Blueprint Genetics

Epileptic Encephalopathy Panel

Test code: NE0401

Is a 203 gene panel that includes assessment of non-coding variants.

In addition, it also includes the maternally inherited mitochondrial genome. Is ideal for patients with a clinical suspicion of epileptic encephalopathy. The genes on this panel are included on the Comprehensive Epilepsy Panel.

The aetiology of the epileptic encephalopathies is variable; common causes of these anomalies are malformations, a metabolic disease or a genetic defect. Genetic testing is very useful in differential diagnosis of hereditary epileptic encephalopathies. Prenatal diagnosis is possible in families with a known genetic etiology. Depending of the specific syndrome and causative gene, epileptic encephalopathy can be inherited in an autosomal recessive, autosomal dominant or X-linked manner. Often, mutations occur as *de novo*. Genetic counseling is therefore very valuable to inform parents that their risk of having further children with similar disease is low. This panel is part of the Comprehensive epilepsy panel.

About Epileptic Encephalopathy

Epileptic encephalopathies are characterized by epileptiform abnormalities associated with progressive cerebral dysfunction. They typically present at an early age and manifest with EEG paroxysmal activity that is often aggressive, seizures that are commonly multi-form and intractable, cognitive, behavioural and neurological deficits that may be relentless and sometimes early death. Cognitive deficits and behavioural disturbances are presumed to be the main, and sometimes the first and only unique, manifestation of electrographic epileptic discharges in epileptic encephalopathies. In the classification of the International League Against Epilepsy, eight age-related epileptic encephalopathy syndromes are recognized. These syndromes include early myoclonic encephalopathy and Ohtahara syndrome (also known as early infantile epileptic encephalopathy with suppression-bursts) in the neonatal period, West syndrome (also known as infantile spasms) and Dravet syndrome in infancy, myoclonic status in nonprogressive encephalopathies, and Lennox-Gastaut syndrome, Landau-Kleffner syndrome, and epilepsy with continuous spike waves during slow wave sleep in childhood and adolescences. Other epileptic syndromes such as migrating partial seizures in infancy and severe epilepsy with multiple independent spike foci may be reasonably added. A common feature is that these disorders are usually refractory to standard antiepileptic drugs (AEDs). The aetiology of the epileptic encephalopathies is variable and includes malformations, metabolic disease and genetic conditions. Genetic testing is very useful in the differential diagnosis of hereditary epileptic encephalopathies. Prenatal diagnosis is possible in families with a known genetic etiology. Depending of the specific syndrome and causative gene, epileptic encephalopathy can be inherited in an autosomal recessive, autosomal dominant or X-linked manner. Often, mutations occur *de novo*.

Availability

Results in 3-4 weeks

Gene set description

Genes in the Epileptic Encephalopathy Panel and their clinical significance

Gene	Associated phenotypes	Inheritance	ClinVar	HGMD
ABAT	GABA-transaminase deficiency	AR	11	12
ACTL6B	Epilepitic encephalopathy	AD/AR	1	3
ADAM22	Early infantile epileptic encephalopathy	AR	2	3
ADAR	Dyschromatosis symmetrica hereditaria, Aicardi-Goutières syndrome	AD/AR	25	226
ADPRHL2	Neurodegeneration, childhood-onset, with brain atrophy	AR		1

ADSL	Adenylosuccinase deficiency	AR	24	57
ALDH7A1	Epilepsy, pyridoxine-dependent	AR	52	123
ALG13	Congenital disorder of glycosylation	XL	5	12
AMT	Glycine encephalopathy	AR	42	95
AP2M1	Epilepitic encephalopathy	AD		
AP3B2	Epileptic encephalopathy, early infantile, 48		6	12
APOPT1	Mitochondrial complex IV deficiency	AR	4	5
ARHGEF9	Epileptic encephalopathy, early infantile	XL	10	23
ARX	Lissencephaly, Epileptic encephalopathy, Corpus callosum, agenesis of, with abnormal genitalia, Partington syndrome, Proud syndrome, Hydranencephaly with abnormal genitalia, Mental retardation	XL	66	93
ASNS*	Asparagine synthetase deficiency	AR	21	26
ATP6V1A	Cutis laxa, autosomal recessive, type IID, Epileptic encephalopathy	AD/AR	8	8
BRAT1	Rigidity and multifocal seizure syndrome, lethal neonatal	AR	19	18
CACNA1A	Migraine, familial hemiplegic, Episodic ataxia, Spinocerebellar ataxia 6, Epileptic encephalopathy, early infantile, 42	AD	135	230
CACNA1B	Dystonia 23, Early infantile epileptic encephalopathy	AD/AR	28	3
CACNA1E	Epileptic encephalopathy	AD	8	6
CASK	Mental retardation and microcephaly with pontine and cerebellar hypoplasia, FG syndrome, Mental retardation	XL	87	112
CDKL5	Epileptic encephalopathy, early infantile, Rett syndrome, atypical, Angelman-like syndrome	XL	312	331
CHD2	Epileptic encephalopathy, childhood-onset	AD	85	59
CLCN4	Mental retardation, X-linked 49	XL	21	17
CLTC			20	14
CNKSR2	Epileptic encephalopathy, X-linked mental retardation, Epilepsy and X-linked mental retardation	XL	7	6
CNPY3	Epileptic encephalopathy	AR	3	3
CNTNAP2	Pitt-Hopkins like syndrome, Cortical dysplasia-focal epilepsy syndrome	AR	45	71
COX6B1	Mitochondrial complex IV deficiency	AR	2	3
CPT2	Carnitine palmitoyltransferase II deficiency	AR	72	111
CYFIP2	Early infantile epileptic encephalopathy, Epilepsy	AD	2	3
D2HGDH	D-2-hydroxyglutaric aciduria 1	AR	13	33
DCX	Lissencephaly, Subcortical laminal heterotopia	XL	131	142

DENND5A	Epileptic encephalopathy, early infantile, 49	AR	6	6
DNM1*	Epileptic encephalopathy, early infantile	AD	28	24
DNM1L	Encephalopathy due to defective mitochondrial and peroxisomal fission 1	AD	17	20
DOCK7	Epilepitic encephalopathy	AR	21	7
ECHS1	Mitochondrial short-chain enoyl-CoA hydratase 1 deficiency	AR	23	33
EEF1A2	Epileptic encephalopathy, early infantile, Mental retardation	AD	17	12
ETHE1	Ethylmalonic encephalopathy	AR	38	36
FAR1*	Peroxisomal fatty acyl-CoA reductase 1 disorder	AR	4	4
FARS2	Combined oxidative phosphorylation deficiency 14, Spastic paraplegia 77, autosomal recessive	AR	17	20
FGF12	Epileptic encephalopathy, early infantile, 47	AD	6	10
FLNA	Frontometaphyseal dysplasia, Osteodysplasty Melnick-Needles, Otopalatodigital syndrome type 1, Otopalatodigital syndrome type 2, Terminal osseous dysplasia with pigmentary defects	XL	133	257
FOXG1	Rett syndrome, congenital variant	AD	106	156
FRRS1L	Epileptic encephalopathy, early infantile, 37	AR	9	6
GABBR2	Epileptic encephalopathy	AD	5	5
GABRA1	Epileptic encephalopathy, early infantile, Epilepsy, childhood absence, Epilepsy, juvenile myoclonic	AD	24	35
GABRB2	Epileptic encephalopathy	AD	19	15
GABRB3	Epilepsy, childhood absence	AD	19	57
GABRG2	Generalized epilepsy with febrile seizures plus, Familial febrile seizures, Dravet syndrome, Epilepsy, childhood absence	AD	34	34
GAMT	Guanidinoacetate methyltransferase deficiency	AR	18	58
GLDC	Glycine encephalopathy	AR	139	425
GNAO1	Epileptic encephalopathy, early infantile, Epileptic encephalopathy, early infantile, 17	AD	26	35
GPHN	Hyperekplexia, Molybdenum cofactor deficiency	AD/AR	35	20
GRIN1	Mental retardation, autosomal dominant 8	AD	37	38
GRIN2A	Epilepsy, focal, with speech disorder	AD	65	95
GRIN2B	Epileptic encephalopathy, early infantile, Mental retardation	AD	64	69
GTPBP3	Combined oxidative phosphorylation deficiency 23	AR	14	15
HCN1	Epileptic encephalopathy, early infantile	AD	13	14

HECW2	Neurodevelopmental disorder with hypotonia, seizures, and absent language	AD	9	10
HEPACAM	Megalencephalic leukoencephalopathy with subcortical cysts, remitting	AD/AR	12	26
HIBCH	3-hydroxyisobutryl-CoA hydrolase deficiency	AR	18	16
HNRNPU	Intellectual disability and seizures	AD	38	66
HTT	Huntington disease, Lopes-Maciel-Rodan syndrome (LOMARS)	AD/AR	8	7
KCNA2	Epileptic encephalopathy, early infantile	AD	15	21
KCNB1	Early infantile epileptic encephalopathy	AD	27	30
KCNMA1	Paroxysmal nonkinesigenic dyskinesia 3 with or without generalized epilepsy (PNKD3), Cerebellar atrophy, developmental delay, and seizures (CADEDS)	AD/AR	5	9
KCNQ2	Epileptic encephalopathy, early infantile, Benign familial neonatal seizures, Myokymia	AD	335	274
KCNQ3	Seizures, benign neonatal	AD	20	24
KCNQ5	Mental retardation, autosomal dominant 46	AD	6	5
KCNT1	Epilepsy, nocturnal frontal lobe	AD	31	39
KCNT2	Epileptic encephalopathy	AD	2	5
KCTD3	Epileptic encephalopathy	AR	1	3
KIF1A	Spastic paraplegia, Neuropathy, hereditary sensory, Mental retardation	AD/AR	63	42
LRPPRC	Leigh syndrome, French-Canadian type	AR	55	17
LYRM7#	Mitochondrial complex III deficiency, nuclear type 8	AR	5	9
MBD5	Mental retardation	AD	62	90
MDH2	Epileptic encephalopathy, early infantile, 51	AR	5	9
MECP2	Angelman-like syndrome, Autism, Rett syndrome, Encephalopathy, Mental retardation	XL	506	1039
MED17	Microcephaly, postnatal progressive, with seizures and brain atrophy	AR	4	4
MEF2C	Mental retardation	AD	45	84
MOCS1*	Molybdenum cofactor deficiency	AR	7	35
MRPL44	Combined oxidative phosphorylation deficiency 16	AR	2	2
MT-ATP6	Neuropathy, ataxia, and retinitis pigmentosa, Leber hereditary optic neuropathy, Ataxia and polyneuropathy, adult-onset, Cardiomyopathy, infantile hypertrophic, Leigh syndrome, Striatonigral degeneration, infantile, mitochondrial	Mitochondrial	19	
MT-ATP8	Cardiomyopathy, apical hypertrophic, and neuropathy, Cardiomyopathy, infantile hypertrophic	Mitochondrial	4	

MT-CO1	Myoglobinuria, recurrent, Leber hereditary optic neuropathy, Sideroblastic anemia, Cytochrome C oxidase deficiency	Mitochondrial	17
MT-CO2	Cytochrome c oxidase deficiency	Mitochondrial	8
MT-CO3	Cytochrome c oxidase deficiency, Leber hereditary optic neuropathy	Mitochondrial	9
MT-CYB	Leber hereditary optic neuropathy	Mitochondrial	69
MT-ND1	Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes, Leber hereditary optic neuropathy, Leber optic atrophy and dystonia	Mitochondrial	21
MT-ND2	Leber hereditary optic neuropathy, Mitochondrial complex I deficiency	Mitochondrial	6
MT-ND3	Leber optic atrophy and dystonia, Mitochondrial complex I deficiency	Mitochondrial	7
MT-ND4	Leber hereditary optic neuropathy, Leber optic atrophy and dystonia, Mitochondrial complex I deficiency	Mitochondrial	11
MT-ND4L	Leber hereditary optic neuropathy	Mitochondrial	2
MT-ND5	Myoclonic epilepsy with ragged red fibers, Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes, Leber hereditary optic neuropathy, Mitochondrial complex I deficiency	Mitochondrial	19
MT-ND6	Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes, Oncocytoma, Leber hereditary optic neuropathy, Leber optic atrophy and dystonia, Mitochondrial complex I deficiency	Mitochondrial	16
MT-RNR1	Deafness, mitochondrial	Mitochondrial	3
MT-RNR2	Chloramphenicol toxicity/resistance	Mitochondrial	2
MT-TA	Leber hereditary optic neuropathy, Mitochondrial multisystemic disorder, Progressive external ophthalmoplegia, Dilated cardiomyopathy (DCM)	Mitochondrial	4
MT-TC	Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes	Mitochondrial	3
MT-TD	Mitochondrial multisystemic disorder	Mitochondrial	1
MT-TE	Diabetes-deafness syndrome, Mitochondrial myopathy, infantile, transient, Mitochondrial myopathy with diabetes	Mitochondrial	5
MT-TF	Myoclonic epilepsy with ragged red fibers, Nephropathy, tubulointerstitial, Encephalopathy, mitochondrial, Epilepsy, mitochondrial, Myopathy, mitochondrial, Mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes	Mitochondrial	7
MT-TG	Hypertrophic cardiomyopathy, Encephalopathy, Myopathy	Mitochondrial	3
MT-TH	Mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes	Mitochondrial	4
MT-TI	Progressive external ophthalmoplegia	Mitochondrial	7
MT-TK	Myoclonic epilepsy with ragged red fibers	Mitochondrial	5

MT-TL1	Cytochrome c oxidase deficiency, Myoclonic epilepsy with ragged red fibers, Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes, Diabetes-deafness syndrome, Cyclic vomiting syndrome, SIDS, susceptibility to	Mitochondrial	14	
MT-TL2	Progressive external ophthalmoplegia, Mitochondrial multisystemic disorder	Mitochondrial	5	
MT-TM	Mitochondrial Myopathy, Leigh syndrome, Mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes	Mitochondrial	1	
MT-TN	Progressive external ophthalmoplegia	Mitochondrial	3	
MT-TP	Mitochondrial multisystemic disorder	Mitochondrial	2	
MT-TQ	Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes, Encephalopathy	Mitochondrial	2	
MT-TR	Dilated cardiomyopathy (DCM)	Mitochondrial	2	
MT-TS1	Myoclonic epilepsy with ragged red fibers, Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes	Mitochondrial	10	
MT-TS2	Mitochondrial multisystemic disorder	Mitochondrial	2	
MT-TT		Mitochondrial	5	
MT-TV	Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes	Mitochondrial	3	
MT-TW	Leigh syndrome, Mitochondrial Myopathy	Mitochondrial	8	
MT-TY		Mitochondrial	4	
MTFMT	Combined oxidative phosphorylation deficiency 15	AR	15	16
MTHFR	Homocystinuria due to MTHFR deficiency	AR	65	122
NACC1	Neurodevelopmental disorder with epilepsy, cataracts, feeding difficulties, and delayed brain myelination (NECFM)	AD	2	3
NDUFAF6	Mitochondrial complex I deficiency, Leigh syndrome	AR	18	10
NDUFS2	Mitochondrial complex I deficiency	AR	5	24
NDUFS4	Mitochondrial complex I deficiency, Leigh syndrome	AR	11	17
NDUFS6	Mitochondrial complex I deficiency	AR	6	7
NDUFS7	Mitochondrial complex I deficiency, Leigh syndrome	AR	5	7
NDUFS8	Mitochondrial complex I deficiency, Leigh syndrome	AR	13	12
NDUFV1	Mitochondrial complex I deficiency	AR	19	35
NECAP1*	Epileptic encephalopathy, early infantile	AR	1	1
NEUROD2	Epileptic encephalopathy	AD		
NRXN1	Pitt-Hopkins like syndrome, Developmental delay with or without dysmorphic facies and autism	AD/AR	99	311

NUBPL	Mitochondrial complex I deficiency	AR	9	10
PARS2	Alpers syndrome	AR	3	6
PCDH19	Epileptic encephalopathy, early infantile	XL	116	200
PHACTR1	Epileptic encephalopathy	AD	4	2
PIGA*	Multiple congenital anomalies-hypotonia-seizures syndrome	XL	24	27
PIGB	Epileptic encephalopathy	AR		
PIGP	Epileptic encephalopathy, early infantile, 55	AR		2
PIGQ	Epileptic encephalopathy	AR	3	4
PIGS	Epileptic encephalopathy	AR		
PLAA	Neurodevelopmental disorder with progressive microcephaly, spasticity, and brain anomalies (NDMSBA)		3	3
PLCB1	Epileptic encephalopathy, early infantile	AR	8	10
PNKP	Epileptic encephalopathy, early infantile, Ataxia-oculomotor	AR	34	23
PNPO	Pyridoxamine 5'-phosphate oxidase deficiency	AR	15	31
POLG	POLG-related ataxia neuropathy spectrum disorders, Sensory ataxia, dysarthria, and ophthalmoparesis, Alpers syndrome, Progressive external ophthalmoplegia with mitochondrial DNA deletions, Mitochondrial DNA depletion syndrome	AD/AR	89	290
PPP3CA	Epilepitic encephalopathy	AD	8	11
PROSC	Epilepsy	AR	7	12
PTPN23	Epileptic encephalopathy	AR	1	4
PURA	Mental retardation	AD	74	47
RMND1*	Combined oxidative phosphorylation deficiency	AR	17	15
RNASEH2A	Aicardi-Goutières syndrome	AR	13	21
RNASEH2B	Aicardi-Goutières syndrome	AR	16	41
ROGDI	Kohlschutter-Tonz syndrome	AR	14	13
SAMHD1	Aicardi-Goutières syndrome, Chilblain lupus 2	AD/AR	25	56
SCN1A	Migraine, familial hemiplegic, Epileptic encephalopathy, early infantile, Generalized epilepsy with febrile seizures plus, Early infantile epileptic encephalopathy 6, Generalized epilepsy with febrile seizures plus, type 2 , Febrile seizures, familial 3A	AD	718	1585
SCN1B	Atrial fibrillation, Brugada syndrome, Generalized epilepsy with febrile seizures plus, Epilepsy, generalized, with febrile seizures plus, type 1, Epileptic encephalopathy, early infantile, 52	AD	16	31
SCN2A	Epileptic encephalopathy, early infantile, Seizures, benign familial infantile	AD	184	261

SCN3A	Epilepsy, Epileptic encephalopathy	AD	13	17
SCN8A	Cognitive impairment, Epileptic encephalopathy, early infantile	AD	91	93
SCO1	Mitochondrial complex IV deficiency	AR	6	5
SDHAF1	Mitochondrial complex II deficiency	AR	4	6
SERAC1	3-methylglutaconic aciduria with deafness, encephalopathy, and Leigh-like syndrome	AR	22	52
SIK1	Epileptic encephalopathy, early infantile	AD	5	6
SLC12A5	Epileptic encephalopathy, early infantile	AD/AR	6	14
SLC13A5	Epileptic encephalopathy, early infantile	AR	18	20
SLC19A3	Thiamine metabolism dysfunction syndrome	AR	32	37
SLC25A1	Combined D-2- and L-2-hydroxyglutaric aciduria	AR	8	24
SLC25A22	Epileptic encephalopathy, early infantile	AR	8	10
SLC2A1	Stomatin-deficient cryohydrocytosis with neurologic defects, Epilepsy, idiopathic generalized, GLUT1 deficiency syndrome	AD/AR	106	275
SLC35A2	Congenital disorder of glycosylation	XL	16	16
SLC6A8*	Creatine deficiency syndrome	XL	38	133
SLC9A6	Mental retardation, syndromic, Christianson	XL	24	28
SNAP25	Myasthenic syndrome, congenital	AD	2	4
SPTAN1	Epileptic encephalopathy, early infantile	AD	16	40
ST3GAL3	Epileptic encephalopathy, early infantile, Mental retardation	AR	3	5
ST3GAL5	Ganglioside GM3 synthase deficiency	AR	10	5
STXBP1	Epileptic encephalopathy, early infantile	AD	140	190
SYN1	Epilepsy, with variable learning disabilities and behavior disorders	XL	12	8
SYNGAP1	Mental retardation	AD	102	83
SYNJ1	Epileptic encephalopathy, early infantile, 53, Parkinson disease 20, early-onset	AR	12	25
SZT2	Epileptic encephalopathy, early infantile	AR	20	24
TBC1D24	Deafness, onychodystrophy, osteodystrophy, mental retardation, and seizures (DOORS) syndrome, Deafness, autosomal dominant, 65, Myoclonic epilepsy, infantile, familial, Epileptic encephalopathy, early infantile, 16, Deafness, autosomal recessive 86	AD/AR	43	55
TBCD	Early-onset progressive encephalopathy with brain atrophy and thin corpus callosum (PEBAT)	AR	17	21
TBCE	Progressive encephalopathy with amyotrophy and optic atrophy (PEAMO)	AR	12	8

TBCK	Hypotonia, infantile, with psychomotor retardation and characteristic facies 3	AR	14	16
TCF4	Corneal dystrophy, Fuchs endothelial, Pitt-Hopkins syndrome	AD	105	146
TRAK1	Epileptic encephalopathy	AR	1	6
TREX1	Vasculopathy, retinal, with cerebral leukodystrophy, Chilblain lupus, Aicardi-Goutières syndrome	AD/AR	30	71
TRIM8	Epileptic encephalopathy	AD	1	2
TSC1	Lymphangioleiomyomatosis, Tuberous sclerosis	AD	177	372
TSC2	Lymphangioleiomyomatosis, Tuberous sclerosis	AD	396	1195
TTC19	Mitochondrial complex III deficiency, nuclear type 2	AR	13	10
UBA5*	Epileptic encephalopathy, early infantile, 44, Spinocerebellar ataxia, autosomal recessive 24	AR	16	15
UBE3A*	Angelman syndrome	AD	176	202
UNC80	Hypotonia, infantile, with psychomotor retardation and characteristic facies 2	AR	26	20
VARS	Early-onset progressive encephalopathy with brain atrophy and thin corpus callosum (PEBAT), Encephalopathy, progressive	AR	12	6
WARS2	Encephalopathy, mitochondrial	AR	6	14
WDR45	Neurodegeneration with brain iron accumulation	XL	46	78
WWOX	Epileptic encephalopathy, early infantile, Spinocerebellar ataxia	AR	43	45
ZEB2*	Mowat-Wilson syndrome	AD	154	287

*Some regions of the gene are duplicated in the genome. Read more.

The gene has suboptimal coverage (means <90% of the gene's target nucleotides are covered at >20x with mapping quality score (MQ>20) reads), and/or the gene has exons listed under Test limitations section that are not included in the panel as they are not sufficiently covered with high quality sequence reads.

The sensitivity to detect variants may be limited in genes marked with an asterisk (*) or number sign (#)

Gene refers to the HGNC approved gene symbol; Inheritance refers to inheritance patterns such as autosomal dominant (AD), autosomal recessive (AR), mitochondrial (mi), X-linked (XL), X-linked dominant (XLD) and X-linked recessive (XLR); ClinVar refers to the number of variants in the gene classified as pathogenic or likely pathogenic in this database (ClinVar); HGMD refers to the number of variants with possible disease association in the gene listed in Human Gene Mutation Database (HGMD). The list of associated, gene specific phenotypes are generated from CGD or Mitomap databases.

Non-coding disease causing variants covered by the panel

Gene	Genomic location HG19	HGVS	RefSeq	RS-number
ADSL	Chr22:40742514	c.-49T>C	NM_000026.2	
AMT	Chr3:49459938	c.-55C>T	NM_000481.3	rs386833677

CACNA1A	Chr19:13317355	c.*1500_*1504dupCTTTT	NM_001127221.1	
CACNA1A	Chr19:13341036	c.5404-13G>A	NM_001127221.1	
CACNA1A	Chr19:13617793		NM_001127221.1	rs965852937
CDKL5	ChrX:18525053	c.-162-2A>G	NM_003159.2	rs786204973
D2HGDH	Chr2:242680425	c.293-23A>G	NM_152783.3	
ETHE1	Chr19:44031407		NM_014297.3	
FGF12	Chr3:191857076	c.*4722T>C	NM_021032.4	
FLNA	ChrX:153581587	c.6023-27_6023-16delTGACTGACAGCC	NM_001110556.1	
GABRA1	Chr5:161274418	c.-248+1G>T	NM_000806.5	
GABRB3	Chr15:27018162	c.-53G>T	NM_000814.5	
GABRB3	Chr15:27019011	c.-902A>T	NM_000814.5	
GABRB3	Chr15:27020313	c.-2204G>A	NM_000814.5	
GABRB3	Chr15:27020399	c.-2290T>C	NM_000814.5	rs546389769
GAMT	Chr19:1399508	c.391+15G>T	NM_138924.2	rs367567416
MEF2C	Chr5:88179125	c.-510_-497delTCTTCCTCCTCCTC	NM_002397.4	
MOCS1	Chr6:39874534	c.*365_*366delAG	NM_005943.5	rs397518419
MOCS1	Chr6:39876810	c.*7+6T>C	NM_005943.5	
MOCS1	Chr6:39894006	c.251-418delT	NM_005943.5	
MTHFR	Chr1:11850973	c.1753-18G>A	NM_005957.4	rs777661576
MTHFR	Chr1:11863212	c.-13-28_-13-27delCT	NM_005957.4	rs786204005
NDUFAF6	Chr8:96046914	c.298-768T>C	NM_152416.3	rs575462405
NDUFAF6	Chr8:96048588	c.420+784C>T	NM_152416.3	rs749738738
PNKP	Chr19:50364799	c.1387-33_1386+49delCCTCCTCCCCTGACCCC	NM_007254.3	rs752902474
RNASEH2B	Chr13:51501530	c.65-13G>A	NM_024570.3	
RNASEH2B	Chr13:51519550	c.511-13G>A	NM_024570.3	
ROGDI	Chr16:4852483	c.46-30_45+37delGGCGGGGC	NM_024589.2	rs786205125
SCN1A	Chr2:166848946	c.4820-14T>G	NM_006920.4	
SCN1A	Chr2:166854699	c.4306-14T>G	NM_006920.4	
SCN1A	Chr2:166908215	c.964+14T>G	NM_006920.4	rs794726837
SCN1A	Chr2:166911289	c.474-13T>A	NM_006920.4	rs1057520357
SERAC1	Chr6:158576548	c.92-165C>T	NM_032861.3	

SERAC1	Chr6:158576622	c.92-239G>C	NM_032861.3	
SLC19A3	Chr2:228560811	c.980-14A>G	NM_025243.3	rs200542114
SLC2A1	Chr1:43395462	c.680-11G>A	NM_006516.2	
SLC2A1	Chr1:43424429	c.-107G>A	NM_006516.2	
SPTAN1	Chr9:131390187	c.6690-17G>A	NM_001130438.2	rs796053325
TBCD	Chr17:80851411	c.1564-12C>G	NM_005993.4	
TSC1	Chr9:135800306	c.363+668G>A	NM_000368.4	
TSC2	Chr16:2098067	c.-30+1G>C	NM_000548.3	rs587778004
TSC2	Chr16:2106052	c.600-145C>T	NM_000548.3	
TSC2	Chr16:2107460	c.848+281C>T	NM_000548.3	rs45517132
TSC2	Chr16:2110656	c.976-15G>A	NM_000548.3	rs45517150
TSC2	Chr16:2127477	c.2838-122G>A	NM_000548.3	
TSC2	Chr16:2138031	c.5069-18A>G	NM_000548.3	rs45484794
TTC19	Chr17:15903121	c.-42G>T	NM_017775.3	rs769078093
WDR45	ChrX:48934430	c.236-18A>G	NM_007075.3	
ZEB2	Chr2:145274987	c.-69-1G>A	NM_014795.3	
ZEB2	Chr2:145274988	c.-69-2A>C	NM_014795.3	

Test Strengths

The strengths of this test include:

- CAP accredited laboratory
- CLIA-certified personnel performing clinical testing in a CLIA-certified laboratory
- Powerful sequencing technologies, advanced target enrichment methods and precision bioinformatics pipelines ensure superior analytical performance
- Careful construction of clinically effective and scientifically justified gene panels
- Some of the panels include the whole mitochondrial genome (please see the Panel Content section)
- Our Nucleus online portal providing transparent and easy access to quality and performance data at the patient level
- Our publicly available analytic validation demonstrating complete details of test performance
- ~2,000 non-coding disease causing variants in our clinical grade NGS assay for panels (please see 'Non-coding disease causing variants covered by this panel' in the Panel Content section)
- Our rigorous variant classification scheme
- Our systematic clinical interpretation workflow using proprietary software enabling accurate and traceable processing of NGS data
- Our comprehensive clinical statements

Test Limitations

The following exons are not included in the panel as they are not sufficiently covered with high quality sequence reads:

GABRG2 (NM_198903:6). Genes with suboptimal coverage in our assay are marked with number sign (#) and genes with partial, or whole gene, segmental duplications in the human genome are marked with an asterisk (*) if they overlap with the UCSC pseudogene regions. Gene is considered to have suboptimal coverage when >90% of the gene's target nucleotides are not covered at >20x with mapping quality score (MQ>20) reads. The technology may have limited sensitivity to detect variants in genes marked with these symbols (please see the Panel content table above).

This test does not detect the following:

- Complex inversions
- Gene conversions
- Balanced translocations
- Some of the panels include the whole mitochondrial genome but not all (please see the Panel Content section)
- Repeat expansion disorders unless specifically mentioned
- Non-coding variants deeper than ±20 base pairs from exon-intron boundary unless otherwise indicated (please see above Panel Content / non-coding variants covered by the panel).

This test may not reliably detect the following:

- Low level mosaicism in nuclear genes (variant with a minor allele fraction of 14.6% is detected with 90% probability)
- Stretches of mononucleotide repeats
- Low level heteroplasmy in mtDNA (>90% are detected at 5% level)
- Indels larger than 50bp
- Single exon deletions or duplications
- Variants within pseudogene regions/duplicated segments
- Some disease causing variants present in mtDNA are not detectable from blood, thus post-mitotic tissue such as skeletal muscle may be required for establishing molecular diagnosis.

The sensitivity of this test may be reduced if DNA is extracted by a laboratory other than Blueprint Genetics.

For additional information, please refer to the Test performance section and see our Analytic Validation.

Test performance

The Blueprint Genetics epileptic encephalopathy panel covers classical genes associated with epileptic encephalopathy. The genes on the panel have been carefully selected based on scientific literature, mutation databases and our experience.

Our panels are sliced from our high-quality whole exome sequencing data. Please see our sequencing and detection performance table for different types of alterations at the whole exome level (Table).

Assays have been validated for different starting materials including EDTA-blood, isolated DNA (no FFPE), saliva and dry blood spots (filter card) and all provide high-quality results. The diagnostic yield varies substantially depending on the assay used, referring healthcare professional, hospital and country. Blueprint Genetics' Plus Analysis (Seq+Del/Dup) maximizes the chance to find a molecular genetic diagnosis for your patient although Sequence Analysis or Del/Dup Analysis may be a cost-effective first line test if your patient's phenotype is suggestive of a specific mutation type.

The genes on the panel have been carefully selected based on scientific literature, mutation databases and our experience.

Our panels are sectioned from our high-quality, clinical grade NGS assay. Please see our sequencing and detection performance table for details regarding our ability to detect different types of alterations (Table).

	Sensitivity % (TP/(TP+FN)	Specificity %
Single nucleotide variants	99.89% (99,153/99,266)	>99.9999%
Insertions, deletions and indels by sequence analysis		
1-10 bps	96.9% (7,563/7,806)	>99.9999%

11-50 bps	99.13% (2,524/2,546)	>99.9999%
Copy number variants (exon level dels/dups)		
1 exon level deletion (heterozygous)	100% (20/20)	NA
1 exon level deletion (homozygous)	100% (5/5)	NA
1 exon level deletion (het or homo)	100% (25/25)	NA
2-7 exon level deletion (het or homo)	100% (44/44)	NA
1-9 exon level duplication (het or homo)	75% (6/8)	NA
Simulated CNV detection		
5 exons level deletion/duplication	98.7%	100.00%
Microdeletion/-duplication sdrs (large CNVs, n=37))		
Size range (0.1-47 Mb)	100% (37/37)	

The performance presented above reached by Blueprint Genetics high-quality, clinical grade NGS sequencing assay with the following coverage metrics

Mean sequencing depth	143X
Nucleotides with >20x sequencing coverage (%)	99.86%

Performance of Blueprint Genetics Mitochondrial Sequencing Assay.

	Sensitivity %	**Specificity %**
ANALYTIC VALIDATION (NA samples; n=4)		
Single nucleotide variants		
Heteroplasmic (45-100%)	100.0% (50/50)	100.0%
Heteroplasmic (35-45%)	100.0% (87/87)	100.0%
Heteroplasmic (25-35%)	100.0% (73/73)	100.0%
Heteroplasmic (15-25%)	100.0% (77/77)	100.0%
Heteroplasmic (10-15%)	100.0% (74/74)	100.0%
Heteroplasmic (5-10%)	100.0% (3/3)	100.0%
Heteroplasmic (<5%)	50.0% (2/4)	100.0%
CLINICAL VALIDATION (n=76 samples)		
All types		
Single nucleotide variants n=2026 SNVs		

Heteroplasmic (45-100%)	100.0% (1940/1940)	100.0%
Heteroplasmic (35-45%)	100.0% (4/4)	100.0%
Heteroplasmic (25-35%)	100.0% (3/3)	100.0%
Heteroplasmic (15-25%)	100.0% (3/3)	100.0%
Heteroplasmic (10-15%)	100.0% (9/9)	100.0%
Heteroplasmic (5-10%)	92.3% (12/13)	99.98%
Heteroplasmic (<5%)	88.9% (48/54)	99.93%
Insertions and deletions by sequence analysis n=40 indels		
Heteroplasmic (45-100%) 1-10bp	100.0% (32/32)	100.0%
Heteroplasmic (5-45%) 1-10bp	100.0% (3/3)	100.0%
Heteroplasmic (<5%) 1-10bp	100.0% (5/5)	99,997%
SIMULATION DATA /(mitomap mutations)		
Insertions, and deletions 1-24 bps by sequence analysis; n=17		
Homoplasmic (100%) 1-24bp	100.0% (17/17)	99.98%
Heteroplasmic (50%)	100.0% (17/17)	99.99%
Heteroplasmic (25%)	100.0% (17/17)	100.0%
Heteroplasmic (20%)	100.0% (17/17)	100.0%
Heteroplasmic (15%)	100.0% (17/17)	100.0%
Heteroplasmic (10%)	94.1% (16/17)	100.0%
Heteroplasmic (5%)	94.1% (16/17)	100.0%
Copy number variants (separate artifical mutations; n=1500)		
Homoplasmic (100%) 500 bp, 1kb, 5 kb	100.0%	100.0%
Heteroplasmic (50%) 500 bp, 1kb, 5 kb	100.0%	100.0%
Heteroplasmic (30%) 500 bp, 1kb, 5 kb	100.0%	100.0%
Heteroplasmic (20%) 500 bp, 1kb, 5 kb	99.7%	100.0%
Heteroplasmic (10%) 500 bp, 1kb, 5 kb	99.0%	100.0%
The performance presented above reached by following coverage metrics at assay level (n=66)		
	Mean of medians	Median of medians
Mean sequencing depth MQ0 (clinical)	18224X	17366X
Nucleotides with >1000x MQ0 sequencing coverage (%) (clinical)	100%	

rho zero cell line (=no mtDNA), mean sequencing depth	12X

Bioinformatics

The target region for each gene includes coding exons and ±20 base pairs from the exon-intron boundary. In addition, the panel includes non-coding variants if listed above (Non-coding variants covered by the panel). Some regions of the gene(s) may be removed from the panel if specifically mentioned in the 'Test limitations" section above. The sequencing data generated in our laboratory is analyzed with our proprietary data analysis and annotation pipeline, integrating state-of-the art algorithms and industry-standard software solutions. Incorporation of rigorous quality control steps throughout the workflow of the pipeline ensures the consistency, validity and accuracy of results. Our pipeline is streamlined to maximize sensitivity without sacrificing specificity. We have incorporated a number of reference population databases and mutation databases such as, but not limited, to 1000 Genomes Project, gnomAD, ClinVar and HGMD into our clinical interpretation software to make the process effective and efficient. For missense variants, *in silico* variant prediction tools such as SIFT, PolyPhen, MutationTaster are used to assist with variant classification. Through our online ordering and statement reporting system, Nucleus, the customer has an access to details of the analysis, including patient specific sequencing metrics, a gene level coverage plot and a list of regions with inadequate coverage if present. This reflects our mission to build fully transparent diagnostics where customers have easy access to crucial details of the analysis process.

Clinical interpretation

We provide customers with the most comprehensive clinical report available on the market. Clinical interpretation requires a fundamental understanding of clinical genetics and genetic principles. At Blueprint Genetics, our PhD molecular geneticists, medical geneticists and clinical consultants prepare the clinical statement together by evaluating the identified variants in the context of the phenotypic information provided in the requisition form. Our goal is to provide clinically meaningful statements that are understandable for all medical professionals regardless of whether they have formal training in genetics.

Variant classification is the corner stone of clinical interpretation and resulting patient management decisions. Our classifications follow the Blueprint Genetics Variant Classification Schemes based on the ACMG guideline 2015. Minor modifications were made to increase reproducibility of the variant classification and improve the clinical validity of the report. Our experience with tens of thousands of clinical cases analyzed at our laboratory allowed us to further develop the industry standard.

The final step in the analysis of sequence variants is confirmation of variants classified as pathogenic or likely pathogenic using bi-directional Sanger sequencing. Variant(s) fulfilling the following criteria are not Sanger confirmed: the variant quality score is above the internal threshold for a true positive call, and visual check-up of the variant at IGV is in-line with the variant call. Reported variants of uncertain significance are confirmed with bi-directional Sanger sequencing only if the quality score is below our internally defined quality score for true positive call. Reported copy number variations with a size <10 exons are confirmed by orthogonal methods such as qPCR if the specific CNV has been seen less than three times at Blueprint Genetics.

Our clinical statement includes tables for sequencing and copy number variants that include basic variant information (genomic coordinates, HGVS nomenclature, zygosity, allele frequencies, in silico predictions, OMIM phenotypes and classification of the variant). In addition, the statement includes detailed descriptions of the variant, gene and phenotype(s) including the role of the specific gene in human disease, the mutation profile, information about the gene's variation in population cohorts and detailed information about related phenotypes. We also provide links to the references used, congress abstracts and mutation variant databases used to help our customers further evaluate the reported findings if desired. The conclusion summarizes all of the existing information and provides our rationale for the classification of the variant.

Identification of pathogenic or likely pathogenic variants in dominant disorders or their combinations in different alleles in recessive disorders are considered molecular confirmation of the clinical diagnosis. In these cases, family member testing can be used for risk stratification within the family. In the case of variants of uncertain significance (VUS), we do not recommend family member risk stratification based on the VUS result. Furthermore, in the case of VUS, we do not recommend the use of genetic information in patient management or genetic counseling.

Our interpretation team analyzes millions of variants from thousands of individuals with rare diseases. Thus, our database, and our understanding of variants and related phenotypes, is growing by leaps and bounds. Our laboratory is therefore well positioned to re-classify previously reported variants as new information becomes available. If a variant previously reported by

Blueprint Genetics is re-classified, our laboratory will issue a follow-up statement to the original ordering health care provider at no additional cost.

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ICD codes

Commonly used ICD-10 codes when ordering the Epileptic Encephalopathy Panel

ICD-10	Disease
F84.2	Rett syndrome
H49.40	Progressive external ophthalmoplegia
G11.9	Hereditary ataxia
C94.2	Acute Megakaryoblastic Leukemia
K59.8	Chronic Intestinal Pseudoobstruction
T36.5	Adverse effect of aminoglycosides
G93.41	Metabolic Encephalopathy
H49.81	Kearns Sayre Syndrome
E88.42	MERFF Syndrome
H47.013	Nonarteritic Anterior Ischemic Optic Neuropathy
G60.2	Neuropathy in association with hereditary ataxia
G30	Alzheimer's Disease
G25.5	Chorea
G40	Epilepsy and recurrent seizures
I42	Cardiomyopathy
N26.9	Focal Segmental Glomerulosclerosis
G31.82	Leigh's Disease
H47.2	Leber's hereditary optic neuropathy
G71.3	Mitochondrial Myopathy
I42.1	Hypertrophic Cardiomyopathy
E11.9	Non-Insulin Dependent Diabetes Mellitus
Z86.74	Personal history of sudden cardiac arrest
H90.3	Sensorineural Hearing Loss

Accepted sample types

- EDTA blood, min. 1 ml
- Purified DNA, min. 3µg*
- Saliva (Oragene DNA OG-500 kit)

Label the sample tube with your patient's name, date of birth and the date of sample collection.

Note that we do not accept DNA samples isolated from formalin-fixed paraffin-embedded (FFPE) tissue.

Resources

- Dravet Syndrome Foundation
- Epilepsy Foundation
- GeneReviews - *MECP2*-Related Disorders
- GeneReviews - *SCN1A*-Related Seizure Disorders
- GeneReviews - *SCN8A*-Related Epilepsy with Encephalopathy
- GeneReviews - *STXBP1* Encephalopathy with Epilepsy
- GeneReviews - SCN1A-Related Seizure Disorders
- Intractable Childhood Epilepsy Alliance
- Kirkpatrick M et al. Guidelines and Quality Standards in the Care of Children with Epilepsy. Neurol Clin. 2016 May;34(2):327-37.
- NORD - Dravet Syndrome Spectrum
- NORD - Landau-Kleffner Syndrome
- NORD - Lennox-Gastaut Syndrome
- NORD - West Syndrome