Comprehensive Epilepsy Panel

Clinical Features

Epilepsy is defined by the occurrence of at least two unprovoked seizures occurring more than 24 hours apart. It is a common neurological disorder that affects at least 0.8% of the population. The International League against Epilepsy (ILAE) classifies seizures into two main categories.[1] Generalized epileptic seizures originate in and rapidly engage both cerebral hemispheres. Tonic-clonic, absence, myoclonic, clonic, tonic, and atonic seizures are common types of generalized seizures. Focal seizures originate from neuronal networks within a single hemisphere. Focal seizures are classified as focal aware (previously simple partial seizures), which do not result in an alteration of consciousness, and focal impaired (previously complex partial seizures), which cause a change in behavior or consciousness. Some types of seizures, such as infantile spasms, do not fit into either category and remain unclassified.

Seizures can be self-limiting or controlled by standard therapeutic treatments in some cases; however, individuals with epileptic encephalopathy have severe seizures that are refractory to treatment, leading to cognitive and behavioral impairment secondary to the epileptic activity. Epilepsy may be an isolated neurological symptom, or it may occur in association with other neurological symptoms or medical problems.[2] Some individuals with epilepsy are diagnosed with an electroclinical syndrome such as West or Ohtahara syndrome based on the presence of characteristic EEG findings and the clinical and family history.[1]

Genetics

Epilepsy can be caused by genetic disorders, metabolic diseases, trauma, infection, and structural brain abnormalities, although the cause is not known in many cases. A genetic etiology underlies epilepsy in approximately 40% of individuals.[3] Genes have been identified that cause both generalized seizures and focal seizures, as well as unclassified epilepsy types such as infantile spasms. The genetic etiology of idiopathic generalized epilepsy (IGE) is frequently complex because it is due to a combination of multiple genetic factors that each confer a small risk for epilepsy and may be modified by environmental influences.[3] Currently, approximately 2% of patients with IGE harbor an identifiable variant in a single gene associated with Mendelian inheritance of epilepsy.[4] However, the percentage of patients with Mendelian epilepsy is higher for specific epilepsy types such as infantile spasms, benign familial neonatal and neonatal-infantile seizures (BFNS and BFNIS), and others.[3,5,6,7] The inheritance pattern can be autosomal dominant, autosomal recessive, or X-linked. Pathogenic variants in a single gene may be associated with different types of seizures (clinical heterogeneity), and conversely, pathogenic variants in different genes can cause the same epilepsy phenotype (genetic heterogeneity).

The Comprehensive Epilepsy panel at GeneDx includes sequencing and deletion/duplication analysis of genes causing Mendelian forms of epilepsy. Many of these genes encode subunits of ion channels involved in stabilizing or propagating neuronal activity, including components of the voltage-gated sodium, potassium, and calcium channels and the ligand-gated gamma-aminobutyric (GABA) channel.[5,7,8,9] The panel also includes non-ion channel genes associated with a variety of neurotransmitter disorders, storage

and other neurometabolic disorders, as well as genes causing syndromic forms of epilepsy, many of which are involved in transcriptional activation or repression.[5,6,8,10,11,12]

Test Methods

Using genomic DNA from the submitted specimen, the complete coding regions and splice site junctions of the genes on this panel are enriched using a proprietary targeted capture system developed by GeneDx for next-generation sequencing with CNV calling (NGS-CNV). The enriched targets are simultaneously sequenced with paired-end reads on an Illumina platform. Bi-directional sequence reads are assembled and aligned to reference sequences based on NCBI RefSeq transcripts and human genome build GRCh37/UCSC hg19. After gene specific filtering, data are analyzed to identify sequence variants and most deletions and duplications involving coding exons. Alternative sequencing or copy number detection methods are used to analyze or confirm regions with inadequate sequence or copy number data by NGS. Reportable variants include pathogenic variants, likely pathogenic variants and variants of uncertain significance. Likely benign and benign variants, if present, are not routinely reported but are available upon request.

The technical sensitivity of sequencing is estimated to be >99% at detecting single nucleotide events. It will not reliably detect deletions greater than 20 base pairs, insertions or rearrangements greater than 10 base pairs, or low-level mosaicism. The copy number assessment methods used with this test cannot reliably detect copy number variants of less than 500 base pairs or mosaicism and cannot identify balanced chromosome aberrations. Assessment of exon-level copy number events is dependent on the inherent sequence properties of the targeted regions, including shared homology and exon size. For the *CHRNA7* and *MAGI2* gene(s), deletion/duplication analysis but not sequencing is performed. For the *ARG1, C12orf57, FGF12, FOXG1, PHGDH, PIGG, PIGT, SLC35A2, SLC6A8*, and *SNAP25* gene(s), sequencing but not deletion/duplication analysis is performed. For the *ARX, ASNS, CHRNA7, FOLR1, GAMT, KCNT1, NR2F1, PCDH19, SCN1B, SHANK3*, and *TUBB2A* genes, only whole gene deletions or duplications may be detected, and deletions/duplications involving the 3' end of the *TSC2* gene (exons 36-42) may not be identified. If indicated based on the patient's specific clinical features, multiplex ligation-dependent probe amplification (MLPA) of the *FOXG1* or *SLC6A8* genes is available as a separate test (test code 906).

Clinical Sensitivity

The clinical sensitivity of sequencing and deletion/duplication analysis of the genes included in the Comprehensive Epilepsy Panel depends in part on the patient's clinical phenotype. In a prior study, 31% of individuals with infantile spasms who were tested using an epilepsy gene panel were found to harbor definitive pathogenic variant(s) to explain the phenotype.[113] Overall, 19% of patients with epilepsy and 17-24% of patients with developmental and epileptic encephalopathies have an identifiable genetic etiology.[114,175] Specific information about the diagnostic yield for each gene in selected populations is summarized in the table below.

Appendix: Genes Included on Comprehensive Epilepsy Panel

Diagnostic Yield of Epilepsy Panel Genes in Selected Populations

Epilepsy Type	Gene	Protein	Inh	Diagnostic Yield in Selected Population(s)
Benign familial neonatal seizures (BFNS)	*KCNQ2*	Potassium voltage-gated channel subfamily KQT member 2	AD	>50% BFNS[6]
	KCNQ3	Potassium voltage-gated channel subfamily KQT member 3	AD	~7% BFNS[6]
Benign familial neonatal-infantile seizures (BFNIS)	*SCN2A*	Sodium channel protein type 2 subunit alpha	AD	Unknown[6]
Benign familial infantile seizures (BFIS)	*PRRT2*	Proline-rich transmembrane protein 2	AD	83% familial and 30% sporadic BFIS[14,15,16]; 62-96% of familial PKD/IC; 36% sporadic PKD/IC[14,17,18]
Familial infantile myoclonic epilepsy (FIME)	*TBC1D24*	TBC1 domain family member 24	AR	Unknown[19,20]
Developmental and epileptic encephalopathy (includes West, Ohtahara, and Lennox Gastaut and other electroclinical syndromes)	*ALDH7A1*	Alpha-aminoadipic semialdehyde dehydrogenase (antiquitin)	AR	>90% pyridoxine-responsive epilepsy[32]
	ALG13	ALG13, UDP-N-acetylglucosaminyltransferase subunit	XL	Rare[92]
	ANKRD11	Ankyrin repeat domain-containing protein	AD	Rare[154]
	ARHGEF9	Cdc42 guanine nucleotide exchange factor (GEF) 9	XL	Rare[94]
	ARX	Aristaless related homeobox	XL	5% males with infantile spasms[6]
	ATP1A3	Sodium/potassium-transporting ATPase subunit alpha-3	AD	Rare in early life epilepsy[131], 78% alternating hemiplegia of childhood[132]
	ATP6AP2	Renin receptor	XL	Rare[45]
	BRAT1	BRCA1 associated ATM activator 1	AR	Rare[123]
	CACNA1A	Voltage-dependent P/Q-type calcium channel subunit alpha-1A	AD	Rare[95]

	CACNA1E	Voltage-dependent R-type calcium channel subunit alpha-1E	AD	Rare[158]
	CACNA1G	Voltage-dependent T-type calcium channel subunit alpha-1G	AD	Rare[159]
	CASK	Peripheral plasma membrane protein CASK	XL	Rare[151]
	CDKL5	Cyclin-dependent kinase-like 5	XL	10-17% infantile spasms[6]
	CHD2	Chromodomain helicase DNA binding protein 2	AD	1% of epileptic encephalopathy[91]
	CLCN4	Chloride voltage-gated channel 4	XL	Rare[133]
	*DNM1***	Dynamin 1	AD	1% of epileptic encephalopathy[92]
	DOCK7	Dedicator of cytokinesis protein 7	AR	Rare[164]
	EEF1A2	Eukaryotic translation elongation factor 1 alpha 2	AD	Rare[96, 97]
	FGF12	Fibroblast growth factor 12	AD	Rare[166]
	FRRS1L	DOMON domain-containing protein FRRS1L	AR	Rare[135]
	GABBR2	Gamma-aminobutyric acid type B receptor subunit 2	AD	Rare[118]
	GABRA1	Gamma-aminobutyric acid receptor subunit alpha-1	AD	Rare[88]
	GABRB2	Gamma-aminobutyric acid (GABA) A receptor, beta 2	AD	Rare[112]
	GABRB3	Gamma-aminobutyric acid (GABA) A receptor, beta 3	AD	Rare[95]
	GABRG2	Gamma-aminobutyric acid receptor subunit gamma-2	AD	Rare[6]
	GNAO1	Guanine nucleotide binding protein (G protein), alpha activating activity polypeptide O	AD	Rare in epileptic encephalopathy and early-onset hyperkinetic movement disorders[136]
	GRIN1	Glutamate receptor, ionotropic, NMDA 1	AD	Rare[94]
	GRIN2A	Glutamate receptor ionotropic, NMDA 2A	AD	Rare[83]
	GRIN2B	Glutamate receptor ionotropic, NMDA 2B	AD	Rare[90]
	HCN1	Potassium/sodium hyperpolarization-activated	AD	Rare[167]

		cyclic nucleotide-gated channel 1		
	IQSEC2	IQ motif and sec7 domain 7	XL	Rare[95]
	KCNA2	Potassium voltage-gated channel subfamily A member 2	AD	Rare[138]
	KCNB1	Potassium channel, voltage gated shab related subfamily B, member 1	AD	Rare[98]
	KCNQ2	Potassium voltage-gated channel subfamily KQT member 2	AD	10% neonatal epileptic encephalopathy[31]
	KCNT1	Potassium channel, sodium activated subfamily T, member 1	AD	35% MMPSI[99-101]; Rare in other epileptic encephalopathies[99]
	MAGI2 (dels only)	Membrane-associated guanylate kinase, WW and PDZ domain-containing protein 2	AD	Rare[43]
	MEF2C	Myocyte-specific enhancer factor 2C	AD	2% epileptic encephalopathy[36]
	NR2F1	Nuclear receptor subfamily 2, group F, member 1	AD	Rare[103]
	PCDH19	Protocadherin-19	XL	2-14% females with infantile/childhood epilepsy[26,27,28,29,30]
	PIGA	Phosphatidylinositol glycan anchor biosynthesis, class A	XL	Rare[109]
	PIGG	GPI ethanolamine phosphate transferase 2	AR	Rare[169]
	PIGN	Phosphatidylinositol glycan anchor biosynthesis, class N	AR	Rare[145]
	PIGO	Phosphatidylinositol glycan anchor biosynthesis, class O	AR	Rare[110]
	PIGT	GPI transamidase component PIG-T	AR	Rare[170]
	PIGV	Phosphatidylinositol glycan anchor biosynthesis, class V	AR	Rare[111]
	PLCB1	1-phoshatidylinositol 4,5-bisphosphate phosphodiesterase beta-1	AR	Rare[152]
	PNPO	Pyridoxine-5'-phosphate oxidase	AR	Rare[40]

	POLG	DNA polymerase subunit gamma-1	AR	63-87% Alpers syndrome[33,34,35]; 4-5% infantile/childhood epileptic encephalopathy[34]
	QARS	Glutaminyl-tRNA synthetase	AR	Rare[104]
	SCN1A	Sodium channel protein type 1 alpha	AD	70-80% Dravet syndrome[6]; 20-24% early-onset cryptic epilepsy[24,25]
	SCN2A	Sodium channel protein type 2 alpha	AD	1-2% early-onset epileptic encephalopathy[37,38]
	SCN8A	Sodium channel protein type 8 subunit alpha	AD	Unknown[39]
	SLC13A5	Solute carrier family 13 (sodium-dependent citrate transporter), member 5	AR	Rare[108]
	SLC25A22	Mitochondrial glutamate carrier 1	AR	Rare[44]
	SLC2A1	Solute carrier family 2, facilitated glucose transporter member 1	AD	91% GLUT1 deficiency[3]; ~10% early-onset absence epilepsy[6]
	SLC35A2	UDP-galactose translocator	XL	Rare[172]
	SLC6A1	Solute carrier family 6 member 1	AD	4% myoclonic-astatic epilepsy (MAE)[149]
	SMC1A	Structural maintenance of chromosomes protein 1A	AD	Rare[151,152]
	SNAP25	Synaptosomal-associated protein 25	AD	Rare[173]
	SPATA5	ATPase family protein 2 homolog	AR	Rare[174]
	SPTAN1	Alpha-II spectrin	AD	Rare[41]
	STX1B	Syntaxin 1B	AD	Rare in MAE and fever-associated epilepsy syndromes[149]
	STXBP1	Syntaxin binding protein 1	AD	35% Ohtahara syndrome[6]; Unknown in Dravet syndrome[88]
	SYNGAP1	Ras/Rap GTPase-activating protein SynGAP	AD	Rare[151]
	SZT2	KICSTOR complex protein SZT2	AR	Rare[149]
	TBL1XR1	F-box-like/WD repeat-containing protein TBL1XR1	AD	Rare[150]
	TSC1	Hamartin	AD	2-4% infantile spasms[21,22,23]
	TSC2	Tuberin	AD	10-16% infantile spasms[21,22,23]
	WWOX	WW domain-containing oxidoreductase	AR	Rare

Autosomal Dominant Focal Epilepsies	*CHRNA4*	Neuronal acetylcholine receptor alpha-4	AD	~10% autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE)[6]
	CHRNB2	Neuronal acetylcholine receptor beta-2	AD	< 5% ADNFLE[6]
	CHRNA2	Neuronal acetylcholine receptor alpha-2	AD	Rare in ADNFLE[6]
	DEPDC5	DEP domain containing 5	AD	5-37% autosomal dominant focal epilepsies, with or without cortical dysplasia[126]
	KCNT1	Potassium channel, sodium-activated subfamily T, member 1	AD	< 5% ADNFLE[99,102]
	LGI1	Leucine-rich glioma-inactivated protein 1	AD	~50% autosomal dominant partial epilepsy with auditory features (ADTLE)[6]
	NPRL3	GATOR complex protein NPRL3	AD	~2% autosomal dominant focal epilepsies, with or without cortical dysplasia[127]
Generalized Epilepsy with Febrile Seizures Plus (GEFS+)	*SCN1A*	Sodium channel protein type 1 alpha	AD	5-10% GEFS+[6]
	SCN1B	Sodium channel subunit beta-1	AD	<5% GEFS+[6]
	GABRG2	Gamma-aminobutyric acid receptor subunit gamma-2	AD	<1% GEFS+[6]
	SCN2A	Sodium channel protein type 2 alpha	AD	Rare[5]
Epilepsy with paroxysmal dyskinesia	*PRRT2*	Proline-rich transmembrane protein 2	AD	62-96% of familial PKD/infantile convulsions (PKD/IC); 36% sporadic PKD/IC[14,17,18]
	KCNMA1	Potassium calcium-activated channel subfamily M alpha 1	AD/ AR	Rare[140]
Progressive Myoclonic Epilepsy	*EPM2A*	Laforin	AR	53% Lafora disease[48]
	NHLRC1 (EPM2B)	NHL repeat-containing protein 1 (malin)	AR	40% Lafora disease[48]
	CSTB (EPM1)*	Cystatin-B	AR	Rare sequencing variants in Unverricht-Lundborg disease[49]
	KCTD7 (EPM3)	BTB/POZ domain-containing protein KCTD7	AR	Rare[50]
	SCARB2 (EPM4)	Lysosome membrane protein 2	AR	~7% progressive myoclonic epilepsy[51]; Unknown in action

				myoclonus-renal failure syndrome[52]
	GOSR2	Golgi SNAP receptor complex member 2	AR	Rare[53,54]
	KCNC1	Potassium voltage-gated channel subfamily C member 1	AD	Rare KCNC1-associated myoclonus epilepsy and ataxia (MEAK)[115]
	FOLR1	Folate receptor alpha	AR	Rare[55]
Rett/atypical Rett syndromes	*MECP2*	Methyl CpG binding protein 2	XL	88% females with Rett syndrome[57]
	CDKL5	Cyclin-dependent kinase-like 5	XL	2-8% females with atypical Rett syndrome[58,59]
	CTNNB1	Catenin beta 1	AD	Rare in Rett-like syndromes[116]
	DDX3X	DEAD-box helicase 3, X-linked	XL	Rare in Rett-like syndromes[117]
	*FOXG1***	Forkhead box protein G1	AD	~1% Rett syndrome overall[60]; 25% congenital variant of Rett[61]
	GABBR2	Gamma-aminobutyric acid type B receptor subunit 2	AD	Rare in epileptic encephalopathy and intellectual disability with Rett-like features[118]
	KCNA2	Potassium voltage-gated channel subfamily A member 2	AD	Rare in Rett-like syndromes[119]
	MBD5	Methyl-CpG-binding domain protein 5	AD	Rare in Rett-like syndromes[62]
	MEF2C	Myocyte-specific enhancer factor 2C	AD	Rare in Rett-like syndromes[63]
	SATB2	SATB homeobox 2	AD	Rare in Rett-like syndromes[120]
	STXBP1	Syntaxin binding protein 1	AD	Rare in Rett-like syndromes[121]
	TBL1XR1	Transducin (beta)-like 1 X-linked receptor 1	AD	Rare in Rett-like syndromes[122]
	WDR45	WD repeat domain 45	XL	Rare in Rett-like syndromes[106, 107]
Angelman/ Angelman-like/ Pitt-Hopkins syndromes	*UBE3A*	Ubiquitin protein ligase E3A	AD	68% maternally inherited 15q11.2 deletion[64]; 11% UBE3A sequencing variant Angelman syndrome[64]
	SLC9A6	Sodium/hydrogen exchanger 6	XL	6% Angelman-like syndrome[65]
	MBD5	Methyl-CpG-binding domain protein 5	AD	Rare in Angelman-like syndrome[66]
	TCF4	Transcription factor 4	AD	36% Pitt-Hopkins syndrome (PHS)[67]; 2% Angelman syndrome[67]

	ATRX	Transcriptional regulator ATRX	XL	95% males with alpha-thalassemia X-linked intellectual disability syndrome[153]
	NRXN1	Neurexin-1	AR	Rare in PHS[68]
	CNTNAP2	Contactin-associated protein-like 2	AR	Rare in PHS[68]
Creatine deficiency syndromes	*SLC6A8***	Solute carrier family 6 (neurotransmitter transporter), member 8	XL	2% males with epilepsy and intellectual disability[46]; 65% males with biochemical creatine deficiency[47]
	*GAMT***	Guanidinoacetate N-methyltransferase	AR	Rare[71]
	GATM	Glycine amidinotransferase, mitochondrial	AR	Rare[71]
Neuronal Ceroid Lipofuscinoses (NCL)	*PPT1 (CLN1)*	Palmitoyl-protein thioesterase 1	AR	98% PPT1 deficiency[72]
	TPP1 (CLN2)	Tripeptidyl-peptidase 1	AR	95% TPP1 deficiency[73]
	CLN3	Battenin	AR	92% Juvenile NCL[74]
	DNAJC5 (CLN4B)	DnaJ homolog subfamily C member 5	AD	25% Kufs disease[75,76]
	CLN5	Ceroid-lipofuscinosis neuronal protein 5	AR	94% Finnish late-infantile NCL[77]; Otherwise rare
	CLN6	Ceroid-lipofuscinosis neuronal protein 6	AR	Rare[77]
	MFSD8 (CLN7)	Major facilitator superfamily domain-containing protein 8	AR	Rare[77]
	CLN8	Ceroid-lipofuscinosis neuronal protein 8	AR	100% Finnish Northern epilepsy[77]; Otherwise rare
	CTSD (CLN10)	Cathepsin D	AR	Rare[77]
	CTSF (CLN13)	Cathepsin F	AR	Rare[77]
	KCTD7 (CLN14)	BTB/POZ domain-containing protein KCTD7	AR	Rare[78]
Metabolic disorders	*ADSL*	Adenylosuccinate lyase	AR	Rare (adenosuccinate lyase deficiency)[79]
	ALDH5A1	Aldehyde dehydrogenase 5 family member A1	AR	96% (SSADH deficiency)[129]
	ARG1	Arginase 1	AR	Rare (argininemia)[155]
	ASNS	Asparagine synthetase (glutamine-hydrolyzing)	AR	Rare (asparagine synthetase deficiency)[130]
	FOLR1	Folate receptor alpha	AR	Rare (cerebral folate deficiency)[56]

	GLDC	Glycine decarboxylase	AR	70-75% glycine encephalopathy (nonketotic hyperglycinemia)[124]
	NGLY1	N-glycanase 1	AR	Rare (congenital disorder of deglycosylation)[143]
	PHGDH	D-3-phosphoglycerate dehydrogenase	AR	Rare (phosphoglycerate dehydrogenase deficiency / Neu-Laxova syndrome)[168]
	SLC19A3	Solute carrier family 19 member 3	AR	Rare (thiamine metabolism dysfunction disorders)[125]
Brain malformations	*ARX*	Aristaless related homeobox	XL	70-95% of X-linked lissencephaly with ambiguous genitalia (XLAG)[156]
	CASK	Peripheral plasma membrane protein CASK	XL	~96% females with microcephaly with pontine and cerebellar hypoplasia (MICPCH)[151]
	CUL4B	Cullin 4B	XL	Rare in cerebral malformations[160]
	DCX	Doublecortin	XL	Up to 100% XL lissencephaly; 10% of classic lissencephaly; 85% females and ~30% males with subcortical band heterotopia (SBH)[161-163]
	FLNA	Filamin A	XL	93% classic bilateral periventricular nodular heterotopia[134]
	PAFAH1B1 (LIS1)	Platelet-activating factor acetylhydrolase IB subunit alpha	AD	~40-65% of classic lissencephaly[162]
	TUBB2A	Tubulin, Beta-2A	AD	Rare[70]
EAST/SeSAME syndrome	*KCNJ10*	ATP-sensitive inward rectifier potassium channel 10	AR	Rare[81,82]
Epilepsy and hemiplegic migraine	*ATP1A2*	Sodium/potassium-transporting ATPase subunit alpha-2	AD	Unknown[6]
Idiopathic generalized epilepsy	*CHRNA7 (dels only)*	Neuronal acetylcholine receptor subunit alpha-7	AD	~1% patients with IGE[56]
Epilepsy associated with other neuro-developmental disorders	*ANKRD11*	Ankyrin repeat domain-containing protein	AD	83% patients with KBG syndrome[154]
	C12orf57	Protein C10	AR	Rare (Temtamy syndrome or TEMTYS)[157]
	DYRK1A	Dual-specificity tyrosine-(Y)-phosphorylation regulated kinase 1A	AD	Rare[93]

	EEF1A2	Eukaryotic translation elongation factor 1 alpha 2	AD	Rare[96]
	EHMT1	Histone-lysine N-methyltransferase EHMT1	AD	~75% of patients with Kleefstra syndrome, including microdeletion of 9q34.3[165]
	GRIN2A	Glutamate receptor ionotropic, NMDA 2A	AD	9-20% atypical Rolandic epilepsy and epilepsy-aphasia[89]; ~2% patients with intellectual disability and epilepsy[83,84]
	GRIN2B	Glutamate receptor ionotropic, NMDA 2B	AD	Unknown[83]
	KANSL1	KAT8 regulatory NSL complex subunit 1	AD	Rare (Koolen-de Vries syndrome, including microdeletion of 17q21.31)[85,86]
	HNRNPU	HNRNPU antisense RNA 1	AD	Rare[137]
	KCNH1	Potassium voltage-gated channel subfamily H member 1	AD	Rare (Temple-Baraitser and Zimmermann-Laband syndromes)[139]
	KDM6A	Lysine demethylase 6A	XL	Rare (Kabuki syndrome)[128]
	NEXMIF (KIAA2022)	Neurite extension and migration factor	XL	Rare[141]
	NALCN	Sodium leak channel, non-selective	AD/ AR	Rare (CLIFAHDD and infantile hypotonia with psychomotor retardation and characteristic facies (IHPRF)[142]
	PACS1	Phosphofurin acidic cluster sorting protein 1	AD	Rare[144]
	PNKP	Bifunctional polynucleotide phosphatase/kinase	AR	Rare[86]
	PPP2R5D	protein phosphatase 2 regulatory subunit B', delta	AD	Rare[146]
	PURA	Transcriptional activator protein Pur-alpha	AD	Rare (Including microdeletion of 5q31.3)[147]
	SHANK3	SH3 and multiple ankyrin repeat domains protein 3	AD	Rare (Phelan-McDermid syndrome, including microdeletion of 22q13.3)[171]
	SMARCA2	Probable global transcription activator SNF2L2	AD	Rare (Nicolaides-Baraitser and Coffin Siris syndromes)[176]

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