3****, FBN2, FBXO22, FBXO25, FBXO34, FBXO40, FERMT3, FFAR1, FFAR2, FGB, FGD6, FGF1, FGGY, FHIT, FHL1, FKBP11, FLNC, FMC1, FN1, FN3KRP, FNDC7, FNTB, FOSL1, FOXA2, FOXRED2, FPR2, FRMD1, FRMPD2, FSIP2, FSTL5, FURIN, FUT1, FYTTD1, FZD9, GABBR1, GABPB2, GABRA4,* ***GABRA6, GABRE****, GABRG1, GABRG3, GABRP, GABRQ, GABRR2, GADD45GIP1, GALNS, GALNT1, GANAB, GAPDHS, GAPT, GARNL3, GAS2L2, GATA3, GATA4, GATM, GBE1, GDAP1, GEMIN2, GFRA1, GHRL, GIPC1, GJD2, GLG1, GLP1R, GMPPA, GNA12, GNPTAB, GOLGA7B, GORAB, GP5, GPI, GPM6A, GPR179, GPR37L1, GRAMD1C, GRAMD4, GRB10, GREB1L, GRHL2, GRIK1, GRIK4, GRIP1, GRM3, GRM4, GRM8, GSPT2, GSTCD, GSTM1, GTF2A2, GTF2IRD2, GTF3C3, GTF3C5, GUCY2D, GUSB, HACD3, HAP1, HARS1, HDAC1, HDAC3, HDAC8, HDAC9, HEATR5B, HECW1, HELZ, HEPHL1, HES1, HES4, HEXB, HGD,* ***HIP1****, HIRA, HIVEP1, HMCN1, HMGB4, HNRNPA1, HNRNPAB, HOXA6, HPS3, HR, HS2ST1, HSPA12A, HSPA1L, HSPE1, HTR1A, HTR1F, HTR2C, HTR6, HYDIN, ICAM3, ID2, IDH1, IDUA, IFNA8, IGFALS, IGHMBP2, IGSF6, IGSF8, IL10, IL12RB1, IL1B, IL1RN, IL27RA, IL6, IMMP2L, IMPDH2, INA, INCENP, ING5, INO80, INPP4A, IP6K3, IQCC, IQGAP2, IQGAP3, ITFG2, ITGA4, ITGA5, ITGB1BP1, ITIH4, ITLN1, ITPRID2, JKAMP, JMJD1C, JRK, JUP, KAT14, KAT6B, KATNAL2, KATNIP, KBTBD13, KCNAB1, KCNAB2, KCNC3, KCND1,* ***KCND2****, KCND3, KCNG1,* ***KCNH5****, KCNIP1, KCNJ2, KCNMB1, KCNMB3, KCNN3,*

Table 4 (*continued*)

Source	Genes
	KCNV2, KCTD13, KCTD14, KCTD19, KCTD3, KDM3A, KDM5A, KDM5B, KDR, KEL, KERA, KHK, KIAA0100, KIAA0319L, KIF13B, KIF1C, KIF3C, KIF5B, KIF6, KIRREL3, KLC2, KLHDC4, KLHDC9, KLHL17, KLHL20, KLHL41, KLHL42, KLRG2, KMT2B, KNL1, KNTC1, KPNA7, KRT1, KRT4, KRT6B, LAMA1, LAMB2, LAMB3, LAMC2, LARGE1, LARP1B, LARP4, LARP7, LCTL, LDLR, LEAP2, LEPR, LGALS3BP, LIFR, LINS1, LIPN, LIPT1, LMAN1L, LMNTD2, LNX1, LORICRIN, LOXL3, LPA, LPAR2, LRFN2, LRFN5, LRIG1, LRP12, LRP1B, LRRC24, LRRC37A3, LRRC4, LRRC40, LRRC4C, LRRC74A, LRRD1, LRRIQ4, LSM1, LYPLA2, LYRM1, LZTR1, MAD1L1, MAGED1, ***MAGI2****, MAGI3, MAP2, MAPK10, MAPK3, MARCHF9, MAST4, MASTL, MATN2, MATN4, MBD3L1, MBL2, MBOAT2, MC3R, MC4R, MCF2L, MCM4, MCMDC2, MCOLN1, MCRS1, MDN1, ME3, MED30, MEGF6, MEIS2, MEPCE, METRN, METTL21A, METTL22, MFN2, MFSD6, MGA, MICAL1, MICAL3, MICALL1, MILR1, MINDY2, MKI67, MKRN2, MLLT1, MLLT3, MMP21, MMP23B, MMP27, MMRN2, MMUT, MOCOS, MORC2, MPL, MPLKIP, MPP4, MPP7, MR1, MRI1, MRPL35, MRPL38, MRPL54, MRPS27, MS4A10, MSC, MSH6, MSR1, MT1A, MTMR9, MUC16, MUC4, MUSK, MUTYH, MYH11, MYH8, MYO16, MYO1B, MYO3B, MYO5C, MYO6, MYOCD, MYOF, MYOM2, MYPN, MYSM1, MYT1, MZT2B, N4BP1, NBEAL1, NCAPD2, NCBP3, NCEH1, NCKAP5, NCOR2, NDC80, NDUFAF1, NDUFB3, NDUFB7, NEB, NECAB1, NECTIN2, NECTIN4, NEDD4, NEIL1, NELL1, NELL2, NEMF, NF2, NFIB, NFIC, NFKBIZ, NFU1, NID1, NID2, NINL, NIPA2, NKAIN3, NLGN1, NLGN4X, NLRP8, NMD3, NMT1, NODAL, NOL3, NOLC1, NOMO2, NOS3, NOTUM, NPAS2, NPAT, NPC1L1, NPR1, NPR2, NQO1, NRG2, NRG3, NRXN2, NRXN3, NTAN1, NTF3, NTN3, NTNG1, NUP160, NUP85, NUTM2F, NUTM2G, NXNL1, NXPE4, OAS2, OCA2, OCSTAMP, OGT, OLAH, OLFM1, OLFML2A, OLFML3, OMG,* ***OPA1****, OPCML, OPN1SW, OPRM1, OR10G9, OR10H2, OR10Q1, OR10Z1, OR11A1, OR4N4, OR51A7, OR51D1, OR5A1, OR5L2, ORC4, ORMDL1, OSBP2, OSBPL5, OSTM1, OTOP1, OTUD7A, OVCH2, P2RX7, PAK6, PAPPA, PAPPA2, PAQR7, PARP10, PAX3, PAX5, PAX6, PCDH11X, PCDH7, PCDH9, PCDHB4, PCDHGA4, PCDHGA5, PCDHGA8, PCED1A, PCGF1, PCIF1, PCNX2, PCNX4, PCSK7, PDCD1, PDE6B, PDIA6, PEG3, PER1, PFAS, PFKFB1, PGAP6, PGBD2, PGBD3, PGK2, PI15, PI4K2A, PIK3AP1, PIK3R4, PIP5K1C, PIR, PITHD1, PKDREJ, PKHD1L1, PLA2G4A, PLAC8L1, PLB1, PLCB4, PLCG2, PLCL1, PLD5, PLEC, PLEKHG6, PLEKHH1, PLIN3, PLIN5, PLK1, PLXDC2, PLXNA3, PLXNB1, PML, PMM1, PMP22, PMPCA, PNLIP, PNPLA6, PODXL, POGLUT2, POLI, PON2, PORCN, PPARGC1B, PPFIA3, PPM1D, PPP1CB, PPP1R12C, PPP1R3C, PPP2R3A, PPP5C, PPP6R2, PRAG1, PRAMEF1, PRCP, PREB, PREX2,* ***PRICKLE2****, PRIMA1, PRKCG, PRKD1, PRKN, PRL, PRMT5, PROCA1, PROM1, PRPF8, PRR22, PRRC2C, PRTG, PSMD7, PTCHD1, PTER, PTGER2, PTGS2, PTH1R, PTK2, PTPN11, PTPRD, PTPRE, PTPRM, PTPRZ1, PYCR1, R3HCC1L, RAB11A, RAB2B, RAB3D, RAB40C, RAD23A, RAD52, RAD54L, RAG2, RANBP3L, RANGAP1, RAP1GAP2, RAPGEFL1, RASA1, RASEF,* ***RBFOX1****, RBFOX3, RBM34, RBPJ, RBSN, RCL1, RDH12, RDH5, RDX, RECQL5, RFX3, RFX4, RGL3, RHBDF1, RICTOR, RIMBP2, RIN2, RIOK2, RIPOR1, RLBP1, RNASEH2C, RNF34, ROBO4, RPAP1, RPGRIP1L, RPH3A, RPL4, RPS6KB2, RRM1, RRNAD1, RRP1B, RRP9, RSRC2, RTN2, RTP1, RUFY1, RUNDC3A, RXFP1, RXFP4,* ***RYR3****, S1PR4, SAMD4B, SAMD7, SAMHD1, SATL1, SBSPON,* ***SCAF4****, SCAMP5,* ***SCN10A, SCN4A****, SCN7A,* ***SCN9A****, SCNM1, SCNN1B, SCNN1D, SDF2, SDK1, SEC23A, SEC24B, SEC24D, SEMA3E, SEMA5A, SEPTIN8, SERHL2,* ***SETD5****, SETDB1, SETX,* ***SEZ6****, SF3B3, SFR1, SGCG, SH3BGR, SH3GLB1, SH3RF1,* ***SHANK1, SHANK2, SHROOM4****, SIDT1, SIRT3, SKI, SLC12A2, SLC12A7, SLC15A3, SLC16A12, SLC16A2, SLC17A2, SLC17A3, SLC18A2, SLC1A1, SLC1A5, SLC1A7, SLC22A1, SLC22A20P, SLC22A5, SLC23A3, SLC24A4, SLC25A39, SLC25A40, SLC26A1, SLC26A2, SLC2A12, SLC30A3, SLC30A8,* ***SLC32A1****, SLC35E4, SLC37A2, SLC37A3, SLC38A10, SLC39A13, SLC3A1, SLC3A2, SLC44A2, SLC4A10, SLC4A3, SLC5A12, SLC5A8, SLC6A3, SLC6A4, SLC6A9, SLC7A11, SLC7A13, SLC7A3, SLC7A4, SLC9A4, SLCO4C1, SLTM, SMARCA1, SMCHD1, SMCO2, SMG6, SMOC2, SMPDL3A, SNAP23,* ***SNAP25****, SNAP47, SNAP91, SNRNP40, SNX19,* ***SNX27****, SOAT1, SOCS2, SOHLH1, SORCS3, SOS1, SOWAHB, SOWAHC, SOX10, SOX11, SP4, SPAG4, SPAG9, SPANXA2, SPATA16, SPATA7, SPATA8, SPDL1,* ***SPG11****, SPHKAP, SPIRE2, SPRED2, SPRY4, SPTB, SQLE, SQSTM1, SRD5A3, SREK1, SRGAP2, SSPOP, SSTR1, SSTR5, ST6GALNAC3, ST7, ST8SIA2, STAB1, STAB2, STAG2, STARD13, STARD9, STC1, STK11, STK31, STRAP, STRIP1, STRIP2, STXBP5L, STYXL1, SUCLG2, SUCO, SULT6B1, SUN1, SV2A, SVIL, SWSAP1, SYCP2, SYN3, SYNCRIP, SYNE1, SYNE2, SYNJ2, SYNM, SYT2, SYT4, SYT9, TACC2, TACR2, TAF1L, TAMALIN, TAP1, TARS1, TBC1D10B, TBC1D8, TBC1D8B, TBL2, TBX18, TCHHL1, TCOF1, TDO2, TEX33, TEX45, TFAM, TFAP2E, TGFB1I1, TGIF1, TH, THAP11, THEMIS, THOP1, THUMPD3, TIGD4, TIMELESS, TK2, TKT, TMC7, TMED7, TMEM132B, TMEM139, TMEM229B, TMEM61, TMEM63A,*

(*continued on next page*)

Table 4 (*continued*)

Source	Genes
	TMEM63B, TMEM68, TMPRSS6, TMPRSS9, TNC, TNIP2, TNIP3, TNK2, TNNI3K, TNR, TNS1, TNS2, TOM1L2, TOP1MT, TOP3B, TPTE2, TRA2B, TRAF5, TRANK1, TRIM24, TRIM29, TRIM50, TRIM66, TRIM69, TRIP11, TRIP4, TRMT44, TRPC6, TRPV5, TSG101, TSNARE1, TSPAN5, TSPAN7, TSSC4, TTBK2, TTC21B, TTC28, TTC3, TTC30A, TTC39A, TTI1, TUBA3E, TUBA8, TULP2, TUT1, TWSG1, TXNRD1, TYK2, U2AF2, UBR4, UBR5, UGGT2, UGT1A9, UGT2B4, UHRF1BP1, UIMC1, UNC13A, ***UNC13B****, UPF1, UPP2, UQCRFS1, USH1C, USH2A, USP19, USP2, USP24, USP28, USP29, USP34, USP36, USP8, UTP20, VAMP5, VCL, VIL1, VOPP1, VPS13C, VPS18, VPS35, VPS39, VPS45, VRK2, VWA3B, VWA8, WDFY3, WDHD1, WDR3, WDR41, WDR59, WDR72, WDR75, WDR91, WHAMM, WNT4, WRAP53, WRN, XDH, XRCC1, YAP1, YTHDC2, YWHAE, YY1, YY1AP1, ZADH2, ZBTB20, ZCCHC8, ZDHHC1, ZDHHC15, ZFR2, ZGPAT, ZGRF1, ZHX3, ZKSCAN2, ZNF165, ZNF208, ZNF221, ZNF248, ZNF302, ZNF317, ZNF318, ZNF343, ZNF345, ZNF354A, ZNF385A, ZNF397, ZNF408, ZNF420, ZNF433, ZNF44, ZNF443, ZNF517, ZNF527, ZNF536, ZNF565, ZNF570, ZNF585B, ZNF598, ZNF654, ZNF655, ZNF675, ZNF727, ZNF774, ZNF789, ZNF813, ZNF814, ZNF844, ZPBP2, ZYG11A, ZYX (n = 1367)*
PubMed	*AAAS, ACAD9, ADORA2A, AIPL1, ARL13B, ARL6IP1, ARSB, ATP6, BRD2, CD99L2,* ***CELSR2****, CLCN7, EEF1B2, ELMO2, ENG, FAN1, FBP1, FBXO7, FCN3, GJB2, GLA, GRINA, GSN, HIKESHI, HOXD, IDH3A, KIAA0586, KLF13, LONP1, MATR3, MBTPS1, ME2, MEFV, MTCO2, MTTF, MTTK, MTTL1, MTTM, MYH1, MYH9, MYO18A, OSTC, PAX2, PAX7, PCDHG, PKP2, POLR1A, PRKACA, PRKAG2, PTPN4, RB1, RHEB, SCA2, SHOC2, SLC16A4, SLC16A7, SLC25A2, SLC29A1, SLC6A12, TAF1C, TAT, TBC1D22A, TECTA,* ***TENM1****, TOR1A, TRAPPC2L, TRPM1, TUBGCP5, TUSC3, UBA1, UBP1, UNC79, ZNF385B (n = 73)*

Bold italics, with a number of mutations identified in the epilepsy phenotypes ≥5.

genes on their gene-disease associations, including 95 genes in the expert panel list of epilepsy (https://search.clinicalgenome.org/kb/gene-validity, until August 2023), while Ambry Genetics curated the gene-disease relationships on 22 genes [52].

We have developed a pathogenic potential and pathogenic feature assessment (PPA) system to evaluate whether (pathogenic potential) and how (pathogenic feature) a gene is associated with a phenotype with criteria on clinical evidence that include phenotype (spectrum) specificity, inheritance pattern, pathogenic genotype, and genotype-phenotype correlation, and on experimental evidence including gene expression profile, and gene KO consequence, and other experiments directly related to gene-disease association [53]. Using the PPA framework, 875 epilepsy-associated genes were assessed with available clinical data (until April 2022), of which 617 genes were evaluated as "pathogenic", 150 genes were evaluated as "possible pathogenic", and 108 genes were "to be confirmed" in pathogenicity. The details of evidence in evaluating the gene-disease association are presented in the Genetic Dependence and Pathogenicity (GD&P) database (https://www.gdap.org.cn/statistic/phenotype). The pathogenic potential and pathogenic features of each gene are essential parts of the gene-disease association and fundamental bases for evaluating the pathogenicity of variants [54].

Recently, two genetic databases for epilepsy have been established. The SAGAS database refers to genes associated with monogenic and polygenic seizures/epilepsy in multiple species [5], among which almost 1000 genes were not included in the present epilepsy-associated gene list due to insufficient clinical evidence. However, attention is required to these genes in searching for potential novel epilepsy genes in further studies. The Gene4epilepsy database is based on previously used epilepsy gene panels and two research resources. Almost 90% of the genes are related to developmental and/or epileptic encephalopathy [6], to which attention is required in application for identifying causative genes in patients with common epilepsies.

This study has several limitations. Generally, the gene-specific burden of variants should be derived from the result of an epidemiological investigation. The data from the HGMD database and the China Epilepsy Gene 1.0 project were just two examples for reference, and attention is required to possible biases in such data. The present gene list did not consider the role of epigenetics and polygenic factors in epilepsy. The 2946 listed epilepsy-associated genes vary in their association with epilepsy, to which attention is required in application.

Table 5
Top 100 genes reported to be associated with epilepsy in HGMD Database and China Epilepsy Gene 1.0 project.

HGMD Database (mutation number)	China Epilepsy Gene 1.0 project (case number) [#]
SCN1A (3374), *MECP2* (939), *KCNQ2* (731), *SCN2A* (662), *CDKL5* (523), *PCDH19* (522), *STXBP1* (404), *SCN8A* (394), *DEPDC5* (298), *ALDH7A1* (261), *SYNGAP1* (231), *GRIN2A* (222), *TPP1* (209), *KCNT1* (180), *PRRT2* (180), *CHD2* (176), *CLN6* (174), *SLC2A1* (154), *FOXG1* (152), *TBC1D24* (137), *CACNA1A* (134), *EPM2A* (121), *PPT1* (121), *GABRG2* (119), *PIGN* (119), *GABRB3* (112), *TSC2* (110), *SLC6A1* (96), *WWOX* (96), *KCNB1* (95), *NHLRC1* (92), *POLG* (89), *ARX* (88), *KCTD7* (86), *IQSEC2* (83), *HNRNPU* (81), *SCN9A* (81), *CLN3* (80), *GABRA1* (80), *GRIN2B* (77), *NEXMIF* (77), *CACNA1H* (76), *SLC13A5* (76), *CLN5* (74), *LGI1* (74), *SPTAN1* (71), *SZT2* (70), *GNAO1* (67), *ADGRV1* (66), *KCNA2* (66), *NPRL3* (65), *GABRB2* (62), *TSC1* (60), *BRAT1* (56), *CLN8* (56), *KCNQ3* (56), *HCN1* (55), *NRXN1* (55), *PIGA* (55), *SPATA5* (53), *WDR45* (52), *CNTNAP2* (50), *PNPO* (50), *SMC1A* (50), *MEF2C* (47), *SCN1B* (47), *EFHC1* (46), *SCN3A* (46), *UBE3A* (45), *ATP1A3* (44), *DNM1* (43), *MFSD8* (42), *STX1B* (41), *ARHGEF9* (38), *PNKP* (38), *RARS2* (38), *CSNK2B* (37), *EEF1A2* (37), *GRIN1* (36), *ZEB2* (36), *ATP1A2* (35), *MBD5* (34), *ITPA* (32), *NBEA* (32), *PURA* (32), *COL4A1* (31), *DYRK1A* (31), *KARS* (30), *PLPBP* (29), *RELN* (29), *WDR26* (29), *ADSL* (28), *CLCN2* (28), *PIGT* (28), *AARS1* (27), *ALG13* (27), *KCNJ10* (27), *SYN1* (27), *CNKSR2* (26), *TANC2* (26)	*SCN1A* (58), *FLNA* (18), *PRRT2* (16), *TSC1* (13), ***CELSR2*** (11), *CHD2* (11), ***HCFC1*** (11), *TSC2* (11), *ADGRV1* (10), *CACNA1A* (10), *SLC2A1* (10), *CACNA1H* (9), *SCN2A* (9), ***ZFHX3*** (9), ***BCOR*** (8), *GABRG2* (8), *KMT2D* (8), *NF1* (8), ***PKD1*** (8), *RELN* (8), ***AFF2*** (7), *MECP2* (7), ***MED12*** (7), ***NEXMIF*** (7), ***PCDH15*** **(7)**, *PCDH19* (7), *SETD1B* (7), *ATP7A* (6), ***BSN*** (6), *CDKL5* (6), ***CELSR1*** (6), *DEPDC5* (6), ***FAT1*** (6), *KCNQ2* (6), *KCNT1* (6), ***LAMA5*** (6), *PCNT* (6), *SCN8A* (6), *SZT2* (6), ***TENM1*** (6), *AIFM1* (5), *ALG13* (5), ***BRWD3*** (5), ***CELSR3*** (5), *DMXL2* (5), ***FRMPD4*** (5), *GRIN2A* (5), *KCNA1* (5), ***RYR2*** (5), ***SHROOM4*** (5), *SYNGAP1* (5), ***UNC13B*** (5), *ABCA2* (4), ***APC2*** (4), *ARX* (4), ***CHD4*** (4), *CNKSR2* (4), *DCHS1* (4), *DCX* (4), *FGD1* (4), *GABRA1* (4), *IQSEC2* (4), *KCNMA1* (4), *LRPPRC* (4), *MGA* (4), *MID2* (4), *NHS* (4), *NPRL3* (4), ***PGM3*** (4), *PI4KA* (4), *PIGA* (4), *RYR1* (4), *TBC1D24* (4), *THOC2* (4), *WDFY3* (4), *ATP1A2* (3), *CPA6* (3), *DYNC1H1* (3), *EFHC1* (3), *GABRB3* (3), *GRIA3* (3), *GRIN2B* (3), *HNRNPU* (3), *IRF2BPL* (3), *KCNK4* (3), *KCNV2* (3), *KDM5C* (3), *KDM6A* (3), *MBD5* (3), ***MPDZ*** (3), ***SBF1*** (3), *SCN9A* (3), *SMC1A* (3), *SYN1* (3), *TUBGCP6* (3), *UNC80* (3), *WWOX* (3), *YWHAG* (3), ***ATP6V0C*** (2), ***UNC79*** (2)

[#] The data were obtained from trio-based whole-exome sequencing analysis on 2757 unrelated cases with epilepsy.

Bold italics, novel epilepsy-associated genes discovered by China Epilepsy Gene 1.0 project.

Underline, identical genes in two databases.

In conclusion, the present study updates the list of epilepsy-associated genes based on currently available clinical-genetic evidence, which is helpful for gene screening in clinical practice. Recognition of epilepsy-associated genes and their relationships with other abnormal phenotypes is potentially useful for the precise clinical molecular diagnosis and management of patients with epilepsy.

Ethical publication statement

All procedures performed were in accordance with the ethical standards of the institutional committee. The present study was approved by the Ethics Committee of the Second Affiliated Hospital of Guangzhou Medical University.

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Declaration of Competing Interest

The authors have stated that they had no interests that might be perceived as posing a conflict or bias.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.seizure.2023.09.021.

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