Blueprint Genetics

Comprehensive Epilepsy Panel

Test code: NE1001

Is ideal for patients with epilepsy. For patients aged 24-60 months living in Europe or the Middle East, please see the Paediatric Epilepsy? Look Beyond no cost program.

The panel covers generalized and focal genetic epilepsies, epileptic encephalopathies, progressive myoclonic epilepsies and epilepsies associated with X-linked mental retardation. Also other syndromes that include epileptic seizures as one of the main manifestation are included as well as hereditary metabolic diseases that manifest as epilepsy. We recommend the panel also to patients with sudden unexplained death. New genomic technologies have led to advances in understanding of the different genomic and genetic architectures across all the major classes of epilepsy, including uncovering a surprising overlap among seemingly different disorders (PMID: 26302787). There is an increasingly wide phenotypic spectrum associated with mutations in several eplepsy genes such as *GABRA1*, *KCNQ2*, *KCNT1*, *SCN8A*, *TBC1D24*, and *DEPDC5*. Thus using a comprehensive epilepsy panel is justifyed. Few studies have applied next generation sequencing technologies to analyze gene panels in unselected epilepsy patient cohorts (PMID: 22612257, 24848745). The reported total diagnostic yield has been 47-48% but the diagnostic yield per gene cannot be estimated from these studies due to small patient cohorts and variable number of genes tested (67 to 265). Recently, it was shown that 25% of sudden unexpected death in epilepsy (SUDEP) patients have mutations in epilepsy genes (PMID: 26704558). This Comprehensive Epilepsy Panel covers the following smaller panels: Idiopathic Generalized and Focal Epilepsy Panel, Epileptic Encephalopathy Panel, NCL and Progressive Myoclonic Epilepsy Panel, Leukodystrophy and Leukoencephalopathy Panel, Epilepsy and X-linked Mental Retardation Panel and Metabolic Epilepsy Panel.

About Epilepsy

Epilepsy is defined by recurrent, unprovoked seizures due to abnormal, synchronized neuronal firing in the brain. It is one of the most common neurological conditions. Approximately 20-30 % of epilepsy cases are caused by acquired conditions, but the remaining 70-80 % of cases are believed to be due to one or more genetic factors. The epilepsies can be broadly grouped into three classes: genetic generalized epilepsy (formerly idiopathic generalized epilepsy); focal epilepsy; and epileptic encephalopathy. There are then several specific syndromes within each class defined by differences in specific seizure types, electroencephalogram (EEG) patterns, magnetic resonance imaging (MRI) findings and age of onset and disease progression. Epilepsy is also one of the features of many multisystemic genetic syndromes and often occurs in neurodegenerative diseases.

Availability

Results in 3-4 weeks

Gene set description

Genes in the Comprehensive Epilepsy Panel and their clinical significance

Gene	Associated phenotypes	Inheritance	ClinVar	HGMD
ABAT	GABA-transaminase deficiency	AR	11	12
ABCA2	Intellectual disability and seizures	AR		4
ABCD1*	Adrenoleukodystrophy	XL	95	663
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
AFG3L2*	Spastic ataxia, Spinocerebellar ataxia	AD/AR	22	40
AGA	Aspartylglucosaminuria	AR	48	37
AIFM1	Deafness, Combined oxidative phosphorylation deficiency 6, Cowchock syndrome	XL	27	31
AIMP1	Leukodystrophy, hypomyelinating	AR	4	5
ALDH3A2	Sjogren-Larsson syndrome	AR	74	111
ALDH5A1	Succinic semialdehyde dehydrogenase deficiency	AR	16	70
ALDH7A1	Epilepsy, pyridoxine-dependent	AR	52	123
ALG13	Congenital disorder of glycosylation	XL	5	12
ALKBH8	Intellectual disability	AR		
AMACR	Alpha-methylacyl-CoA racemase deficiency, Bile acid synthesis defect	AR	3	8
AMT	Glycine encephalopathy	AR	42	95
ANKRD11*	KBG syndrome	AD	142	132
AP2M1	Epilepitic encephalopathy	AD		
AP3B2	Epileptic encephalopathy, early infantile, 48		6	12
AP4B1	Spastic paraplegia 47, autosomal recessive	AR	17	18
AP4E1	Stuttering, familial persistent, 1, Spastic paraplegia 51, autosomal recessive	AR	7	15
AP4M1	Spastic paraplegia 50, autosomal recessive	AR	16	13
AP4S1*	Spastic paraplegia 52, autosomal recessive	AR	9	8
APOPT1	Mitochondrial complex IV deficiency	AR	4	5
ARG1	Hyperargininemia	AR	28	54
ARHGEF9	Epileptic encephalopathy, early infantile	XL	10	23
ARID1B	Coffin-Siris syndrome, Mental retardation	AD	153	185
ARSA	Metachromatic leukodystrophy	AR	113	246
ARX	Lissencephaly, Epileptic encephalopathy, Corpus callosum, agenesis of, with abnormal genitalia, Partington syndrome, Proud syndrome, Hydranencephaly with abnormal genitalia, Mental retardation	XL	66	93
ASAH1	Spinal muscular atrophy with progressive myoclonic epilepsy, Farber lipogranulomatosis	AR	16	71
ASNS*	Asparagine synthetase deficiency	AR	21	26

ASPA	Aspartoacylase deficiency (Canavan disease)	AR	54	102
ASXL3	Bainbridge-Ropers syndrome	AD	45	49
ATP13A2	Parkinson disease (Kufor-Rakeb syndrome)	AR	21	40
ATP1A3	Alternating hemiplegia of childhood, Dystonia 12	AD	79	112
ATP6V1A	Cutis laxa, autosomal recessive, type IID, Epileptic encephalopathy	AD/AR	8	8
ATRX	Carpenter-Waziri syndrome, Alpha-thalassemia/mental retardation syndrome, Holmes-Gang syndrome, Juberg-Marsidi syndrome, Smith-Fineman-Myers syndrome, Mental retardation-hypotonic facies syndrome	XL	65	165
BRAT1	Rigidity and multifocal seizure syndrome, lethal neonatal	AR	19	18
BTD	Biotinidase deficiency	AR	170	247
C12ORF57	Corpus callosum hypoplasia, recessive, Temtamy syndrome	AR	7	6
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
CACNA1D	Primary aldosteronism, seizures, and neurologic abnormalities, Sinoatrial node dysfunction and deafness	AD/AR	7	8
CACNA1E	Epileptic encephalopathy	AD	8	6
CACNA1H	Childhood absence epilepsy	AD	9	55
CACNB4	Episodic ataxia, Epilepsy, idiopathic generalized, susceptibility to, 9	AD	2	7
CASK	Mental retardation and microcephaly with pontine and cerebellar hypoplasia, FG syndrome, Mental retardation	XL	87	112
CASR	Hypocalcemia, Neonatal hyperparathyroidism, Familial Hypocalciuric hypercalcemia with transient Neonatal hyperparathyroidism	AD/AR	104	396
CC2D1A	Mental retardation, autosomal recessive 3	AR	3	7
CDK9		AR		1
CDKL5	Epileptic encephalopathy, early infantile, Rett syndrome, atypical, Angelman-like syndrome	XL	312	331
CERS1	Epilepsy, progressive myoclonic	AR	11	1
CHD2	Epileptic encephalopathy, childhood-onset	AD	85	59
CHRNA2	Epilepsy, nocturnal frontal lobe	AD	3	7
CHRNA4	Epilepsy, nocturnal frontal lobe	AD	8	18
CHRNB2	Epilepsy, nocturnal frontal lobe	AD	9	13
CLCN2	Leukoencephalopathy with ataxia, Epilepsy	AD/AR	30	36
CLCN4	Mental retardation, X-linked 49	XL	21	17

CLN3	Neuronal ceroid lipofuscinosis, type 3	AR	100	72
CLN5	Neuronal ceroid lipofuscinosis, type 5	AR	62	47
CLN6	Neuronal ceroid lipofuscinosis, type 6	AR	41	83
CLN8	Neuronal ceroid lipofuscinosis, type 8	AR	45	44
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
COA7	Spinocerebellar ataxia, Charcot-Marie-Tooth disease	AR	2	7
COL4A1	Schizencephaly, Anterior segment dysgenesis with cerebral involvement, Retinal artery tortuosity, Porencephaly, Angiopathy, hereditary, with nephropathy, aneurysms, and muscle cramps, Brain small vessel disease	AD	58	107
COL4A3BP	Mental retardation, autosomal dominant 34	AD	6	7
COX15	Leigh syndrome, Cardioencephalomyopathy, fatal infantile, due to cytochrome c oxidase deficiency	AR	7	5
COX6B1	Mitochondrial complex IV deficiency	AR	2	3
CPT2	Carnitine palmitoyltransferase II deficiency	AR	72	111
CSF1R	Leukoencephalopathy, diffuse hereditary, with spheroids	AD	56	83
CSNK2B	Intellectual disability and seizures	AD	7	5
CSTB	Epilepsy, progressive myoclonic	AR	19	15
CTC1	Cerebroretinal microangiopathy with calcifications and cysts	AR	21	33
CTSD	Ceroid lipofuscinosis, neuronal	AR	12	18
CTSF	Neuronal ceroid lipofuscinosis	AR	8	11
CUL4B	Mental retardation, syndromic, Cabezas	XL	23	38
CYFIP2	Early infantile epileptic encephalopathy, Epilepsy	AD	2	3
CYP27A1	Cerebrotendinous xanthomatosis	AR	69	110
D2HGDH	D-2-hydroxyglutaric aciduria 1	AR	13	33
DARS	Hypomyelination with brainstem and spinal cord involvement and leg spasticity	AR	11	17
DARS2	Leukoencephalopathy with brain stem and spinal cord involvement and lactate elevation	AR	27	61
DCX	Lissencephaly, Subcortical laminal heterotopia	XL	131	142
DDC	Aromatic l-amino acid decarboxylase deficiency	AR	14	51

DDX3X	Mental retardation, X-linked 102	XL	84	51
DEGS1	Leukodystrophy, hypomyelinating	AR		
DENND5A	Epileptic encephalopathy, early infantile, 49	AR	6	6
DEPDC5	Epilepsy, familial focal, with variable foci	AD	87	78
DHFR*	Megaloblastic anemia due to dihydrofolate reductase deficiency	AR	2	5
DHPS		AR		
DNAJC5	Kufs disease,, Ceroid lipofuscinosis, neuronal 4, Parry	AD	2	2
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
DPYD	5-fluorouracil toxicity, Schizophrenia	AD/AR	62	86
DPYS	Dihydropyriminidase deficiency	AR	8	29
DYRK1A	Mental retardation	AD	94	77
EARS2	Combined oxidative phosphorylation deficiency	AR	14	30
ECHS1	Mitochondrial short-chain enoyl-CoA hydratase 1 deficiency	AR	23	33
ECM1	Lipoid proteinosis	AR	13	61
EEF1A2	Epileptic encephalopathy, early infantile, Mental retardation	AD	17	12
EFHC1	Epilepsy, myoclonic juvenile, Epilepsy, severe intractable, Epilepsy, juvenile absence	AD/AR	5	38
EIF2B1	Leukoencephalopathy with vanishing white matter, Ovarioleukodystrophy	AR	7	9
EIF2B2	Leukoencephalopathy with vanishing white matter, Ovarioleukodystrophy	AR	12	28
EIF2B3	Leukoencephalopathy with vanishing white matter, Ovarioleukodystrophy	AR	6	22
EIF2B4	Leukoencephalopathy with vanishing white matter, Ovarioleukodystrophy	AR	8	30
EIF2B5	Leukoencephalopathy with vanishing white matter, Ovarioleukodystrophy	AR	20	98
EIF3F	Intellectual disability	AR		
EPM2A	Epilepsy, progressive myoclonic	AR	17	77
EPRS	Leukodystrophy, hypomyelinating	AR	6	6
ETFA	Glutaric aciduria, Multiple acyl-CoA dehydrogenase deficiency	AR	8	29
ETFB	Glutaric aciduria, Multiple acyl-CoA dehydrogenase deficiency	AR	6	15
ETFDH	Glutaric aciduria, Multiple acyl-CoA dehydrogenase deficiency	AR	43	190
ETHE1	Ethylmalonic encephalopathy	AR	38	36

FA2H	Spastic paraplegia	AR	18	51
FAM126A	Leukodystrophy, hypomyelinating	AR	8	12
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
FDFT1	Growth retardation, developmental delay, and facial dysmorphism		3	5
FDX1L	Myopathy	AR	1	2
FGF12	Epileptic encephalopathy, early infantile, 47	AD	6	10
FH	Hereditary leiomyomatosis and renal cell cancer	AD/AR	178	207
FLNA	Frontometaphyseal dysplasia, Osteodysplasty Melnick-Needles, Otopalatodigital syndrome type 1, Otopalatodigital syndrome type 2, Terminal osseous dysplasia with pigmentary defects	XL	133	257
FOLR1	Cerebral folate deficiency	AR	10	28
FOXG1	Rett syndrome, congenital variant	AD	106	156
FOXRED1	Leigh syndrome, Mitochondrial complex I deficiency	AR	15	8
FRRS1L	Epileptic encephalopathy, early infantile, 37	AR	9	6
FUT8	Congenital disorder of glycosylation	AR	4	4
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
GALC	Krabbe disease	AR	107	243
GAMT	Guanidinoacetate methyltransferase deficiency	AR	18	58
GCDH	Glutaric aciduria	AR	90	241
GCH1	Dopa-Responsive Dystonia Hyperphenylalaninemia, BH4-deficient, GTP Cyclohydrolase 1-Deficient Dopa-Responsive Dystonia	AD/AR	48	240
GFAP	Alexander disease	AD	114	131
GFM1	Combined oxidative phosphorylation deficiency	AR	19	19
GFM2	Combined oxidative phosphorylation deficiency	AR	5	6
GJC2	Spastic paraplegia, Lymphedema, hereditary, Leukodystrophy, hypomyelinating	AD/AR	26	57

GLB1	GM1-gangliosidosis, Mucopolysaccharidosis (Morquio syndrome)	AR	90	220
GLDC	Glycine encephalopathy	AR	139	425
GLRB	Hyperekplexia 2	AR	6	18
GNAO1	Epileptic encephalopathy, early infantile, Epileptic encephalopathy, early infantile, 17	AD	26	35
GNB1	Mental retardation, autosomal dominant 42	AD	15	24
GNE	Inclusion body myopathy, Nonaka myopathy, Sialuria	AD/AR	78	214
GOLGA2	Microcephaly, seizures, and developmental delay	AR		2
GOSR2*	Epilepsy, progessive myoclonic	AR	6	4
GPAA1	Cerebellar atrophy, developmental delay, and seizures (CADEDS)	AR	7	9
GPHN	Hyperekplexia, Molybdenum cofactor deficiency	AD/AR	35	20
GRIA3	Mental retardation	XL	12	23
GRIA4	Intellectual disability and seizures		5	5
GRIK2	Mental retardation, autosomal recessive 6	AR	2	7
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
GRN	Frontotemporal lobar degeneration with TDP43 inclusions, GRN-related, Neuronal ceroid lipofuscinosis	AD/AR	43	214
GTPBP3	Combined oxidative phosphorylation deficiency 23	AR	14	15
HACE1	Spastic paraplegia and psychomotor retardation with or without seizures	AR	13	13
HCN1	Epileptic encephalopathy, early infantile	AD	13	14
HCN2	Epilepsy	AD/AR	1	8
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
HSD17B10	17-beta-hydroxysteroid dehydrogenase X deficiency, Mental retardation, syndromic	XL	10	15
HSPD1*	Spastic paraplegia, Leukodystrophy, hypomyelinating	AD/AR	5	5
HTRA1	Cerebral arteriopathy with subcortical infarcts and leukoencephalopathy type 2 (CADASIL2), Cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL)	AD/AR	25	46

HTT	Huntington disease, Lopes-Maciel-Rodan syndrome (LOMARS)	AD/AR	8	7
IBA57	Multiple mitochondrial dysfunctions syndrome 3, Spastic paraplegia 74, autosomal recessive	AR	14	23
ICK	Endocrine-cerebroosteodysplasia, Epilepsy, juvenile myoclonic	AD/AR	1	3
IQSEC2	Mental retardation	XL	55	56
IRF2BPL	Neurodevelopmental disorder with hypotonia, seizures, and absent language	AD	9	2
KCNA1	Episodic ataxia/myokymia syndrome	AD	24	45
KCNA2	Epileptic encephalopathy, early infantile	AD	15	21
KCNB1	Early infantile epileptic encephalopathy	AD	27	30
KCNC1	Epilepsy, progressive myoclonic	AD	5	3
KCNH1	Temple-Baraitser syndrome, Zimmermann-Laband syndrome 1	AD/AR	16	13
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
KCTD7*	Epilepsy, progressive myoclonic	AR	18	20
KDM5C	Mental retardation, syndromic, Claes-Jensen	XL	47	55
KIAA2022	Mental retardation	XL	42	40
KIF1A	Spastic paraplegia, Neuropathy, hereditary sensory, Mental retardation	AD/AR	63	42
KMT2E				4
L2HGDH	L-2-hydroxyglutaric aciduria	AR	15	79
LGI1	Epilepsy, familial temporal lobe	AD	28	54
LMNB1	Leukodystrophy, demyelinating, adult-onset, autosomal dominant	AD	2	35
LRPPRC	Leigh syndrome, French-Canadian type	AR	55	17
LYRM7#	Mitochondrial complex III deficiency, nuclear type 8	AR	5	9
MACF1	Lissencephaly	AD	1	9

MAGI2	Nephrotic syndrome 15	AR	7	27
MARS2	Combined oxidative phosphorylation deficiency	AR	8	5
MBD5	Mental retardation	AD	62	90
MBOAT7	Mental retardation, autosomal recessive 57	AR	5	5
MDH2	Epileptic encephalopathy, early infantile, 51	AR	5	9
MECP2	Angelman-like syndrome, Autism, Rett syndrome, Encephalopathy, Mental retardation	XL	506	1039
MED12	Ohdo syndrome, Mental retardation, with Marfanoid habitus, FG syndrome, Opitz-Kaveggia syndrome, Lujan-Fryns syndrome	XL	29	30
MED17	Microcephaly, postnatal progressive, with seizures and brain atrophy	AR	4	4
MEF2C	Mental retardation	AD	45	84
MFSD8	Ceroid lipofuscinosis, neuronal	AR	27	47
MIPEP	Combined oxidative phosphorylation deficiency 31	AR	5	8
MLC1	Megalencephalic leukoencephalopathy with subcortical cysts	AR	39	108
MOCS1*	Molybdenum cofactor deficiency	AR	7	35
MRPL44	Combined oxidative phosphorylation deficiency 16	AR	2	2
MTFMT	Combined oxidative phosphorylation deficiency 15	AR	15	16
MTHFR	Homocystinuria due to MTHFR deficiency	AR	65	122
MTOR	Smith-Kingsmore syndrome	AD	26	24
NACC1	Neurodevelopmental disorder with epilepsy, cataracts, feeding difficulties, and delayed brain myelination (NECFM)	AD	2	3
NBEA	Epilepsy	AD	3	13
NDST1	Mental retardation, autosomal recessive 46	AR	4	7
NDUFAF3	Mitochondrial complex I deficiency	AR	6	9
NDUFAF5	Mitochondrial complex I deficiency	AR	8	12
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
NEU1	Sialidosis	AR	22	62
NEUROD2	Epileptic encephalopathy	AD		
NFU1	Multiple mitochondrial dysfunctions syndrome 1	AR	6	15
NHLRC1	Epilepsy, progressive myoclonic	AR	14	70
NKX6-2	Spastic ataxia 8, autosomal recessive, with hypomyelinating leukodystrophy	AR	4	8
NOTCH3	Cerebral arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), Lateral meningocele syndrome	AD	87	364
NPRL3	Epilepsy, familial focal, with variable foci 3	AD	21	10
NRXN1	Pitt-Hopkins like syndrome, Schizophrenia	AD/AR	99	311
NT5C2	Spastic paraplegia 45	AR	8	7
NUBPL	Mitochondrial complex I deficiency	AR	9	10
NUS1	Congenital disorder of glycosylation, type 1aa		4	5
OFD1	Simpson-Golabi-Behmel syndrome, Retinitis pigmentosa, Orofaciodigital syndrome, Joubert syndrome	XL	153	160
OPHN1	Mental retardation, with cerebellar hypoplasia and distinctive facial appearance	XL	28	42
P4HTM	Intellectual disability and seizures	AR		
PARS2	Alpers syndrome	AR	3	6
PCDH19	Epileptic encephalopathy, early infantile	XL	116	200
PGK1	Phosphoglycerate kinase 1 deficiency	XL	16	26
PHACTR1	Epileptic encephalopathy	AD	4	2
PHF6	Borjeson-Forssman-Lehmann syndrome	XL	22	29
PIGA*	Multiple congenital anomalies-hypotonia-seizures syndrome	XL	24	27
PIGB	Epileptic encephalopathy	AR		
PIGC		AR	4	4
PIGG	Mental retardation, autosomal recessive 53	AR	7	6
PIGN*	Multiple congenital anomalies-hypotonia-seizures syndrome 1	AR	33	34
PIGO	Hyperphosphatasia with mental retardation syndrome 2	AR	18	20
PIGP	Epileptic encephalopathy, early infantile, 55	AR		2
PIGQ	Epileptic encephalopathy	AR	3	4
PIGS	Epileptic encephalopathy	AR		

PIGT	Multiple congenital anomalies-hypotonia-seizures syndrome 3	AR	13	12
PIGV	Hyperphosphatasia with mental retardation syndrome 1	AR	9	16
PIGW	Hyperphosphatasia with mental retardation syndrome 5	AR	6	4
PITRM1		AR		2
PLAA	Neurodevelopmental disorder with progressive microcephaly, spasticity, and brain anomalies (NDMSBA)		3	3
PLCB1	Epileptic encephalopathy, early infantile	AR	8	10
PLP1	Spastic paraplegia, Pelizaeus-Merzbacher disease	XL	60	348
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
POLR3A	Leukodystrophy, hypomyelinating	AR	29	91
POLR3B	Leukodystrophy, hypomyelinating	AR	19	58
PPP2CA		AD		2
PPP3CA	Epilepitic encephalopathy	AD	8	11
PPT1*	Ceroid lipofuscinosis, neuronal	AR	94	77
PRICKLE1	Epilepsy, progressive myoclonic	AD/AR	3	16
PRIMA1	Epilepsy, nocturnal frontal lobe	AR		1
PRODH*	Hyperprolinemia	AR	52	10
PROSC	Epilepsy	AR	7	12
PRRT2	Episodic kinesigenic dyskinesia, Seizures, benign familial infantile, 2, Convulsions, familial infantile, with paroxysmal choreoathetosis	AD	42	99
PSAP	Krabbe disease, atypical, Metachromatic leukodystrophy due to saposin-b deficiency, Combined saposin deficiency, Gaucher disease, atypical, due to saposin C deficiency	AR	18	26
PTPN23	Epileptic encephalopathy	AR	1	4
PTS	Hyperphenylalaninemia, BH4-deficient	AR	34	112
PUM1	Ataxia	AD	3	11
PURA	Mental retardation	AD	74	47
PYCR2#	Leukodystrophy, hypomyelinating 10	AR	11	13
QARS	Microcephaly, progressive, seizures, and cerebral and cerebellar atrophy	AR	14	10

QDPR	Hyperphenylalaninemia, BH4-deficient	AR	14	66
RAB39B	Waisman parkinsonism-mental retardation syndrome, Mental retardation	XL	6	17
RALA	Intellectual disability	AD		1
RARS	Leukodystrophy, hypomyelinating 9	AR	12	11
RELN	Lissencephaly, Epilepsy, familial temporal lobe	AD/AR	25	44
RMND1*	Combined oxidative phosphorylation deficiency	AR	17	15
RNASEH2A	Aicardi-Goutières syndrome	AR	13	21
RNASEH2B	Aicardi-Goutières syndrome	AR	16	41
RNASEH2C	Aicardi-Goutières syndrome	AR	6	14
RNASET2	Leukoencephalopathy, cystic, without megalencephaly	AR	8	12
RNF216*	Cerebellar ataxia and hypogonadotropic hypogonadism (Gordon Holmes syndrome)	AR	10	14
ROGDI	Kohlschutter-Tonz syndrome	AR	14	13
RORB	Epilepsy	AD	3	9
SAMHD1	Aicardi-Goutières syndrome, Chilblain lupus 2	AD/AR	25	56
SCARB2	Epilepsy, progressive myoclonic	AR	23	27
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
SCN9A	Paroxysmal extreme pain disorder, Small fiber neuropathy, Erythermalgia, primary, Geberalized epilepsy with febrile seizures plus, type 7, Insensitivity to pain, congenital, autosomal recessive	AD/AR	61	125
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
SERPINI1	Encephalopathy, familial, with neuroserpin inclusion bodies	AD	5	9
SIK1	Epileptic encephalopathy, early infantile	AD	5	6

SLC12A5	Epileptic encephalopathy, early infantile	AR	6	14
SLC13A5	Epileptic encephalopathy, early infantile	AR	18	20
SLC19A3	Thiamine metabolism dysfunction syndrome	AR	32	37
SLC1A4	Spastic tetraplegia, thin corpus callosum, and progressive microcephaly	AR	4	8
SLC25A1	Combined D-2- and L-2-hydroxyglutaric aciduria	AR	8	24
SLC25A15*	Hyperornithinemia-hyperammonemia-homocitrullinemia syndrome	AR	24	36
SLC25A22	Epileptic encephalopathy, early infantile	AR	8	10
SLC25A42		AR	1	1
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
SLC39A8	Congenital disorder of glycosylation, type IIn	AR	7	6
SLC46A1	Folate malabsorption	AR	17	23
SLC6A1	Myoclonic-astastic epilepsy	AD	38	41
SLC6A8*	Creatine deficiency syndrome	XL	38	133
SLC9A6	Mental retardation, syndromic, Christianson	XL	24	28
SMARCA2	Nicolaides-Baraitser syndrome	AD	41	73
SMC1A	Cornelia de Lange syndrome	XL	73	87
SMS	Mental retardation, Snyder-Robinson	XL	11	14
SNAP25	Myasthenic syndrome, congenital	AD	2	4
SNORD118	Leukoencephalopathy, brain calcifications, and cysts (Labrune syndrome)	AR	6	39
SOX10	Peripheral demyelinating neuropathy, central dysmyelination, Waardenburg syndrome, and Hirschsprung disease, Kallmann syndrome	AD	56	148
SPATA5	Schizophrenia, Epilepsy, hearing loss, and mental retardation syndrome (EHLMRS)	AR	27	27
SPTAN1	Epileptic encephalopathy, early infantile	AD	16	40
SPTBN4	Myopathy, congenital, with neuropathy and deafness	AR	6	7
ST3GAL3	Epileptic encephalopathy, early infantile, Mental retardation	AR	3	5
ST3GAL5	Ganglioside GM3 synthase deficiency	AR	10	5
STX1B	Generalized epilepsy with febrile seizures plus	AD	11	9
STXBP1	Epileptic encephalopathy, early infantile	AD	140	190
SUMF1	Multiple sulfatase deficiency	AR	21	53

SUOX	Sulfocysteinuria	AR	8	29
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
TAF1	Dystonia 3, torsion, X-linked, Mental retardation, X-linked, syndromic 33	XL	13	14
TBC1D20	Warburg micro syndrome 4	AR	6	6
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
TBL1XR1*	Mental retardation, autosomal dominant 41, Pierpont syndrome	AD	25	23
TCF4	Corneal dystrophy, Fuchs endothelial, Pitt-Hopkins syndrome	AD	105	146
TPK1	Thiamine metabolism dysfunction syndrome 5	AR	14	11
TPP1	Spinocerebellar ataxia, Neuronal ceroid lipofuscinosis type 2	AR	75	112
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
TUBB4A*	Leukodystrophy, hypomyelinating, Dystonia	AD	39	42
UBA5*	Epileptic encephalopathy, early infantile, 44, Spinocerebellar ataxia, autosomal recessive 24	AR	16	15
UBE2A	Mental retardation, syndromic, Nascimento	XL	9	25
UBE3A*	Angelman syndrome	AD	176	202
UNC80	Hypotonia, infantile, with psychomotor retardation and characteristic facies 2	AR	26	20

VAMP2		AD		
VARS	Early-onset progressive encephalopathy with brain atrophy and thin corpus callosum (PEBAT), Encephalopathy, progressive	AR	12	6
VPS13A	Choreoacanthocytosis	AR	19	115
WARS2	Encephalopathy, mitochondrial	AR	6	14
WASF1	Intellectual disability and seizures	AD	3	3
WDR26	Skraban-Deardorff syndrome	AD	13	34
WDR45	Neurodegeneration with brain iron accumulation	XL	46	78
WWOX	Epileptic encephalopathy, early infantile, Spinocerebellar ataxia	AR	43	45
YY1	Gabriele-de Vries syndrome (GADEVS)	AD	8	23
ZEB2*	Mowat-Wilson syndrome	AD	154	287
ZFYVE26	Spastic paraplegia 15	AR	63	39

*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	
AIFM1	ChrX:129274636	c.697-44T>G	NM_004208.3	
ALDH3A2	Chr17:19561044	c.681-14T>A/G	NM_001031806.1	
ALDH3A2	Chr17:19561044	c.681-14T>A	NM_001031806.1	
ALDH3A2	Chr17:19561044	c.681-14T>G	NM_001031806.1	
AMT	Chr3:49459938	c.-55C>T	NM_000481.3	rs386833677
ARG1	Chr6:131901748	c.306-611T>C	NM_000045.3	
ARSA	Chr22:51064121	c.1108-12C>G	NM_000487.5	rs757806374

ARSA	Chr22:51064129	c.1108-20A>G	NM_000487.5	
BTD	Chr3:15683399	c.310-15delT	NM_000060.2	rs587783008
BTD	Chr3:15687154	c.*159G>A	NM_000060.2	rs530872564
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
CASR	Chr3:121994640	c.1378-19A>C	NM_001178065.1	
CDKL5	ChrX:18525053	c.-162-2A>G	NM_003159.2	rs786204973
CLN3	Chr16:28493392	c.1056+34C>A	NM_000086.2	
CLN3	Chr16:28497984	c.461-13G>C	NM_000086.2	rs386833721
CLN6	Chr15:68506515	c.297+113G>C	NM_017882.2	
COL4A1	Chr13:110802675	c.*35C>A	NM_001845.4	
COL4A1	Chr13:110802678	c.*32G>A/T	NM_001845.4	
COL4A1	Chr13:110802679	c.*31G>T	NM_001845.4	
CSF1R	Chr5:149440654	c.1859-119G>A	NM_005211.3	
D2HGDH	Chr2:242680425	c.293-23A>G	NM_152783.3	
DARS2	Chr1:173797449	c.228-22T>C	NM_018122.4	
DARS2	Chr1:173797449	c.228-22T>A	NM_018122.4	
DARS2	Chr1:173797450	c.228-21_228-20delTTinsC	NM_018122.4	
DARS2	Chr1:173797450	c.228-21_228-20delTTinsCC	NM_018122.4	
DARS2	Chr1:173797455	c.228-16C>A	NM_018122.4	
DARS2	Chr1:173797455	c.228-16C>G	NM_018122.4	
DARS2	Chr1:173797456	c.228-15C>G	NM_018122.4	
DARS2	Chr1:173797456	c.228-15C>A	NM_018122.4	
DARS2	Chr1:173797459	c.228-12C>A	NM_018122.4	
DARS2	Chr1:173797460	c.228-11C>G	NM_018122.4	
DEPDC5	Chr22:32150851	c.-57G>C	NM_001242896.1	
EFHC1	Chr6:52284844		NM_018100.3	rs559477321
EIF2B5	Chr3:183855941	c.685-13C>G	NM_003907.2	
ETFDH	Chr4:159593534	c.-75A>G	NM_004453.2	
ETFDH	Chr4:159602711	c.176-636C>G	NM_004453.2	

ETHE1	Chr19:44031407		NM_014297.3	
FDFT1	Chr8:11660094		NM_004462.3	
FDFT1	Chr8:11689003	c.880-24_880-23delTCinsAG	NM_004462.3	
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		NM_000814.5	
GABRB3	Chr15:27020313	c.-2204G>A	NM_000814.5	
GABRB3	Chr15:27020399	c.-2290T>C	NM_000814.5	rs546389769
GALC	Chr14:88401064	c.*12G>A	NM_000153.3	rs372641636
GALC	Chr14:88459574	c.-66G>C	NM_000153.3	rs146439771
GALC	Chr14:88459575	c.-67T>G	NM_000153.3	rs571945132
GALC	Chr14:88459917	c.-74T>A	NM_001201402.1	
GALC	Chr14:88459971	c.-128C>T	NM_001201402.1	rs181956126
GAMT	Chr19:1399508	c.391+15G>T	NM_138924.2	rs367567416
GCDH	Chr19:13010271	c.1244-11A>G	NM_000159.3	
GCH1	Chr14:55369403	c.-22C>T	NM_000161.2	
GJC2	Chr1:228337558	c.-170A>G	NM_020435.3	
GJC2	Chr1:228337561	c.-167A>G	NM_020435.3	
GJC2	Chr1:228337709	c.-20+1G>C	NM_020435.3	
GRN	Chr17:42422701	c.-9A>G	NM_002087.2	
GRN	Chr17:42422705	c.-8+3A>T	NM_002087.2	rs63751020
GRN	Chr17:42422705	c.-8+3A>G	NM_002087.2	
GRN	Chr17:42422707	c.-8+5G>C	NM_002087.2	rs63750313
L2HGDH	Chr14:50735527	c.906+354G>A	NM_024884.2	
MEF2C	Chr5:88179125	c.-510_-497delTCTTCCTCCTCCTC	NM_002397.4	
MLC1	Chr22:50502853	c.895-226T>G	NM_015166.3	
MLC1	Chr22:50523373	c.-42C>T	NM_015166.3	rs771159578
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
NDUFAF5	Chr20:13767051	c.223-907A>C	NM_024120.4	
NDUFAF6	Chr8:96046914	c.298-768T>C	NM_152416.3	rs575462405
NDUFAF6	Chr8:96048588	c.420+784C>T	NM_152416.3	rs749738738
NOTCH3	Chr19:15303132	c.341-26_341-24delAAC	NM_000435.2	
OFD1	ChrX:13768358	c.935+706A>G	NM_003611.2	rs730880283
OFD1	ChrX:13773245	c.1130-22_1130-19delAATT	NM_003611.2	rs312262865
OFD1	ChrX:13773249	c.1130-20_1130-16delTTGGT	NM_003611.2	
PGK1	ChrX:77381262	c.1214-25T>G	NM_000291.3	
PLP1	ChrX:103031997	c.4+78_4+85delGGGGGTTC	NM_000533.3	
PLP1	ChrX:103041680	c.453+28_453+46delTAACAAGGGGTGGGGGAAA	NM_000533.3	
PLP1	ChrX:103042405	c.454-322G>A	NM_000533.3	
PLP1	ChrX:103042413	c.454-314T>A/G	NM_000533.3	
PLP1	ChrX:103042413	c.454-314T>A	NM_000533.3	
PLP1	ChrX:103042413	c.454-314T>G	NM_000533.3	
PNKP	Chr19:50364799	c.1387-33_1386+49delCCTCCTCCCCTGACCCC	NM_007254.3	rs752902474
POLR3A	Chr10:79737218	c.*18C>T	NM_007055.3	
POLR3A	Chr10:79743781	c.3337-11T>C	NM_007055.3	
POLR3A	Chr10:79769273	c.1909+22G>A	NM_007055.3	rs191875469
POLR3A	Chr10:79769277	c.1909+18G>A	NM_007055.3	rs267608677
POLR3B	Chr12:106804589	c.967-15A>G	NM_018082.5	
POLR3B	Chr12:106831447	c.1857-12A>G	NM_018082.5	rs528038639
PPT1	Chr1:40539203	c.*526_*529delATCA	NM_000310.3	rs386833624
PPT1	Chr1:40558194	c.125-15T>G	NM_000310.3	rs386833629
PRRT2	Chr16:29825620	c.*345G>A	NM_001256443.1	
PSAP	Chr10:73583679	c.778-26C>A	NM_001042465.1	
PTS	Chr11:112098994	c.84-323A>T	NM_000317.2	rs794726657
PTS	Chr11:112099026	c.84-291A>G	NM_000317.2	
PTS	Chr11:112100215	c.164-716A>T	NM_000317.2	

PTS	Chr11:112101310	c.187-38dupG	NM_000317.2	
QDPR	Chr4:17500790	c.436+2552A>G	NM_000320.2	
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	
SNORD118	Chr17:8076761		NR_033294.1	rs116395281
SNORD118	Chr17:8076761		NR_033294.1	
SNORD118	Chr17:8076762		NR_033294.1	rs201787275
SOX10	Chr22:38379877	c.-84-2A>T	NM_006941.3	
SOX10	Chr22:38412215	c.-31954C>T	NM_006941.3	rs606231342
SOX10	Chr22:38412781	c.-32520C>G	NM_006941.3	
SPTAN1	Chr9:131390187	c.6690-17G>A	NM_001130438.2	rs796053325
TAF1	ChrX:70749635			rs397509359
TBCD	Chr17:80851411	c.1564-12C>G	NM_005993.4	
TPP1	Chr11:6637752	c.887-18A>G	NM_000391.3	
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	
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

This panel does not detect the expansion of a 12-nucleotide repeat (rs193922905) in the promoter region of *CSTB*. The following exons are not included in the panel as they are not sufficiently covered with high quality sequence reads: *AP4S1* (NM_001254727:6), *DEGS1* (NM_001321541:3), *DHPS* (NM_001206974:1), *GABRG2* (NM_198903:6), *SLC39A8* (NM_001135148:1). 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

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).

Assays have been validated for various sample types including EDTA-blood, isolated DNA (excluding from formalin fixed paraffin embedded tissue), saliva and dry blood spots (filter cards). These sample types were selected in order to maximize the likelihood for high-quality DNA yield. The diagnostic yield varies depending on the assay used, referring healthcare professional, hospital and country. Plus analysis increases the likelihood of finding a genetic diagnosis for your patient, as large deletions and duplications cannot be detected using sequence analysis alone. Blueprint Genetics' Plus Analysis is a combination of both sequencing and deletion/duplication (copy number variant (CNV)) analysis.

Performance of Blueprint Genetics high-quality, clinical grade NGS sequencing assay for panels.

	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	99.2% (7,745/7,806)	>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%
Size range (0.1-47 Mb)	100% (25/25)	

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.

		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=2084 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%)	92.9%(12/13)	99.98%
Heteroplasmic (<5%)	88.7% (47/53)	99.93%
Insertions and deletions by sequence analysis n=42 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)	>0.9999
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 and regulatory 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 including, 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, ordering providers have access to the details of the analysis, including patient specific sequencing metrics, a gene level coverage plot and a list of regions with <20X sequencing depth if applicable. This reflects our mission to build fully transparent diagnostics where ordering providers can easily visualize the 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 is orthogonal confirmation. Sequence variants classified as pathogenic, likely pathogenic and variants of uncertain significance (VUS) are confirmed using bi-directional Sanger sequencing when they do not meet our stringent NGS quality metrics for a true positive call. Reported heterozygous and homo/hemizygous copy number variations with a size <10 and <3 target exons are confirmed by orthogonal methods such as qPCR if the specific CNV has been seen and confirmed 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, abstracts and variant databases used to help ordering providers 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. We do not recommend using variants of uncertain significance (VUS) for family member risk stratification or patient management. Genetic counseling is recommended.

Our interpretation team analyzes millions of variants from thousands of individuals with rare diseases. Our internal database and our understanding of variants and related phenotypes increases with every case analyzed. 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 Comprehensive Epilepsy Panel

ICD-10	Disease
G40.9	Epilepsy
E75.4	Neuronal ceroid lipofuscinosis

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

- CURE: Citizens United for Research in Epilepsy
- Epilepsy Foundation
- GeneReviews - *DEPDC5*-Related Epilepsy
- GeneReviews - *MECP2*-Related Disorders
- GeneReviews - *SCN1A*-Related Seizure Disorders
- GeneReviews - *SCN8A*-Related Epilepsy with Encephalopathy
- GeneReviews - *STXBP1* Encephalopathy with Epilepsy
- GeneReviews - Autosomal Dominant Nocturnal Frontal Lobe Epilepsy
- GeneReviews - Autosomal Dominant Partial Epilepsy with Auditory Features
- GeneReviews - Leukodystrophy
- GeneReviews - Leukodystrophy Overview
- GeneReviews - Neuronal Ceroid Lipofuscinosis
- International Bureau for Epilepsy
- International League Against Epilepsy
- 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 - Batten Disease
- NORD - Leukodystrophy
- NORD - Progressive Myoclonus Epilepsy
- NORD - Sudden Unexplained Death in Childhood
- SUDEP Action
- Sudden Unexpected Death in Epilepsy Institute