Blueprint Genetics

Metabolic Myopathy and Rhabdomyolysis Panel

Test code: ME1401

Is a 127 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 medical condition associated with rhabdomyolysis. The genes on this panel are included in the Comprehensive Metabolism Panel.

About Metabolic Myopathy and Rhabdomyolysis

Rhabdomyolysis is a medical condition in which damaged striated skeletal muscles break down easily and rapidly. Some end products of this lysis, such as myoglobin, are toxic to kidneys and may cause acute renal failure. Symptoms include muscle pain and vomiting. Common and important causes of rhabdomyolysis include several common situations, such as drugs and toxins, infections, hyperthermia, strong physical exercise and car accidents. However, recurrent rhabdomyolysis is often genetic in nature. The genetic causes for rhabdomyolysis include metabolic myopathy, disorders of intramuscular calcium release, mitochondrial disorders and muscular dystrophies. Metabolic myopathies are a group of genetic muscular diseases resulting from defective metabolism affecting primarily muscles. These myopathies are typically subdivided into three categories: i) glycogen storage diseases, ii) lipid storage diseases and iii) disorders of purine metabolism, all of which are associated with specific enzymatic defects that prevent adequate energy and ATP levels for muscle cells. This panel includes genes associated with all medical conditions that can cause rhabdomyolysis of genetic origin. The prevalence of rhabdomyolysis is not known.

Availability

4 weeks

Gene Set Description

Genes in the Metabolic Myopathy and Rhabdomyolysis Panel and their clinical significance

Gene	Associated phenotypes	Inheritance	ClinVar	HGMD
ACAD9	Acyl-CoA dehydrogenase family, deficiency	AR	26	61
ACADL	Long chain acyl-CoA dehydrogenase deficiency	AD/AR		1
ACADM	Acyl-CoA dehydrogenase, medium chain, deficiency	AR	104	169
ACADVL	Acyl-CoA dehydrogenase, very long chain, deficiency	AR	119	282
ADCK3	Coenzyme Q10 deficiency, Progressive cerebellar ataxia and atrophy, Spinocerebellar ataxia	AR	45	43
AGL	Glycogen storage disease	AR	142	245
AHCY	Hypermethioninemia with S-adenosylhomocysteine hydrolase deficiency	AR	3	9
ALDOA	Glycogen storage disease	AR	3	8
AMPD1	Myoadenylate deaminase deficiency	AR	5	10
ANO5	Gnathodiaphyseal dysplasia, LGMD2L and distal MMD3 muscular dystrophies	AD/AR	64	121

ATP2A1	Brody myopathy	AR	19	18
B3GALNT2	Muscular dystrophy-dystroglycanopathy	AR	18	14
B4GAT1	Muscular dystrophy-dystroglycanopathy (congenital with brain and eye anomalies), type A, 13	AR	3	5
C10ORF2	Perrault syndrome, Mitochondrial DNA depletion syndrome, Progressive external ophthalmoplegia with mitochondrial DNA deletions, autosomal dominant, 3	AD/AR	37	80
CAPN3	Muscular dystrophy, limb-girdle, Eosinophilic myositis	AD/AR	184	437
CASQ1	Myopathy, vacuolar, with CASQ1 aggregates	AD	2	5
CAV3	Creatine phosphokinase, elevated serum, Hypertrophic cardiomyopathy (HCM), Long QT syndrome, Muscular dystrophy, limb-girdle, type IC, Myopathy, distal, Tateyama type, Rippling muscle disease 2	AD/AR	23	50
CHKB	Muscular dystrophy, congenital, megaconial	AR	11	27
COQ2	Coenzyme Q10 deficiency	AR	16	31
CPT2	Carnitine palmitoyltransferase II deficiency	AR	72	111
CTDP1	Congenital cataracts, facial dysmorphism, and neuropathy	AR	1	1
DAG1	Muscular dystrophy-dystroglycanopathy	AR	12	10
DGUOK	Mitochondrial DNA depletion syndrome, Portal hypertension, noncirrhotic, Progressive external ophthalmoplegia with mitochondrial DNA deletions, autosomal recessive 4	AR	23	62
DMD	Becker muscular dystrophy, Duchenne muscular dystrophy, Dilated cardiomyopathy (DCM)	XL	832	3915
DNAJB6	Muscular dystrophy, limb-girdle	AD	11	17
DPM1	Congenital disorder of glycosylation	AR	9	8
DPM2	Congenital disorder of glycosylation	AR	2	2
DYSF	Miyoshi muscular dystrophy, Muscular dystrophy, limb-girdle, Myopathy, distal, with anterior tibial onset	AR	244	529
EMD	Emery-Dreifuss muscular dystrophy	XL	48	113
ENO3	Glycogen storage disease	AR	3	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
FDX1L	Myopathy	AR	1	2
FHL1*	Myopathy with postural muscle atrophy, Emery-Dreifuss muscular dystrophy, Reducing bod myopathy	XL	26	62
FKRP	Muscular dystrophy-dystroglycanopathy	AR	66	140

FKTN	Muscular dystrophy-dystroglycanopathy, Dilated cardiomyopathy (DCM), Muscular dystrophy-dystroglycanopathy (limb-girdle)	AD/AR	45	58
FLAD1	Lipid storage myopathy due to FLAD1 deficiency (LSMFLAD)	AR	9	10
GAA	Glycogen storage disease	AR	193	573
GBE1	Glycogen storage disease	AR	36	70
GMPPB	Muscular dystrophy-dystroglycanopathy (congenital with brain and eye anomalies), Limb-girdle muscular dystrophy-dystroglycanopathy	AR	19	41
GYG1	Glycogen storage disease, Polyglucosan body myopathy 2	AR	9	16
GYS1	Glycogen storage disease	AR	8	5
HADHA	Trifunctional protein deficiency, Long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency	AR	65	71
HADHB	Trifunctional protein deficiency	AR	20	65
ISCU	Myopathy with lactic acidosis	AR	3	3
LAMA2	Muscular dystrophy, congenital merosin-deficient	AR	199	301
LAMP2	Danon disease	XL	62	101
LARGE	Muscular dystrophy-dystroglycanopathy	AR	19	27
LDHA	Glycogen storage disease	AR	1	9
LPIN1	Myoglobinuria, acute, recurrent	AR	6	29
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, Deafness, mitochondrial	Mitochondrial	17	
MT-CO2	Cytochrome c oxidase deficiency	Mitochondrial	8	
MT-CO3	Cytochrome c oxidase deficiency, Leber hereditary optic neuropathy	Mitochondrial	9	
MT-CYB		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		Mitochondrial	4
MT-TC	Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes	Mitochondrial	3
MT-TD		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		Mitochondrial	3
MT-TH		Mitochondrial	4
MT-TI		Mitochondrial	7
MT-TK	Myoclonic epilepsy with ragged red fibers, Leigh syndrome	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	Mitochondrial multisystemic disorder, Progressive external ophthalmoplegia, Mitochondrial Myopathy, Mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes	Mitochondrial	5
MT-TM	Leigh syndrome, Mitochondrial multisystemic disorder	Mitochondrial	1
MT-TN	Progressive external ophthalmoplegia, Mitochondrial multisystemic disorder	Mitochondrial	3
MT-TP		Mitochondrial	2
MT-TQ	Mitochondrial multisystemic disorder	Mitochondrial	2
MT-TR	Encephalopathy, mitochondrial	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	Hypertrophic cardiomyopathy (HCM), Leigh syndrome, Mitochondrial multisystemic disorder, Mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes	Mitochondrial	3	
MT-TW	Leigh syndrome, Myopathy, mitochondrial	Mitochondrial	8	
MT-TY	Mitochondrial multisystemic disorder	Mitochondrial	4	
MYH3	Arthrogryposis	AD/AR	21	45
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
OPA3	Optic atrophy, 3-methylglutaconic aciduria	AD/AR	13	15
PDSS2	Coenzyme Q10 deficiency	AR	8	4
PFKM	Glycogen storage disease	AR	12	26
PGAM2	Glycogen storage disease	AR	4	11
PGK1	Phosphoglycerate kinase 1 deficiency	XL	16	26
PGM1	Congenital disorder of glycosylation	AR	11	35
PHKA1	Glycogen storage disease	XL	9	8
PHKB	Glycogen storage disease	AR	9	26
PNPLA2	Neutral lipid storage disease with myopathy	AR	13	35
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
POLG2	Progressive external ophthalmoplegia with mitochondrial DNA deletions	AD	5	14
POMGNT1	Muscular dystrophy-dystroglycanopathy	AR	96	88
POMGNT2	Muscular dystrophy-dystroglycanopathy (congenital with brain and eye anomalies), type A, 8	AR	6	9
POMK	Congenital muscular dystrophy-dystroglycanopathy with brain and eye anomalies, type A, 12, Congenital muscular dystrophy-dystroglycanopathy with brain and eye anomalies, type C, 12, Muscle-eye brain disease, Walker-Warburg syndrome	AR	6	8
POMT1	Muscular dystrophy-dystroglycanopathy	AR	47	96
POMT2	Muscular dystrophy-dystroglycanopathy	AR	45	73
PYGM	Glycogen storage disease	AR	77	168
RBCK1	Polyglucosan body myopathy	AR	11	14
RRM2B	Progressive external ophthalmoplegia with mitochondrial DNA deletions, Mitochondrial DNA depletion syndrome	AD/AR	41	41

RYR1	Central core disease, Malignant hyperthermia, Minicore myopathy with external ophthalmoplegia, Centronuclear myopathy, Minicore myopathy, Multicore myopathy	AD/AR	241	666
SCN4A	Hyperkalemic periodic paralysis, Myotonia, potassium-aggravated, Paramyotonia congenita, Myasthenic syndrome, congenital, Normokalemic potassium-sensitive periodic paralysis	AD/AR	57	126
SGCA	Muscular dystrophy, limb-girdle	AR	60	100
SGCB	Muscular dystrophy, limb-girdle	AR	37	64
SGCD	Muscular dystrophy, limb-girdle, Dilated cardiomyopathy (DCM)	AR	21	27
SGCG	Muscular dystrophy, limb-girdle	AR	33	63
SIL1	Marinesco-Sjogren syndrome	AR	14	49
SLC22A5	Carnitine deficiency, systemic primary	AR	98	151
SLC25A20	Carnitine-acylcarnitine translocase deficiency	AR	15	42
STAC3	Native American myopathy		3	4
SUCLA2	Mitochondrial DNA depletion syndrome	AR	9	29
SUCLG1	Mitochondrial DNA depletion syndrome	AR	12	28
TANGO2	Metabolic encephalomyopathic crises, recurrent, with rhabdomyolysis, cardiac arrhythmias, and neurodegeneration (MECRCN)	AR	13	9
TCAP	Muscular dystrophy, limb-girdle, Hypertrophic cardiomyopathy (HCM), Dilated cardiomyopathy (DCM)	AD/AR	12	28
TK2	Mitochondrial DNA depletion syndrome	AR	38	52
TNPO3	Muscular dystrophy, limb-girdle	AD	3	5
TRIM32	Bardet-Biedl syndrome, Muscular dystrophy, limb-girdle	AR	13	16
TYMP	Mitochondrial DNA depletion syndrome	AR	84	94

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Some, or all, of the gene is duplicated in the genome. Read more.

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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 (#). Due to possible limitations these genes may not be available as single gene tests.

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
ACADM	Chr1:76200457	c.388-19T>A	NM_000016.4	
ACADM	Chr1:76211473	c.600-18G>A	NM_000016.4	rs370523609
ACADVL	Chr17:7123160	c.-144_-132delCCCAGCATGCCCCinsT	NM_000018.3	
ACADVL	Chr17:7125469	c.822-27C>T	NM_001270447.1	rs374911841
ACADVL	Chr17:7125485	c.822-11T>G	NM_001270447.1	
ACADVL	Chr17:7126199	c.1146+15C>T	NM_001270447.1	rs202237278
ACADVL	Chr17:7126948	c.1252-15A>G	NM_001270447.1	rs765390290
ACADVL	Chr17:7127894	c.1747+23C>T	NM_001270447.1	rs147546456
ADCK3	Chr1:227174508	c.*72dupG	NM_020247.4	
AGL	Chr1:100381954	c.4260-12A>G	NM_000028.2	rs369973784
CAPN3	Chr15:42678352	c.380-13T>A	NM_000070.2	
CAPN3	Chr15:42695919	c.1746-20C>T	NM_000070.2	
CAPN3	Chr15:42697047	c.-188G>C	NM_173089.1	
CAPN3	Chr15:42702715	c.2184+21G>A	NM_000070.2	rs763572829
CAPN3	Chr15:42702770	c.2185-16A>G	NM_000070.2	
DGUOK	Chr2:74177650	c.444-62C>A	NM_080916.2	
DGUOK	Chr2:74177701	c.444-11C>G	NM_080916.2	rs536746349
DMD	ChrX:31165653	c.10554-18C>G	NM_004006.2	
DMD	ChrX:31200680	c.9974+175T>A	NM_004006.2	
DMD	ChrX:31224814	c.9564-30A>T	NM_004006.2	
DMD	ChrX:31225211	c.9564-427T>G	NM_004006.2	
DMD	ChrX:31226400	c.9563+1215A>G	NM_004006.2	
DMD	ChrX:31229031	c.9362-1215A>G	NM_004006.2	
DMD	ChrX:31241047	c.9361+117A>G	NM_004006.2	
DMD	ChrX:31279293	c.9225-160A>G	NM_004006.2	
DMD	ChrX:31279418	c.9225-285A>G	NM_004006.2	
DMD	ChrX:31279420	c.9225-287C>A	NM_004006.2	
DMD	ChrX:31279780	c.9225-647A>G	NM_004006.2	rs398124091

DMD	ChrX:31279781	c.9225-648A>G	NM_004006.2	rs398124084
DMD	ChrX:31332523	c.9224+9192C>A	NM_004006.2	
DMD	ChrX:31382270	c.9085-15519G>T	NM_004006.2	
DMD	ChrX:31613687	c.8217+32103G>T	NM_004006.2	
DMD	ChrX:31627738	c.8217+18052A>G	NM_004006.2	
DMD	ChrX:31697714	c.7661-11T>C	NM_004006.2	
DMD	ChrX:31897527	c.6913-4037T>G	NM_004006.2	
DMD	ChrX:31983146	c.6614+3310G>T	NM_004006.2	rs797045526
DMD	ChrX:32274692	c.6290+30954C>T	NM_004006.2	
DMD	ChrX:32305833	c.6118-15A>G	NM_004006.2	
DMD	ChrX:32360414	c.5740-15G>T	NM_004006.2	
DMD	ChrX:32366860	c.5326-215T>G	NM_004006.2	
DMD	ChrX:32379144	c.5325+1743_5325+1760delTATTAAAAAATGGGTAGA	NM_004006.2	
DMD	ChrX:32398808	c.4675-11A>G	NM_004006.2	
DMD	ChrX:32460274	c.3787-843C>A	NM_004006.2	
DMD	ChrX:32470726	c.3603+2053G>C	NM_004006.2	
DMD	ChrX:32479316	c.3432+2240A>G	NM_004006.2	
DMD	ChrX:32479520	c.3432+2036A>G	NM_004006.2	
DMD	ChrX:32669100	c.961-5831C>T	NM_004006.2	rs398124099
DMD	ChrX:32669194	c.961-5925A>C	NM_004006.2	
DMD	ChrX:32716130	c.832-15A>G	NM_004006.2	rs72470513
DMD	ChrX:32756908	c.650-39498A>G	NM_004006.2	
DMD	ChrX:32827744	c.531-16T>A/G	NM_004006.2	
DMD	ChrX:32827744	c.531-16T>A	NM_004006.2	
DMD	ChrX:32827744	c.531-16T>G	NM_004006.2	
DMD	ChrX:32841967	c.265-463A>G	NM_004006.2	
DMD	ChrX:33032666	c.93+5590T>A	NM_004006.2	
DMD	ChrX:33192452	c.31+36947G>A	NM_004006.2	
DMD	ChrX:33229483	c.-54T>A	NM_004006.2	
DYSF	Chr2:71817308	c.3443-33A>G	NM_003494.3	rs786205083
DYSF	Chr2:71840553	c.4410+13T>G	NM_003494.3	
DYSF	Chr2:71889030	c.4886+1249G>T	NM_003494.3	
DYSF	Chr2:71900503	c.5668-824C>T	NM_003494.3	
DYSF	Chr2:71913729	c.*107T>A	NM_003494.3	rs11903223
EMD	ChrX:153608559	c.266-27_266-10delTCTGCTACCGCTGCCCCC	NM_000117.2	

ETFDH	Chr4:159593534	c.-75A>G	NM_004453.2	
ETFDH	Chr4:159602711	c.176-636C>G	NM_004453.2	
FKRP	Chr19:47249328	c.-272G>A	NM_024301.4	
FKTN	Chr9:108368857	c.648-1243G>T	NM_006731.2	
GAA	Chr17:78078341	c.-32-13T>G	NM_000152.3	rs386834236
GAA	Chr17:78078341	c.-32-13T>A	NM_000152.3	
GAA	Chr17:78078351	c.-32-3C>A/G	NM_000152.3	
GAA	Chr17:78078352	c.-32-2A>G	NM_000152.3	
GAA	Chr17:78078353	c.-32-1G>C	NM_000152.3	
GAA	Chr17:78078369	c.-17C>T	NM_000152.3	
GAA	Chr17:78082266	c.1076-22T>G	NM_000152.3	rs762260678
GAA	Chr17:78090422	c.2190-345A>G	NM_000152.3	
GAA	Chr17:78092432	c.2647-20T>G	NM_000152.3	
GBE1	Chr3:81542964	c.2053-3358_2053-3350delGTGTGGTGGinsTGTTTTTTACATGACAGGT	NM_000158.3	rs869320698
GMPPB	Chr3:49761246	c.-87C>T	NM_013334.3	rs780961444
GYG1	Chr3:148717967	c.481+3276C>G	NM_004130.3	
HADHB	Chr2:26500642	c.442+614A>G	NM_000183.2	
HADHB	Chr2:26500691	c.442+663A>G	NM_000183.2	
ISCU	Chr12:108961426	c.418+382G>C	NM_213595.2	rs767000507
LAMA2	Chr6:129633984	c.3175-22G>A	NM_000426.3	rs777129293
LAMA2	Chr6:129636608	c.3556-13T>A	NM_000426.3	rs775278003
LAMA2	Chr6:129714172	c.5235-18G>A	NM_000426.3	rs188365084
LAMA2	Chr6:129835506	c.8989-12C>G	NM_000426.3	rs144860334
OPA1	Chr3:193334932	c.449-34dupA	NM_130837.2	
OPA1	Chr3:193374829	c.2179-40G>C	NM_130837.2	
PFKM	Chr12:48535459	c.1626-64A>G	NM_001166686.1	
PGK1	ChrX:77381262	c.1214-25T>G	NM_000291.3	
PGM1	Chr1:64113966	c.1199-222G>T	NM_001172818.1	
POMT1	Chr9:134379574	c.-30-2A>G	NM_007171.3	
POMT2	Chr14:77751989	c.1333-14G>A	NM_013382.5	
PYGM	Chr11:64523631	c.661-601G>A	NM_005609.2	
PYGM	Chr11:64525847	c.425-26A>G	NM_005609.2	rs764313717
RYR1	Chr19:38997317	c.8692+131G>A	NM_000540.2	
RYR1	Chr19:39074134	c.14647-1449A>G	NM_000540.2	rs193922886
SGCA	Chr17:48246419	c.585-31_585-23delTCTGCTGAC	NM_000023.2	

SGCA	Chr17:48246421	c.585-31_585-24delTCTGCTGA	NM_000023.2	
SGCA	Chr17:48247492	c.748-12_748-11delCTinsAA	NM_000023.2	
SGCG	Chr13:23755086	c.-127_-121delACAGTTG	NM_000231.2	rs1422849467
SGCG	Chr13:23755215	c.-1+1G>T	NM_000231.2	
SIL1	Chr5:138283180	c.1030-18G>A	NM_022464.4	rs769052639
SLC22A5	Chr5:131714054	c.394-16T>A	NM_003060.3	rs775097754
SLC22A5	Chr5:131722665	c.825-52G>A	NM_003060.3	

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: *B3GALNT2* (NM_001277155:2), *TK2* (NM_001271934:3). 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 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).

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.

The performance metrics listed below are from an initial validation performed at our main laboratory in Finland. The performance metrics of our laboratory in Seattle, WA, are equivalent.

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%
Microdeletion/-duplication sdrs (large CNVs, n=37))		
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.

	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 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. If the test includes the mitochondrial genome the target region gene list contains the mitochondrial genes. 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 suboptimal coverage (<20X for nuclear genes and <1000X for mtDNA) 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 ACMG guideline 2015.

The final step in the analysis is orthogonal confirmation. Sequence and copy number variants classified as pathogenic, likely pathogenic and variants of uncertain significance (VUS) are confirmed using bi-directional Sanger sequencing or by orthogonal methods such as qPCR/ddPCR when they do not meet our stringent NGS quality metrics for a true positive call.

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.

CPT code(s) *

81161, 81404 x7, 81405 x15, 81406 x12, 81407 x2, 81408 x3, 81479, 81460, 81465

* The CPT codes provided are based on AMA guidelines and are for informational purposes only. CPT coding is the sole responsibility of the billing party. Please direct any questions regarding coding to the payer being billed.

ICD Codes

Refer to the most current version of ICD-10-CM manual for a complete list of ICD-10 codes.

Sample Requirements

- Blood (min. 1ml) in an EDTA tube
- Extracted DNA, min. 2 µg in TE buffer or equivalent
- Saliva (Please see Sample Requirements for accepted saliva kits)

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

We do not accept DNA samples isolated from formalin-fixed paraffin-embedded (FFPE) tissue. In addition, if the patient is affected with a hematological malignancy, DNA extracted from a non-hematological source (e.g. skin fibroblasts) is strongly recommended.

Please note that, in rare cases, mitochondrial genome (mtDNA) variants may not be detectable in blood or saliva in which case DNA extracted from post-mitotic tissue such as skeletal muscle may be a better option.

Read more about our sample requirements here.

For Patients

Other

- American College of Rheumatology - Metabolic Myopathies
- Association for Glycogen Storage Disease
- Association for Glycogen Storage Disease UK
- Children's Fund for Glycogen Storage Disease Research
- Patient.info - Rhabdomyolysis