Blueprint Genetics

Ataxia Panel

Test code: NE2101

Is ideal for patients with a clinical suspicion of ataxia when repeat expansion variants are excluded either as clinically incompatible or by previous testing.

Hereditary ataxia can be inherited in an autosomal recessive, autosomal dominant or X-linked manner. The clinical utility of a multi-gene panel for diagnosis of hereditary ataxias has been shown to be efficient, cost effective and enabled a molecular diagnosis in many refractory cases (PMID: 24030952). By sequencing 58 known human ataxia genes in 50 heterogeneous patients with ataxia who had been extensively investigated and were refractory to diagnosis, the overall detection rate of 18% was achieved. It was 40% in those with a childhood or adolescent onset progressive disorder and 75% in those with an adolescent onset and a family history.

About Ataxia

The hereditary ataxias including cerebellar ataxias, episodic ataxias and spinocerebellar ataxias are a group of genetic disorders characterized by slowly progressive incoordination of gait and often associated with poor coordination of hands, speech, and eye movements. Frequently, atrophy of the cerebellum occurs. The episodic ataxias are characterized by periods of unsteady gait often associated with nystagmus or dysarthria. Myokymia, vertigo, or hearing loss may occur in some of the subtypes. The prevalence of the autosomal dominant cerebellar ataxias (ADCAs) is estimated to be approximately 1-5:100,000. Most ADCAs are spinocerebellar ataxias (SCA) or episodic ataxias. Autosomal recessive types of hereditary ataxia account for approximately 3:100,000 with Friedreich ataxia, ataxia-telangiectasia, and ataxia oculomotor apraxia being most common. Most of the spastic ataxias are recessively inherited.

Availability

Results in 3-4 weeks

Gene set description

Genes in the Ataxia Panel and their clinical significance

Gene	Associated phenotypes	Inheritance	ClinVar	HGMD
ABCB7	Anemia, sideroblastic, and spinocerebellar ataxia	XL	8	9
ABHD12	Polyneuropathy, hearing loss, ataxia, retinitis pigmentosa, and cataract	AR	16	20
ACO2	Optic atrophy, Infantile cerebellar-retinal degeneration	AR	16	15
ADCK3	Coenzyme Q10 deficiency, Progressive cerebellar ataxia and atrophy, Spinocerebellar ataxia	AR	45	43
ADPRHL2	Neurodegeneration, childhood-onset, with brain atrophy	AR		1
AFG3L2*	Spastic ataxia, Spinocerebellar ataxia	AD/AR	22	40
AGTPBP1	Neuropathy	AR	3	1
AHI1	Joubert syndrome	AR	62	93
ALDH5A1	Succinic semialdehyde dehydrogenase deficiency	AR	16	70
ANO10	Spinocerebellar ataxia	AR	19	18

APTX	Ataxia, early-onset, with oculomotor apraxia and hypoalbuminemia	AR	14	46
ARL13B	Joubert syndrome	AR	11	10
ARL6	Bardet-Biedl syndrome, Retinitis pigmentosa	AR	14	21
ATCAY	Ataxia, cerebellar, Cayman	AR	1	3
ATM	Breast cancer, Ataxia-Telangiectasia	AD/AR	1047	1109
ATP1A3	Alternating hemiplegia of childhood, Dystonia 12	AD	79	112
ATP2B3	Spinocerebellar ataxia, X-linked 1	XL	6	7
ATP8A2	Dysequilibrium syndrome	AR	9	11
BBS1	Bardet-Biedl syndrome	AR	66	103
BBS10	Bardet-Biedl syndrome	AR	90	107
BBS12	Bardet-Biedl syndrome	AR	36	58
BBS2	Bardet-Biedl syndrome, Retinitis pigmentosa	AR	58	91
BBS4	Bardet-Biedl syndrome	AR	25	53
BBS5	Bardet-Biedl syndrome	AR	18	31
BBS7	Bardet-Biedl syndrome	AR	19	43
BBS9	Bardet-Biedl syndrome	AR	27	52
BEAN1	Spinocerebellar ataxia	AD	1	2
C10ORF2	Perrault syndrome, Mitochondrial DNA depletion syndrome, Progressive external ophthalmoplegia with mitochondrial DNA deletions, autosomal dominant, 3	AR	37	80
C12ORF4	Autism spectrum disorder, Developmental delay with variable intellectual impairment and behavioral abnormalities	AR	1	5
C5ORF42	Orofaciodigital syndrome, Joubert syndrome	AR	97	103
CA8	Cerebellar ataxia, mental retardation, and dysequilibrium syndrome	AR	4	4
CACNA1A	Migraine, familial hemiplegic, Episodic ataxia, Spinocerebellar ataxia 6, Epileptic encephalopathy, early infantile, 42	AD	135	230
CACNA1G	Spinocerebellar ataxia 42		8	11
CACNB4	Episodic ataxia, Epilepsy, idiopathic generalized, susceptibility to, 9	AD	2	7
CAMTA1	Cerebellar ataxia, nonprogressive, with mental retardation	AD	38	8
CAPN1	Spastic paraplegia 76, autosomal recessive	AR	6	16
CASK	Mental retardation and microcephaly with pontine and cerebellar hypoplasia, FG syndrome, Mental retardation	XL	87	112
CC2D2A	COACH syndrome, Joubert syndrome, Meckel syndrome	AR	76	91

CCDC88C	Spinocerebellar ataxia	AD	6	10
CEP290*	Bardet-Biedl syndrome, Leber congenital amaurosis, Joubert syndrome, Senior-Loken syndrome, Meckel syndrome	AR	130	289
CEP41	Joubert syndrome	AR/Digenic	7	11
CLCN2	Leukoencephalopathy with ataxia, Epilepsy	AD/AR	30	36
CLN5	Neuronal ceroid lipofuscinosis, type 5	AR	62	47
CLPP	Deafness	AR	4	13
COA7	Spinocerebellar ataxia, Charcot-Marie-Tooth disease	AR	2	7
COASY	Neurodegeneration with brain iron accumulation 6	AR	3	3
COX20	Mitochondrial complex IV deficiency	AR	4	1
CP*	Aceruloplasminemia, Hypoceruloplasminemia	AR	62	57
CSTB	Epilepsy, progressive myoclonic	AR	19	15
CWF19L1	Spinocerebellar ataxia	AR	9	4
CYP27A1	Cerebrotendinous xanthomatosis	AR	69	110
CYP2U1	Spastic paraplegia 56, autosomal recessive	AR	14	19
DHPS		AR		
DNAJC19	3-methylglutaconic aciduria	AR	3	6
DNMT1	Neuropathy, hereditary sensory, Cerebellar ataxia, deafness, and narcolepsy	AD	9	20
DOCK3	Ataxia	AR	3	5
EBF3	Hypotonia, ataxia, and delayed development syndrome (HADDS)	AD	32	26
EEF2	Spinocerebellar ataxia	AD	1	2
ELOVL4	Stargardt disease, Icthyosis, spastic quadriplegia, and mental retardation, Spinocerebellar ataxia	AD/AR	13	14
ELOVL5	Spinocerebellar ataxia	AD	2	5
FA2H	Spastic paraplegia	AR	18	51
FBXL4	Mitochondrial DNA depletion syndrome	AR	55	47
FDXR	Auditory neuropathy and optic atrophy	AR	5	19
FGF14	Spinocerebellar ataxia	AD	9	10
FLVCR1	Ataxia, posterior column, with retinitis pigmentosa	AR	9	15
FMR1	Premature ovarian failure, Fragile X syndrome, Fragile X tremor/ataxia syndrome	XL	13	76
FXN*	Friedreich ataxia	AR	13	63

GBA2	Cerebellar ataxia with spasticity	AR	11	22
GFAP	Alexander disease	AD	114	131
GOSR2*	Epilepsy, progessive myoclonic	AR	6	4
GRID2	Spinocerebellar ataxia	AR	11	20
GRM1	Spinocerebellar ataxia	AR	5	17
GSS	Glutathione synthetase deficiency	AR	8	38
HARS2	Perrault syndrome	AR	7	3
HIBCH	3-hydroxyisobutryl-CoA hydrolase deficiency	AR	18	16
INPP5E	Joubert syndrome, Mental retardation, truncal obesity, retinal dystrophy, and micropenis (MORM syndrome)	AR	25	50
IRF2BPL	Neurodevelopmental disorder with hypotonia, seizures, and absent language	AD	9	2
ITM2B	Dementia, familial Danish, Retinal dystrophy with inner retinal dysfunction and ganglion cell abnormalities, Cerebral amyloid angiopathy	AD	3	6
ITPR1	Spinocerebellar ataxia	AD	35	89
KCNA1	Episodic ataxia/myokymia syndrome	AD	24	45
KCNC3	Spinocerebellar ataxia	AD	7	11
KCND3	Brugada syndrome, Spinocerebellar ataxia 19, Spinocerebellar ataxia 22	AD	7	29
KCNJ10	Seizures, sensorineural deafness, ataxia, mental retardation, and electrolyte imbalance (SESAME syndrome), Pendred syndrome, Enlarged vestibular aqueduct	AR/Digenic	13	29
KIF1C*	Spastic ataxia	AR	7	17
KIF7	Acrocallosal syndrome, Hydrolethalus syndrome, Al-Gazali-Bakalinova syndrome, Joubert syndrome	AR/Digenic	24	44
LAMA1	Poretti-Boltshauser syndrome	AR	32	40
LARS2	Perrault syndrome, Hydrops, lactic acidosis, and sideroblastic anemia (HLASA)	AR	14	14
LMNB1	Leukodystrophy, demyelinating, adult-onset, autosomal dominant	AD	2	35
LRPPRC	Leigh syndrome, French-Canadian type	AR	55	17
MARS2	Combined oxidative phosphorylation deficiency	AR	8	5
MECR	Dystonia, childhood-onset, with optic atrophy and basal ganglia abnormalities (DYTOABG)	AR	7	6
MKKS	Bardet-Biedl syndrome, McKusick-Kaufman syndrome	AR	21	59
MKS1	Bardet-Biedl syndrome, Meckel syndrome	AR	50	52
MME	Spinocerebellar ataxia 43, Charcot-Marie-Tooth disease, axonal, type 2T	AD/AR	14	21

MRE11A	Ataxia-telangiectasia-like disorder-1	AR	57	56
MSTO1	Myopathy, mitochondrial, and ataxia	AD/AR	7	8
MTFMT	Combined oxidative phosphorylation deficiency 15	AR	15	16
MTPAP	Spastic ataxia	AR	1	2
MTTP	Abetalipoproteinemia	AR	12	69
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
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
NKX6-2	Spastic ataxia 8, autosomal recessive, with hypomyelinating leukodystrophy	AR	4	8
NOL3	Myoclonus, familial cortical	AD	1	3
NPHP1	Nephronophthisis, Joubert syndrome, Senior-Loken syndrome	AR	19	76
NUBPL	Mitochondrial complex I deficiency	AR	9	10
OFD1	Simpson-Golabi-Behmel syndrome, Retinitis pigmentosa, Orofaciodigital syndrome, Joubert syndrome	XL	153	160
OPA1	Optic atrophy, Optic atrophy 1, Optic atrophy with or without deafness, Ophthalmoplegia, myopathy, ataxia, and neuropathy, Behr synrome, Mitochondrial DNA depletion syndrome 14	AD/AR	96	390
OPHN1	Mental retardation, with cerebellar hypoplasia and distinctive facial appearance	XL	28	42
PAX6	Aniridia, cerebellar ataxia, and mental retardation (Gillespie syndrome), Keratitis, Coloboma, ocular, Cataract with late-onset corneal dystrophy, Morning glory disc anomaly, Foveal hypoplasia, Aniridia, Optic nerve hypoplasia, Peters anomaly	AD	144	550
PDYN	Spinocerebellar ataxia	AD	4	11
PEX7	Refsum disease, Rhizomelic CDP type 1	AR	44	53
PHYH	Refsum disease	AR	12	36
PNKD	Paroxysmal non-kinesigenic dyskinesia	AD	5	5
PNKP	Epileptic encephalopathy, early infantile, Ataxia-oculomotor	AR	34	23
PNPLA6	Laurence-Moon syndrome, Boucher-Neuhauser syndrome, Spastic paraplegia 39	AR	26	58

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
PRKCG	Spinocerebellar ataxia	AD/AR	28	47
PRRT2	Episodic kinesigenic dyskinesia, Seizures, benign familial infantile, 2, Convulsions, familial infantile, with paroxysmal choreoathetosis	AD	42	99
PUM1	Ataxia	AD	3	11
RNF216*	Cerebellar ataxia and hypogonadotropic hypogonadism (Gordon Holmes syndrome)	AR	10	14
RPGRIP1L	COACH syndrome, Joubert syndrome, Meckel syndrome, Retinal degeneration in ciliopathy, modifier	AD/AR	39	49
RUBCN	Spinocerebellar ataxia	AR	4	4
SACS	Spastic ataxia, Charlevoix-Saguenay	AR	254	262
SCYL1	Spinocerebellar ataxia, autosomal recessive 21	AR	12	6
SERAC1	3-methylglutaconic aciduria with deafness, encephalopathy, and Leigh-like syndrome	AR	22	52
SETX	Ataxia with oculomotor apraxia, Amyotrophic lateral sclerosis, juvenile, Spinocerebellar ataxia	AD/AR	36	210
SIL1	Marinesco-Sjogren syndrome	AR	14	49
SLC1A3	Episodic ataxia	AD	2	17
SLC20A2	Basal ganglia calcification, idiopathic, 1	AD	22	71
SLC25A46	Neuropathy, hereditary motor and sensory, type VIB	AR	14	17
SLC2A1	Stomatin-deficient cryohydrocytosis with neurologic defects, Epilepsy, idiopathic generalized, GLUT1 deficiency syndrome	AD/AR	106	275
SLC52A2	Brown-Vialetto-Van Laere syndrome	AR	27	25
SLC9A1	Spinocerebellar ataxia, autosomal recessive 19 (Lichtenstein-Knorr syndrome)	AR	2	4
SLC9A6	Mental retardation, syndromic, Christianson	XL	24	28
SNX14	Spinocerebellar ataxia	AR	15	18
SPG7	Spastic paraplegia	AR	69	111
SPTBN2	Spinocerebellar ataxia	AD/AR	18	28
STUB1	Spinocerebellar ataxia	AR	13	28
SYNE1	Spinocerebellar ataxia, autosomal recessive 8	AD/AR	83	136
SYT14*	Spinocerebellar ataxia	AR	5	3
TCTN1	Joubert syndrome	AR	6	6

TCTN2	Joubert syndrome, Meckel syndrome	AR	20	15
TCTN3	Orofaciodigital syndrome (Mohr-Majewski syndrome), Joubert syndrome	AR	9	12
TDP1	Spinocerebellar ataxia, with axonal neuropathy	AR	1	3
TGM6	Spinocerebellar ataxia	AD	8	24
TMEM138	Joubert syndrome	AR	6	8
TMEM216	Joubert syndrome, Meckel syndrome	AR	17	8
TMEM231	Joubert syndrome, Meckel syndrome	AR	12	19
TMEM237	Joubert syndrome	AR	7	11
TMEM240	Spinocerebellar ataxia	AD	8	6
TMEM67	Nephronophthisis, COACH syndrome, Joubert syndrome, Meckel syndrome	AR	87	170
TPP1	Spinocerebellar ataxia, Neuronal ceroid lipofuscinosis type 2	AR	75	112
TRIM32	Bardet-Biedl syndrome, Muscular dystrophy, limb-girdle	AR	13	16
TTBK2	Spinocerebellar ataxia	AD	4	9
TTC19	Mitochondrial complex III deficiency, nuclear type 2	AR	13	10
TTC8	Bardet-Biedl syndrome, Retinitis pigmentosa	AR	5	16
TTPA	Ataxia with isolated vitamin E deficiency	AR	29	30
TUBB4A*	Leukodystrophy, hypomyelinating, Dystonia	AD	39	42
UBA5*	Epileptic encephalopathy, early infantile, 44, Spinocerebellar ataxia, autosomal recessive 24	AR	16	15
UBTF	Neurodegeneration, childhood-onset, with brain atrophy	AR	3	1
UCHL1	Parkinson disease 5, autosomal dominant, Spastic paraplegia 79, autosomal recessive	AD/AR	5	5
VAMP1	Spastic ataxia	AD	3	6
VLDLR	Cerebellar ataxia, mental retardation, and dysequilibrium syndrome	AR	11	24
WDPCP	Meckel-Gruber syndrome, modifier, Bardet-Biedl syndrome, Congenital heart defects, hamartomas of tongue, and polysyndactyly	AR	6	8
WDR81	Dysequilibrium syndrome	AR	8	17
WFS1	Wolfram syndrome, Deafness, Wolfram-like syndrome, autosomal dominant, Deafness, autosomal dominant 6/14/38, Cataract 41	AD/AR	69	362
WWOX	Epileptic encephalopathy, early infantile, Spinocerebellar ataxia	AR	43	45
ZFYVE26	Spastic paraplegia 15	AR	63	39
ZNF423	Nephronophthisis, Joubert syndrome	AD/AR	10	7

*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
ADCK3	Chr1:227174508	c.*72dupG	NM_020247.4	
ATM	Chr11:108093770	c.-174A>G	NM_000051.3	
ATM	Chr11:108094508	c.-31+595G>A	NM_000051.3	
ATM	Chr11:108098321	c.-30-1G>T	NM_000051.3	rs869312754
ATM	Chr11:108138753	c.2639-384A>G	NM_000051.3	
ATM	Chr11:108141209	c.2839-579_2839-576delAAGT	NM_000051.3	
ATM	Chr11:108151710	c.3403-12T>A	NM_000051.3	rs201370733
ATM	Chr11:108158168	c.3994-159A>G	NM_000051.3	rs864622543
ATM	Chr11:108164028	c.4612-12A>G	NM_000051.3	
ATM	Chr11:108179837	c.5763-1050A>G	NM_000051.3	rs774925473
ATM	Chr11:108214779	c.8418+681A>G	NM_000051.3	rs748635985
BBS1	Chr11:66291105	c.951+58C>T	NM_024649.4	
BBS4	Chr15:73001820	c.77-216delA	NM_033028.4	rs113994189
BBS5	Chr2:170354110	c.619-27T>G	NM_152384.2	
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
CEP290	Chr12:88462434	c.6012-12T>A	NM_025114.3	rs752197734
CEP290	Chr12:88494960	c.2991+1655A>G	NM_025114.3	rs281865192
CEP290	Chr12:88508350	c.1910-11T>G	NM_025114.3	

CEP290	Chr12:88534822	c.103-18_103-13delGCTTTT	NM_025114.3	
FMR1	ChrX:147031110	c.*746T>C	NM_002024.5	rs183130936
GSS	Chr20:33537864	c.129+1663A>G	NM_000178.2	rs1474111175
GSS	Chr20:33543525	c.-9+5G>A	NM_000178.2	
KCNJ10	Chr1:160039811	c.-1+1G>T	NM_002241.4	rs796052606
MTTP	Chr4:100512792	c.619-5_619-2delTTTA	NM_000253.2	rs755155385
MTTP	Chr4:100522736	c.1237-28A>G	NM_000253.2	
NDUFAF6	Chr8:96046914	c.298-768T>C	NM_152416.3	rs575462405
NDUFAF6	Chr8:96048588	c.420+784C>T	NM_152416.3	rs749738738
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	
OPA1	Chr3:193334932	c.449-34dupA	NM_130837.2	
OPA1	Chr3:193374829	c.2179-40G>C	NM_130837.2	
PAX6	Chr11:31685945	c.*125537G>T	NM_000280.4	rs606231388
PAX6	Chr11:31812434	c.1033-42_1033-26delATGTGTTCCTCAGTAACinsG	NM_000280.4	
PAX6	Chr11:31816377	c.524-41T>G	NM_000280.4	
PAX6	Chr11:31823338	c.142-14C>G	NM_000280.4	rs1131692291
PAX6	Chr11:31828391	c.-52+5delG	NM_000280.4	
PAX6	Chr11:31828391	c.-52+3_-52+6delAAGTinsTG	NM_000280.4	
PAX6	Chr11:31828392	c.-52+3_-52+4delAA	NM_000280.4	
PAX6	Chr11:31828395	c.-52+1delG	NM_000280.4	
PAX6	Chr11:31828396	c.-52+1G>A	NM_000280.4	
PAX6	Chr11:31828456	c.-115_-112delACTA	NM_000280.4	rs1011844558
PAX6	Chr11:31828461	c.-118_-117delTT	NM_000280.4	
PAX6	Chr11:31828469	c.-125dupG	NM_000280.4	
PAX6	Chr11:31828474	c.-128-1G>T	NM_000280.4	
PAX6	Chr11:31828474	c.-128-2delA	NM_000280.4	rs1131692282
PAX6	Chr11:31832372	c.-138_-129+3delCCTCATAAAGGTG	NM_000280.4	
PAX6	Chr11:31832374	c.-129+2T>A	NM_000280.4	
PAX6	Chr11:31832375	c.-129+1G>A	NM_000280.4	

PEX7	Chr6:137143759	c.-45C>T	NM_000288.3	rs267608252
PNKP	Chr19:50364799	c.1387-33_1386+49delCCTCCTCCCCTGACCCC	NM_007254.3	rs752902474
PRRT2	Chr16:29825620	c.*345G>A	NM_001256443.1	
SERAC1	Chr6:158576548	c.92-165C>T	NM_032861.3	
SERAC1	Chr6:158576622	c.92-239G>C	NM_032861.3	
SIL1	Chr5:138283180	c.1030-18G>A	NM_022464.4	rs769052639
SLC20A2	Chr8:42328683	c.289+937G>A	NM_006749.4	
SLC2A1	Chr1:43395462	c.680-11G>A	NM_006516.2	
SLC2A1	Chr1:43424429	c.-107G>A	NM_006516.2	
SLC52A2	Chr8:145582843	c.-110-1G>A	NM_024531.4	
STUB1	Chr16:732729	c.*240T>C	NM_005861.2	
SYNE1	Chr6:152640163	c.16237-13C>G	NM_182961.3	
SYNE1	Chr6:152643033	c.15918-12A>G	NM_182961.3	rs606231134
TMEM231	Chr16:75575364	c.824-11T>C	NM_001077416.2	
TPP1	Chr11:6637752	c.887-18A>G	NM_000391.3	
TTC19	Chr17:15903121	c.-42G>T	NM_017775.3	rs769078093
WFS1	Chr4:6271704	c.-43G>T	NM_006005.3	

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

Repeat expansion variants are not detected by this panel. The following exons are not included in the panel as they are not

sufficiently covered with high quality sequence reads: *BEAN1* (NM_001178020:5), *CC2D2A* (NM_020785:7), *DHPS* (NM_001206974:1), *RPGRIP1L* (NM_015272:23), *SYT14* (NM_001146261:3), *TCTN1* (NM_001173976:2;NM_024549:6). 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

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.

#}

ICD codes

Commonly used ICD-10 codes when ordering the Ataxia Panel

ICD-10	Disease
G11.9	Cerebellar ataxia
G11.8	Spinocerebellar ataxia

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

- Ataxia Study Group
- Ataxia UK
- Episodic Ataxia
- GeneReviews - Episodic Ataxia Type 1
- GeneReviews - Episodic Ataxia Type 2
- GeneReviews - Hereditary Ataxia
- NORD - Autosomal Dominant Hereditary Ataxia
- NORD - Spinocerebellar Ataxia with Axonal Neuropathy
- National Ataxia Foundation
- Spinocerebellar Ataxia Australia
- euro-ataxia