# Comprehensive Epilepsy Panel, Sequencing and Deletion/Duplication

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Epilepsy is a neurological disorder that causes recurrent unprovoked seizures and affects approximately 1% of the population.[1] It can be subclassified by seizure type (ie, focal, generalized, generalized and focal, or unknown) and can take idiopathic or syndromic forms. An estimated 30% of epilepsy cases are believed to have a genetic contribution,[2] and there is high genetic heterogeneity and significant phenotypic overlap between conditions. In addition to clinical evaluation and nonlaboratory testing, genetic testing can be useful to identify the basis of a patient's epilepsy and to inform prognosis, optimal treatment and management, recurrence risk, and testing of at-risk relatives.[3]

## Featured ARUP Testing

Comprehensive Epilepsy Panel, Sequencing and Deletion/Duplication 3001591

**Method:** Massively Parallel Sequencing

Recommended test to establish a diagnosis or determine the genetic etiology of an epilepsy or seizure disorder

If a familial sequence variant has been previously identified, targeted sequencing for that variant may be appropriate; refer to the Laboratory Test Directory for additional information.

## Disease Overview

According to guidelines from the National Society of Genetic Counselors, patients with unexplained epilepsy, regardless of age of onset, should be offered genetic testing.

Both focal and generalized epilepsy can have a genetic cause. Factors that increase the likelihood of a genetic cause include[4,5]:

- Earlier age of seizure onset
- Presence of neurodevelopmental comorbidities such as intellectual disability, developmental delay, autism spectrum disorder, and/or encephalopathy
- Drug-resistant epilepsy
- A family history of epilepsy

## Genetics

### Genes

This panel includes genes associated with Mendelian forms of idiopathic epilepsy and syndromic epilepsy in which seizures are a major or presenting feature.

Refer to Genes Tested for additional details.

### Etiology

Epilepsy may have infectious, structural, genetic, metabolic, immune, or unknown causes. An estimated 30% of epilepsy has a genetic cause.[2] Pathogenic germline variants in numerous genes have been associated with epilepsy.

### Inheritance

Epilepsy may occur sporadically or as a familial trait with autosomal dominant, autosomal recessive, or X-linked inheritance. De novo variation is a common cause of sporadic epileptic encephalopathy.

### Penetrance

Variable; influenced by gene and variant.

# Test Interpretation

## Methodology

This test is performed using the following sequence of steps:

- Selected genomic regions, primarily coding exons and exon-intron boundaries, from the targeted genes are isolated from extracted genomic DNA using a probe-based hybrid capture enrichment workflow.
- Enriched DNA is sequenced by massively parallel sequencing (MPS; also known as next generation sequencing, or NGS), followed by paired-end read alignment and variant calling using a custom bioinformatics pipeline. The pipeline includes an algorithm for detection of large deletions and duplications.
- Sanger sequencing is performed as necessary to fill in regions of low coverage and, in certain situations, to confirm variant calls.
- Large deletion/duplication calls made using MPS are confirmed by an orthogonal exon-level microarray when sample quality and technical conditions allow.

## Clinical Sensitivity

Dependent on clinical phenotype.

## Analytic Sensitivity/Specificity

| Variant Class | Analytic Sensitivity (PPA) Estimate[a] (%) and 95% Credibility Region | Analytic Specificity (NPA) Estimate (%) |
|---|---|---|
| SNVs | >99 (96.9-99.4) | >99.9 |
| Deletions 1-10 bp[b] | 93.8 (84.3-98.2) | >99.9 |
| Insertions 1-10 bp[b] | 94.8 (86.8-98.5) | >99.9 |
| Exon-level[c] deletions | 97.8 (90.3-99.8) [2 exons or larger]<br>62.5 (38.3-82.6) [Single exon] | >99.9 |
| Exon-level[c] duplications | 83.3 (56.4-96.4) [3 exons or larger] | >99.9 |

[a]PPA values are derived from larger methods-based MPS and/or Sanger validations. These values do not apply to testing performed by multiplex ligation-dependent probe amplification (MLPA) unless otherwise indicated.

[b]Variants greater than 10 bp may be detected, but the analytic sensitivity may be reduced.

[c]In most cases, a single exon deletion or duplication is less than 450 bp and 3 exons span a genomic region larger than 700 bp.

bp, base pairs; NPA, negative percent agreement; PPA, positive percent agreement; SNVs, single nucleotide variants

## Limitations

- A negative result does not exclude a heritable form of epilepsy.
- Diagnostic errors can occur due to rare sequence variations.
- Interpretation of this test result may be impacted if the patient has had an allogeneic stem cell transplantation.
- The following will not be evaluated:
  - Variants outside the coding regions and intron-exon boundaries of the targeted gene(s)
  - Variants in the mitochondrial genome
  - Regulatory region and deep intronic variants
  - Deletions/duplications in the *DYNC1H1*, *EMP2A*, *FARS2*, *SLC19A3*, and *WWOX* genes
  - Breakpoints of large deletions/duplications
  - Gene conversion events, complex inversions, and translocations
  - Repeat expansions (including common expansions in *ATN1* exon 5, *ARX*, and *CSTB* 5'UTR)
  - This assay does not assess for *PMM2*-associated hyperinsulinemic hypoglycemia and polycystic kidney disease (HIPKD)
  - SNVs and small deletions/insertions will not be called in the following exons due to technical limitations of the assay:

- *ABAT* (NM_001386615) 6
- *ABAT* (NM_001386616) partial exon 16(Chr16:8875107-8875145)
- *ADSL* (NM_001363840) 14
- *ALG13* (NM_001099922, NM_001257231) partial exon 24(ChrX:110987954-110988035)
- *ALG9* (NM_001352420, NM_001352421) 15
- *ALG9* (NM_001352415, NM_001352416, NM_001352419) 16
- *ALG9* (NM_001352417) 17
- *ANKRD11* (NM_013275, NM_001256183) partial exon 9(Chr16:89345816-89346020)
- *ANKRD11* (NM_001256182) partial exon 10(Chr16:89345816-89346020)
- *ANKRD11* (NM_013275, NM_001256183) 13
- *ANKRD11* (NM_001256182) 14
- *AP3B2* (NM_001348440) 5
- *ARHGEF9* (NM_001353923) 1
- *ARV1* (NM_001346992) 4
- *ARX* (NM_139058) partial exon 2(ChrX:25031469-25031834)
- *BRAT1* (NM_001350626) partial exon 14(Chr7:2578419-2578578)
- *BTD* (NM_001370752) 5
- *BTD* (NM_001370753) 4
- *CARS2* (NM_001352253) 9
- *CLN5* (NM_001366624) 4
- *CUL4B* (NM_001369145) 1
- *DMXL2* (NM_001378459) 32
- *DMXL2* (NM_001378463) partial exon 32(Chr15:51755500-51755555)
- *DMXL2* (NM_001378457, NM_001378458) 34
- *DNM1* (NM_001374269) 22
- *EHMT1* (NM_024757, NM_001145527, NM_001354263, NM_001354611) 1
- *EHMT1* (NM_001354259) 16
- *EHMT1* (NM_001354612) partial exon 9(Chr9:140657293-140657296)
- *EHMT1* (NM_001354611) partial exon 10(Chr9:140657293-140657296)
- *EPM2A* (NM_001368129, NM_001368132) 3
- *EPM2A* (NM_001368130) partial exon 3(Chr6:145956295-145956360)
- *FKTN* (NM_001351497) 6
- *FKTN* (NM_001351498) partial exon 9(Chr9:108382363-108382373)
- *FOXG1* (NM_005249) partial exon 1(Chr14:29236682-29236856)
- *GABBR2* (NM_005458, NM_001375347) 1
- *GABRG2* (NM_001375344) 7
- *GPHN* (NM_001377519, NM_001377514) 5
- *GPHN* (NM_001377515, NM_001377516, NM_001377517, NM_001377518) 9
- *GPHN* (NM_001377514, NM_001377515, NM_001377516) 10
- *GPHN* (NM_001377514) 11
- *KCNQ2* (NM_001382235) 15
- *KCTD7* (NM_001167961) 5
- *KDM5C* (NM_001353979, NM_001353981, NM_001353982, NM_001353984) 26
- *KIF1A* (NM_001379636) 36
- *KIF1A* (NM_001379639) 37
- *KIF1A* (NM_001379635, NM_001379638, NM_001379646) 38
- *MBD5* (NM_001378120) partial exon 9(Chr2:149241026-149241704)
- *NR2F1* (NM_005654) partial exon 1(Chr5:92920778-92920891)
- *NTRK2* (NM_001369547) 13
- *PLPBP* (NM_001349349) partial exon 1(Chr8:37620073-37620157)
- *PLPBP* (NM_001349349) 5
- *PLPBP* (NM_001349346) partial exon 6(Chr8:37632827-37632836)
- *RORB* (NM_001365023) 1
- *SAMHD1* (NM_001363733) 16
- *SLC19A3* (NM_001371413, NM_001371414) 3
- *SLC9A6* (NM_001379110) 14

- *SMARCA2* (NM_003070, NM_001289396, NM_001289397, NM_139045) 5
- *SPTAN1* (NM_001375318, NM_001375312) 2
- *SPTAN1* (NM_001375310) 50
- *SPTAN1* (NM_001363759) 52
- *SPTAN1* (NM_001375318) 53
- *ST3GAL3* (NM_001350619, NM_001350620) 12
- *ST3GAL3* (NM_001350621) 6,13
- STXBP1 (NM_001374313, NM_001374314) 19
- *SYNGAP1* (NM_006772) partial exon 19(Chr6:33419581-33419683)
- *SZT2* (NM_001365999) 22
- *TPK1* (NM_001350884) 3
- *TPK1* (NM_001350883) 4
- *TPK1* (NM_001350882) 5
- *TPK1* (NM_001350895) 7
- *TPK1* (NM_001350881) 9
- *TSEN54* (NM_207346) 1
- *UBE3A* (NM_001354523) 5
- *UNC80* (NM_001371986) 27

- The following may not be detected:
  - Deletions/duplications/insertions of any size by MPS
  - Large duplications less than 3 exons in size
  - Noncoding transcripts
  - Some variants due to technical limitations in the presence of pseudogenes, repetitive, or homologous regions
  - Low-level somatic or mosaic variants

## Genes Tested

| Gene Symbol (OMIM Number) | Associated Disorders | Inheritance |
|---|---|---|
| *AARS1* (601065) | Developmental and epileptic encephalopathy 29 | AR |
| | Hereditary diffuse leukoencephalopathy with spheroids 2 | AD |
| *ABAT* (137150) | GABA-transaminase deficiency | AR |
| *ADGRG1* (604110) | Bilateral frontoparietal polymicrogyria; bilateral perisylvian polymicrogyria | AR |
| *ADSL* (608222) | Adenylosuccinase deficiency | AR |
| *ALDH5A1* (610045) | Succinic semialdehyde dehydrogenase deficiency | AR |
| *ALDH7A1* (107323) | Pyridoxine-dependent epilepsy | AR |
| *ALG1* (605907) | Congenital disorder of glycosylation type Ik | AR |
| *ALG13* (300776) | Developmental and epileptic encephalopathy 36 | XL |
| *ALG3* (608750) | Congenital disorder of glycosylation type Id | AR |
| *ALG6* (604566) | Congenital disorder of glycosylation type Ic | AR |
| *ALG8* (608103) | Congenital disorder of glycosylation type Ih | AR |

| Gene Symbol (OMIM Number) | Associated Disorders | Inheritance |
|---|---|---|
| *ALG9* (606941) | Congenital disorder of glycosylation type Il; Gillessen-Kaesbach-Nishimura syndrome | AR |
| *AMACR* (604489) | Alpha-methylacyl-CoA racemase deficiency | AR |
| *AMT* (238310) | Glycine encephalopathy | AR |
| *ANKRD11* (611192) | KBG syndrome | AD |
| *AP3B2* (602166) | Developmental and epileptic encephalopathy 48 | AR |
| *ARFGEF2* (605371) | Periventricular heterotopia with microcephaly | AR |
| *ARG1* (608313) | Argininemia | AR |
| *ARHGEF9* (300429) | Developmental and epileptic encephalopathy 8 | XL |
| *ARV1* (611647) | Developmental and epileptic encephalopathy 38 | AR |
| *ARX* (300382 | Developmental and epileptic encephalopathy 1; Proud syndrome; XL lissencephaly 2 with ambiguous genitalia; XL intellectual developmental disorder 29 | XL |
| *ASAH1* (613468) | Spinal muscular atrophy with progressive myoclonic epilepsy | AR |
| *ASNS* (108370) | Asparagine synthetase deficiency | AR |
| *ATN1* (607462) | Congenital hypotonia, epilepsy, developmental delay, and digital anomalies | AD |
| *ATP1A1* (182310) | Hypomagnesemia, seizures, and impaired intellectual development 2 | AD |
| *ATP1A3* (182350) | Alternating hemiplegia of childhood 2; developmental and epileptic encephalopathy 99 | AD |
| *ATP6AP2* (300556) | Syndromic intellectual developmental disorder Hedera type | XL |
| *ATP7A* (300011) | Menkes disease | XL |
| *ATRX* (300032) | Alpha-thalassemia/mental retardation syndrome; XL intellectual disability-hypotonic facies syndrome | XL |
| *BCKDK* (614901) | Branched-chain keto acid dehydrogenase kinase deficiency | AR |
| *BRAT1* (614506) | Neurodevelopmental disorder with cerebellar atrophy and with or without seizures; rigidity and multifocal seizure syndrome, lethal neonatal | AR |
| *BTD* (609019) | Biotinidase deficiency | AR |
| *C12orf57* (615140) | Temtamy syndrome | AR |
| *CACNA1A* (601011) | Developmental and epileptic encephalopathy 42; episodic ataxia type 2; familial hemiplegic migraine 1 | AD |
| *CACNA1D* (114206) | Primary aldosteronism, seizures, and neurologic abnormalities | AD |

| Gene Symbol (OMIM Number) | Associated Disorders | Inheritance |
|---|---|---|
| *CACNA1E* (601013) | Developmental and epileptic encephalopathy 69 | AD |
| *CACNA2D2* (607082) | Cerebellar atrophy with seizures and variable developmental delay | AR |
| *CAD* (114010) | Developmental and epileptic encephalopathy 50 | AR |
| *CARS2* (612800) | Combined oxidative phosphorylation deficiency 27 | AR |
| *CASK* (300172) | FG syndrome 4; intellectual developmental disorder and microcephaly with pontine and cerebellar hypoplasia | XL |
| *CDKL5* (300203) | Developmental and epileptic encephalopathy 2 | XL |
| *CHD2* (602119) | Developmental and epileptic encephalopathy 94 | AD |
| *CHRNA4* (118504) | Nocturnal frontal lobe epilepsy 1 | AD |
| *CHRNB2* (118507) | Nocturnal frontal lobe epilepsy 3 | AD |
| *CLCN4* (302910) | Raynaud-Claes syndrome | XL |
| *CLN3* (607042) | Neuronal ceroid lipofuscinosis 3 | AR |
| *CLN5* (608102) | Neuronal ceroid lipofuscinosis 5 | AR |
| *CLN6* (606725) | Neuronal ceroid lipofuscinosis types 6A and 6B (Kufs type) | AR |
| *CLN8* (607837) | Neuronal ceroid lipofuscinosis 8; northern epilepsy variant | AR |
| *CLTC* (118955) | Intellectual developmental disorder 56 | AD |
| *CNKSR2* (300724) | XL syndromic intellectual developmental disorder (Houge type) | XL |
| *CNTNAP2* (604569) | Pitt-Hopkins like syndrome 1 | AR |
| *COL4A1* (120130) | Brain small vessel disease with or without ocular anomalies | AD |
| *CPT2* (600650) | CPT II deficiency (infantile or neonatal lethal) | AR |
| | Susceptibility to acute infection-induced encephalopathy 4 | AD/AR |
| *CSTB* (601145) | Progressive myoclonic epilepsy 1A (Unverricht and Lundborg) | AR |
| *CTSD* (116840) | Neuronal ceroid lipofuscinosis 10 | AR |
| *CTSF* (603539) | Neuronal ceroid lipofuscinosis13 (Kufs type) | AR |
| *CUL4B* (300304) | XL syndromic intellectual developmental disorder, Cabezas type | XL |
| *DCX* (300121) | XL lissencephaly or subcortical laminal heterotopia | XL |

| Gene Symbol (OMIM Number) | Associated Disorders | Inheritance |
|---|---|---|
| *DDX3X* (300160) | XL syndromic intellectual developmental disorder, Snijders Blok type | XL |
| *DEAF1* (602635) | Neurodevelopmental disorder with hypotonia, impaired expressive language, and with or without seizures | AR |
| | Vulto-van Silfout-de Vries syndrome | AD |
| *DEPDC5* (614191) | Familial focal epilepsy with variable foci 1 | AD |
| *DHDDS* (608172) | Developmental delay and seizures with or without movement abnormalities | AD |
| | Congenital disorder of glycosylation type 1bb/retinitis pigmentosa 59 | AR |
| *DIAPH1* (602121) | Seizures, cortical blindness, microcephaly syndrome | AR |
| *DMXL2* (612186) | Developmental and epileptic encephalopathy 81 | AR |
| *DNAJC5* (611203) | Neuronal ceroid lipofuscinosis 4 (Kufs type) | AD |
| *DNM1* (602377) | Developmental and epileptic encephalopathy 31 | AD |
| *DNM1L* (603850) | Lethal encephalopathy due to defective mitochondrial peroxisomal fission 1 | AR/AD |
| *DOCK7* (615730) | Developmental and epileptic encephalopathy 23 | AR |
| *DPAGT1* (191350) | Congenital disorder of glycosylation type Ij | AR |
| *DPM1* (603503) | Congenital disorder of glycosylation type Ie | AR |
| *DPYD* (612779) | Dihydropyrimidine dehydrogenase deficiency | AR |
| *DYNC1H1* (600112) | Complex cortical dysplasia with other brain malformations | AD |
| *DYRK1A* (600855) | Intellectual developmental disorder 7 | AD |
| *EEF1A2* (602959) | Developmental and epileptic encephalopathy 33; intellectual developmental disorder 38 | AD |
| *EHMT1* (607001) | Kleefstra syndrome 1 | AD |
| *EPM2A* (607566) | Progressive myoclonic epilepsy 2A (Lafora) | AR |
| *FARS2* (611592) | Combined oxidative phosphorylation deficiency 14 | AR |
| *FGF12* (601513) | Developmental and epileptic encephalopathy 47 | AD |
| *FKTN* (607440) | Muscular dystrophy-dystroglycanopathy (congenital with brain and eye anomalies) type A4 | AR |
| *FLNA* (300017) | Neuronal intestinal pseudoobstruction; periventricular heterotopia 1 | XL |
| *FOLR1* (136430) | Neurodegeneration due to cerebral folate transport deficiency | AR |

| Gene Symbol (OMIM Number) | Associated Disorders | Inheritance |
|---|---|---|
| *FOXG1* (164874) | Congenital variant Rett syndrome | AD |
| *FRRS1L* (604574) | Developmental and epileptic encephalopathy 37 | AR |
| *GABBR2* (607340) | Developmental and epileptic encephalopathy 59; neurodevelopmental disorder with poor language and loss of hand skills | AD |
| *GABRA1* (137160) | Developmental and epileptic encephalopathy 19; susceptibility to childhood absence or juvenile myoclonic epilepsy | AD |
| *GABRB2* (600232) | Developmental and epileptic encephalopathy 92 | AD |
| *GABRB3* (137192) | Developmental and epileptic encephalopathy 43; susceptibility to childhood absence epilepsy | AD |
| *GABRD* (137163) | Idiopathic generalized epilepsy 10; susceptibility to juvenile myoclonic epilepsy; susceptibility to generalized epilepsy with febrile seizures type 5 | AD |
| *GABRG2* (137164) | Developmental and epileptic encephalopathy 74; familial febrile seizures 8; generalized epilepsy with febrile seizures plus type 3 | AD |
| *GALC* (606890) | Krabbe disease | AR |
| *GAMT* (601240) | Cerebral creatine deficiency syndrome 2 | AR |
| *GATM* (602360) | Cerebral creatine deficiency syndrome 3 | AR |
| *GFAP* (137780) | Alexander disease | AD |
| *GNAO1* (139311) | Developmental and epileptic encephalopathy 17; neurodevelopmental disorder with involuntary movements | AD |
| *GNB1* (139380) | Intellectual developmental disorder 42 | AD |
| *GOSR2* (604027) | Congenital muscular dystrophy with or without seizures; progressive myoclonic epilepsy 6 | AR |
| *GPHN* (603930) | Molybdenum cofactor deficiency C | AR |
| *GRIA3* (305915) | XL syndromic intellectual developmental disorder (Wu type) | XL |
| *GRIN1* (138249) | Developmental and epileptic encephalopathy 101 | AR |
| | Neurodevelopmental disorder with or without hyperkinetic movements and seizures | AR/AD |
| *GRIN2A* (138253) | Epilepsy, focal, with speech disorder and with or without impaired intellectual development | AD |
| *GRIN2B* (138252) | Developmental and epileptic encephalopathy 27; intellectual developmental disorder 6 with or without seizures | AD |
| *HACE1* (610876) | Spastic paraplegia and psychomotor retardation with or without seizures | AR |
| *HCN1* (602780) | Developmental and epileptic encephalopathy 24; generalized epilepsy with febrile seizures plus type 10 | AD |
| *HECW2* (617245) | Neurodevelopmental disorder with hypotonia, seizures, and absent language | AD |
| *HNRNPU* (602869) | Developmental and epileptic encephalopathy 54 | AD |

| Gene Symbol (OMIM Number) | Associated Disorders | Inheritance |
|---|---|---|
| *HSD17B10* (300256) | HSD10 mitochondrial disease | XL |
| *IQSEC2* (300522) | XL intellectual developmental disorder 1 | XL |
| *ITPA* (147520) | Developmental and epileptic encephalopathy 35 | AR |
| *KANSL1* (612452) | Koolen-De Vries syndrome | AD |
| *KCNA1* (176260) | Episodic ataxia/myokymia syndrome | AD |
| *KCNA2* (176262) | Developmental and epileptic encephalopathy 32 | AD |
| *KCNB1* (600397) | Developmental and epileptic encephalopathy 26 | AD |
| *KCNC1* (176258) | Progressive myoclonic epilepsy 7 | AD |
| *KCNH1* (603305) | Temple-Baraitser syndrome; Zimmermann-Laband syndrome 1 | AD |
| *KCNJ10* (602208) | SESAME syndrome | AR |
| *KCNJ11* (600937) | Permanent neonatal diabetes 2 with or without neurologic features | AD |
| *KCNMA1* (600150) | Cerebellar atrophy, developmental delay, and seizures | AR |
| | Liang-Wang syndrome paroxysmal nonkinesigenic dyskinesia 3 with or without generalized epilepsy; susceptibility to idiopathic generalized epilepsy 16 | AD |
| *KCNQ2* (602235) | Benign neonatal seizures 1; developmental and epileptic encephalopathy 7 | AD |
| *KCNQ3* (602232) | Benign neonatal seizures 2 | AD |
| *KCNT1* (608167) | Developmental and epileptic encephalopathy 14; nocturnal frontal lobe epilepsy 5 | AD |
| *KCTD7* (611725) | Progressive myoclonic epilepsy 3 with or without intracellular inclusions | AR |
| *KDM5C* (314690) | XL syndromic intellectual developmental disorder (Claes-Jensen type) | XL |
| *KIF1A* (601255) | NESCAV syndrome | AD |
| *LGI1* (604619) | Familial temporal lobe epilepsy 1 | AD |
| *MBD5* (611472) | Intellectual developmental disorder 1 | AD |
| *MDH2* (154100) | Developmental and epileptic encephalopathy 51 | AR |
| *MECP2* (300005) | Rett syndrome; severe neonatal encephalopathy; XL autism susceptibility 3; XL syndromic intellectual developmental disorder (Lubs type or 13) | XL |
| *MED17* (603810) | Postnatal progressive microcephaly with seizures and brain atrophy | AR |

| Gene Symbol (OMIM Number) | Associated Disorders | Inheritance |
|---|---|---|
| *MEF2C* (600662) | Neurodevelopmental disorder with hypotonia, stereotypic hand movements, and impaired language | AD |
| *MFSD8* (611124) | Neuronal ceroid lipofuscinosis 7 | AR |
| *MOCS2* (603708) | Molybdenum cofactor deficiency B | AR |
| *MOGS* (601336) | Congenital disorder of glycosylation type IIb | AR |
| *MPDU1* (604041) | Congenital disorder of glycosylation type If | AR |
| *MTHFR* (607093) | Homocystinuria due to MTHFR deficiency | AR |
| *MTOR* (601231) | Smith-Kingsmore syndrome | AD |
| *NDE1* (609449) | Lissencephaly 4 with microcephaly | AR |
| *NECAP1* (611623) | Developmental and epileptic encephalopathy 21 | AR |
| *NEDD4L* (606384) | Periventricular nodular heterotopia 7 | AD |
| *NEU1* (608272) | Sialidosis type I or II | AR |
| *NEXMIF* (300524) | XL intellectual developmental disorder 98 | XL |
| *NGLY1* (610661) | Congenital disorder of deglycosylation 1 | AR |
| *NHLRC1* (608072) | Progressive myoclonic epilepsy 2B (Lafora) | AR |
| *NPRL2* (607072) | Familial focal epilepsy with variable foci 2 | AD |
| *NPRL3* (600928) | Familial focal epilepsy with variable foci 3 | AD |
| *NR2F1* (132890) | Bosch-Boonstra-Schaaf optic atrophy syndrome | AD |
| *NRXN1* (600565) | Pitt-Hopkins-like syndrome 2 | AR |
| *NSD1* (606681) | Sotos syndrome | AD |
| *NTRK2* (600456) | Developmental and epileptic encephalopathy 58; obesity, hyperphagia, and developmental delay | AD |
| *OPHN1* (300127) | XL syndromic intellectual developmental disorder (Billuart type) | XL |
| *PACS1* (607492) | Schuurs-Hoeijmakers syndrome | AD |
| *PAFAH1B1* (601545) | Lissencephaly 1 | AD |
| *PCDH19* (300460) | Developmental and epileptic encephalopathy 9 | XL |
| *PEX1* (602136) | Peroxisome biogenesis disorder 1A (Zellweger) or 1B (NALD/IRD) | AR |

| Gene Symbol (OMIM Number) | Associated Disorders | Inheritance |
|---|---|---|
| *PEX12* (601758) | Peroxisome biogenesis disorder 3A (Zellweger) | AR |
| *PEX2* (170993) | Peroxisome biogenesis disorder 5A (Zellweger) | AR |
| *PEX3* (603164) | Peroxisome biogenesis disorder 10A (Zellweger) or 10B | AR |
| *PEX6* (601498) | Peroxisome biogenesis disorder 4A (Zellweger) or 4B | AR |
| *PHF6* (300414) | Borjeson-Forssman-Lehmann syndrome | XL |
| *PHGDH* (606879) | Phosphoglycerate dehydrogenase deficiency | AR |
| *PIGA* (311770) | Multiple congenital anomalies-hypotonia-seizures syndrome 2; neurodevelopmental disorder with epilepsy and hemochromatosis | XL |
| *PIGG* (616918) | Neurodevelopmental disorder with or without hypotonia, seizures, and cerebellar atrophy | AR |
| *PIGN* (606097) | Multiple congenital anomalies-hypotonia-seizures syndrome 1 | AR |
| *PIGO* (614730) | Hyperphosphatasia with impaired intellectual development syndrome 2 | AR |
| *PIGQ* (605754) | Multiple congenital anomalies-hypotonia-seizures syndrome 4 | AR |
| *PIGT* (610272) | Multiple congenital anomalies-hypotonia-seizures syndrome 3 | AR |
| *PIGV* (610274) | Hyperphosphatasia with impaired intellectual development syndrome 1 | AR |
| *PLCB1* (607120) | Developmental and epileptic encephalopathy 12 | AR |
| *PLPBP* (604436) | Early-onset vitamin B6-dependent epilepsy | AR |
| *PMM2* (601785) | Congenital disorder of glycosylation type Ia | AR |
| *PNKP* (605610) | Microcephaly, seizures, and developmental delay | AR |
| *PNPO* (603287) | Pyridoxamine 5'-phosphate oxidase deficiency | AR |
| *POLG* (174763) | Mitochondrial DNA depletion syndrome type 4A (Alpers type) or 4B (MNGIE type); mitochondrial recessive ataxia syndrome (includes SANDO and SCAE) | AR |
| *PPT1* (600722) | Neuronal ceroid lipofuscinosis 1 | AR |
| *PRICKLE2* (608501) | Early-onset epilepsy | AD |
| *PRRT2* (614386) | Benign familial infantile seizures 2; episodic kinesigenic dyskinesia 1; familial infantile convulsions with paroxysmal choreoathetosis | AD |
| *PSAP* (176801) | Atypical Gaucher disease; atypical Krabbe disease; combined SAP deficiency; metachromatic leukodystrophy due to SAP-b deficiency | AR |
| *PTPN23* (606584) | Neurodevelopmental disorder and structural brain anomalies with or without seizures and spasticity | AR |

| Gene Symbol (OMIM Number) | Associated Disorders | Inheritance |
|---|---|---|
| *PURA* (600473) | Neurodevelopmental disorder with neonatal respiratory insufficiency, hypotonia, and feeding difficulties | AD |
| *QARS1* (603727) | Microcephaly, progressive, seizures, and cerebral and cerebellar atrophy | AR |
| *QDPR* (612676) | Hyperphenylalaninemia BH4-deficient C | AR |
| *RELN* (600514) | Familial temporal lobe epilepsy 7 | AD |
| | Lissencephaly 2 (Norman-Roberts type) | AR |
| *RFT1* (611908) | Congenital disorder of glycosylation type In | AR |
| *RNASEH2A* (606034) | Aicardi-Goutieres syndrome 4 | AR |
| *RNASEH2B* (610326) | Aicardi-Goutieres syndrome 2 | AR |
| *RNASEH2C* (610330) | Aicardi-Goutieres syndrome 3 | AR |
| *ROGDI* (614574) | Kohlschutter-Tonz syndrome | AR |
| *RORB* (601972) | Susceptibility to idiopathic generalized epilepsy 15 | AD |
| *SAMHD1* (606754) | Aicardi-Goutieres syndrome 5 | AR |
| *SATB2* (608148) | Glass syndrome | AD |
| *SCARB2* (602257) | Progressive myoclonic epilepsy 4 with or without renal failure | AR |
| *SCN1A* (182389) | Dravet syndrome; developmental and epileptic encephalopathy 6B (non-Dravet); familial febrile seizures 3A; familial hemiplegic migraine 3; generalized epilepsy with febrile seizures plus type 2 | AD |
| *SCN1B* (600235) | Developmental and epileptic encephalopathy 52 | AR |
| | Generalized epilepsy with febrile seizures plus type 1 | AD |
| *SCN2A* (182390) | Benign familial infantile seizures 3; developmental and epileptic encephalopathy 11; episodic ataxia type 9 | AD |
| *SCN3A* (182391) | Developmental and epileptic encephalopathy 62; familial focal epilepsy with variable foci 4 | AD |
| *SCN8A* (600702) | Benign familial infantile seizures 5; developmental and epileptic encephalopathy 13 | AD |
| *SERPINI1* (602445) | Familial encephalopathy with neuroserpin inclusion bodies | AD |
| *SETBP1* (611060) | Intellectual developmental disorder 29; Schinzel-Giedion midface retraction syndrome | AD |
| *SLC12A5* (606726) | Developmental and epileptic encephalopathy 34 | AR |
| | Susceptibility to idiopathic generalized epilepsy 14 | AD |
| *SLC13A5* (608305) | Developmental and epileptic encephalopathy 25, with amelogenesis imperfecta | AR |

| Gene Symbol (OMIM Number) | Associated Disorders | Inheritance |
|---|---|---|
| *SLC19A3* (606152) | Thiamine metabolism dysfunction syndrome 2 (biotin- or thiamine-responsive encephalopathy type 2) | AR |
| *SLC1A2* (600300) | Developmental and epileptic encephalopathy 41 | AD |
| *SLC25A12* (603667) | Developmental and epileptic encephalopathy 39 | AR |
| *SLC25A22* (609302) | Developmental and epileptic encephalopathy 3 | AR |
| *SLC2A1* (138140) | GLUT1 deficiency syndrome 1 infantile onset | AD/AR |
| | Dystonia 9; GLUT1 deficiency syndrome 2, childhood onset: stomatin-deficient cryohydrocytosis with neurologic defects; susceptibility to idiopathic generalized epilepsy 12 | AD |
| *SLC35A2* (314375) | Congenital disorder of glycosylation type IIm | XL |
| *SLC6A1* (137165) | Myoclonic-atonic epilepsy | AD |
| *SLC9A6* (300231) | XL syndromic intellectual developmental disorder (Christianson type) | XL |
| *SMARCA2* (600014) | Blepharophimosis-impaired intellectual development syndrome; Nicolaides-Baraitser syndrome | AD |
| *SMC1A* (300040) | Cornelia de Lange syndrome 2; developmental and epileptic encephalopathy 85 with or without midline brain defects | XL |
| *SMS* (300105) | XL syndromic intellectual developmental disorder (Snyder-Robinson type) | XL |
| *SNAP25* (600322) | Congenital myasthenic syndrome 18 | AD |
| *SPATA5* (613940) | Neurodevelopmental disorder with hearing loss, seizures, and brain abnormalities | AR |
| *SPTAN1* (182810) | Developmental and epileptic encephalopathy 5 | AD |
| *ST3GAL3* (606494) | Developmental and epileptic encephalopathy 15 | AR |
| *ST3GAL5* (604402) | Salt and pepper developmental regression syndrome | AR |
| *STRADA* (608626) | Polyhydramnios, megalencephaly, and symptomatic epilepsy | AR |
| *STX1B* (601485) | Generalized epilepsy with febrile seizures plus type 9 | AD |
| *STXBP1* (602926) | Developmental and epileptic encephalopathy 4 | AD/AR |
| *SUOX* (606887) | Sulfite oxidase deficiency | AR |
| *SYN1* (313440) | XL epilepsy 1 with variable learning disabilities and behavior disorders | XL |
| *SYNGAP1* (603384) | Intellectual developmental disorder 5 | AD |
| *SYNJ1* (604297) | Early-onset Parkinson disease 20; developmental and epileptic encephalopathy 53 | AR |
| *SZT2* (615463) | Developmental and epileptic encephalopathy 18 | AR |

| Gene Symbol (OMIM Number) | Associated Disorders | Inheritance |
|---|---|---|
| *TBC1D24* (613577) | Developmental and epileptic encephalopathy 16; DOORS syndrome; familial infantile myoclonic epilepsy; rolandic epilepsy with paroxysmal exercise-induce dystonia and writer's cramp | AR |
| *TBL1XR1* (608628) | Intellectual developmental disorder 41; Pierpont syndrome | AD |
| *TCF4* (602272) | Pitt-Hopkins syndrome | AD |
| *TPK1* (606370) | Thiamine metabolism dysfunction syndrome 5 (episodic encephalopathy type) | AR |
| *TPP1* (607998) | Neuronal ceroid lipofuscinosis 2 | AR |
| *TREX1* (606609) | Aicardi-Goutieres syndrome 1 | AR/AD |
| | Vasculopathy, retinal, with cerebral leukoencephalopathy and systemic manifestations | AD |
| *TSC1* (605284) | Tuberous sclerosis-1 | AD |
| *TSC2* (191092) | Tuberous sclerosis-2 | AD |
| *TSEN54* (608755) | Pontocerebellar hypoplasia (types 2A, 4, 5) | AR |
| *UBA5* (610552) | Developmental and epileptic encephalopathy 44 | AR |
| *UBE3A* (601623) | Angelman syndrome | AD |
| *UNC80* (612636) | Infantile hypotonia with psychomotor retardation and characteristic facies 2 | AR |
| *VPS13A* (605978) | Choreoacanthocytosis | AR |
| *WDR45* (300526) | Neurodegeneration with brain iron accumulation 5 | XL |
| *WWOX* (605131) | Developmental and epileptic encephalopathy 28; spinocerebellar ataxia, 12 | AR |
| *ZEB2* (605802) | Mowat-Wilson syndrome | AD |

AD, autosomal dominant; AR, autosomal recessive; XL, X-linked

## References


1. Fiest KM, Sauro KM, Wiebe S, et al. Prevalence and incidence of epilepsy: a systematic review and meta-analysis of international studies. *Neurology*. 2017;88(3):296-303.

2. International League Against Epilepsy Consortium on Complex Epilepsies. Genetic determinants of common epilepsies: a meta-analysis of genome-wide association studies. *Lancet Neurol*. 2014;13(9):893-903.

3. Sheidley BR, Malinowski J, Bergner AL, et al. Genetic testing for the epilepsies: a systematic review. *Epilepsia*. 2022;63(2):375-387.

4. Smith L, Malinowski J, Ceulemans S, et al. Genetic testing and counseling for the unexplained epilepsies: an evidence-based practice guideline of the National Society of Genetic Counselors. *J Genet Couns*. 2023;32(2):266-280.

5. Symonds JD, McTague A. Epilepsy and developmental disorders: next generation sequencing in the clinic. *Eur J Paediatr Neurol*. 2020;24:15-23.