Blueprint Genetics

Retinitis Pigmentosa Panel

Test code: OP0901

Is a 153 gene panel that includes assessment of non-coding variants.

In addition, it also includes the maternally inherited mitochondrial genome. Is ideal for patients with a clinical suspicion /diagnosis of isolated retinitis pigmentosa. The genes included on this panel are included in the Retinal Dystrophy Panel.

For patients with syndromic retinitis pigmentosa, we recommend the Retinal Dystrophy Panel.

The panel covers genes associated with autosomal recessive, autosomal dominant and X-linked forms of retinitis pigmentosa (RP). Clinical utility of this panel is estimated to be 57% for patients with autosomal recessive or dominant RP and 85% for patients with X-linked RP. Differential diagnosis includes choroideremia, gyrate atrophy of choroid and retina and X-linked retinoschisis. For patients with syndromic RP, we recommend to choose Retinal Dystrophy Panel.

About Retinitis Pigmentosa

Retinitis pigmentosa (RP) is a group of inherited disorders in which abnormalities of the photoreceptors (rods and cones) or the retinal pigment epithelium lead to progressive visual loss. RP can be isolated or syndromic. Nonsyndromic RP is extremely heterogeneous, both clinically and genetically, and it may be inherited in an autosomal dominant, autosomal recessive, or X-linked manner. Autosomal dominant RP is estimated to account for 15-25% of cases, autosomal recessive RP for 5-20% and X-linked 5-15% (GeneReviews). Sporadic cases are common (40-50%). Severity is partly correlated with the pattern of inheritance with X-linked cases having the most severe course. The major causative genes are *USH2A*, which is implicated in autosomal recessive RP, *RHO*, accounting for approximately 28% of autosomal dominant RP and *RPGR*, which is estimated to explain 70% of X-linked RP. The prevalence of RP is reported to be 1:4,000 to 1:5,000.

Availability

Results in 3-4 weeks

Gene set description

Genes in the Retinitis Pigmentosa Panel and their clinical significance

Gene	Associated phenotypes	Inheritance	ClinVar	HGMD
ABCA4	Stargardt disease, Retinitis pigmentosa, Cone rod dystrophy, Retinal dystrophy, early-onset severe, Fundus flavimaculatus	AR	308	1231
ABHD12	Polyneuropathy, hearing loss, ataxia, retinitis pigmentosa, and cataract	AR	16	20
ADIPOR1*	Complement system	AD/AR		4
AGBL5	Retinitis pigmentosa 75	AR	2	9
AHI1	Joubert syndrome	AR	62	93
AIPL1	Retinitis pigmentosa, Cone rod dystrophy, Leber congenital amaurosis	AD/AR	10	79
ARHGEF18	Retinitis pigmentosa 78	AR	5	6
ARL2BP	Retinitis pigmentosa with or without situs inversus	AR	4	4
ARL3	Retinitis pigmentosa, Joubert syndrome	AD/AR		1

ARL6	Bardet-Biedl syndrome, Retinitis pigmentosa	AR	14	21
BBS1	Bardet-Biedl syndrome	AR	66	103
BBS2	Bardet-Biedl syndrome, Retinitis pigmentosa	AR	58	91
BEST1	Vitreoretinochoroidopathy, Microcornea, Rod-cone dystrophy, Posterior staphyloma, Bestrophinopathy, Vitelliform macular dystrophy, Cataract, Retinitis pigmentosa, Macular dystrophy, vitelliform, adult-onset, Retinitis pigmentosa 50, Macular dystrophy, vitelliform 2, Best macular dystrophy, Bestrophinopathy, autosomal recessive	AD/AR	62	318
C1QTNF5	Late-onset retinal degeneration	AD	27	7
C21ORF2	Retinal dystrophy with or without macular staphyloma (RDMS), Spondylometaphyseal dysplasia, axial (SMDAX)	AR	13	22
C2ORF71	Retinitis pigmentosa	AR	17	51
C8ORF37	Retinitis pigmentosa, Cone rod dystrophy	AR	8	17
CA4	Retinitis pigmentosa 17	AD	3	10
CDHR1	Retinitis pigmentosa, Cone rod dystrophy	AR	12	48
CEP290*	Bardet-Biedl syndrome, Leber congenital amaurosis, Joubert syndrome, Senior-Loken syndrome, Meckel syndrome	AR	130	289
CERKL	Retinitis pigmentosa	AR	20	37
CHM	Choroideremia	XL	46	284
CLN3	Neuronal ceroid lipofuscinosis, type 3	AR	100	72
CLRN1	Retinitis pigmentosa, Usher sydnrome, type 3A	AR	24	39
CNGA1	Retinitis pigmentosa	AR	14	33
CNGB1	Retinitis pigmentosa	AR	25	61
CRB1	Retinitis pigmentosa, Pigmented paravenous chorioretinal atrophy, Leber congenital amaurosis	AR	54	334
CRX	Cone rod dystrophy, Leber congenital amaurosis	AD/AR	30	106
CTNNA1	Macular dystrophy, patterned 2	AD	6	10
CWC27	Retinitis pigmentosa with or without skeletal anomalies (RPSKA)	AR	5	7
CYP4V2	Retinitis pigmentosa, Bietti crystalline corneoretinal dystrophy	AR	31	94
DHDDS	Retinitis pigmentosa	AR	5	8
DHX38	Retinitis pigmentosa	AR		1
EYS*	Retinitis pigmentosa	AR	97	321
FAM161A	Retinitis pigmentosa	AR	14	20
FLVCR1	Ataxia, posterior column, with retinitis pigmentosa	AR	9	15

GNPTG	Mucolipidosis	AR	45	46
GUCY2D	Cone rod dystrophy, Leber congenital amaurosis	AD/AR	34	235
HGSNAT	Mucopolysaccharidosis (Sanfilippo syndrome), Retinitis pigmentosa	AR	43	72
HK1	Hemolytic anemia, nonspherocytic, due to hexokinase deficiency, Retinitis pigmentosa 79, Neuropathy, motor and sensory, Russe type (Charcot-Marie-Tooth disease type 4G)	AD/AR	9	7
IDH3A	Leber congenital amaurosis			7
IDH3B	Retinitis pigmentosa	AR	2	3
IFT140	Short -rib thoracic dysplasia with or without polydactyly, Asphyxiating thoracic dysplasia (ATD; Jeune)	AR	38	63
IMPDH1	Retinitis pigmentosa, Leber congenital amaurosis	AD	7	23
IMPG2	Retinitis pigmentosa, Vitelliform macular dystrophy	AD/AR	25	40
INPP5E	Joubert syndrome, Mental retardation, truncal obesity, retinal dystrophy, and micropenis (MORM syndrome)	AR	25	50
KIAA1549	Retinitis pigmentosa	AR	1	6
KIZ	Retinitis pigmentosa 69	AR	3	4
KLHL7	Retinitis pigmentosa, Retinitis pigmentosa 42, Cold-induced sweating syndrome 3	AD/AR	12	11
LCA5	Leber congenital amaurosis	AR	10	49
LRAT	Retinitis pigmentosa, juvenile, Leber congenital amaurosis, Retinitis punctata albescens, Retinal-dystrophy, early-onset severe	AR	8	23
MAK	Retinitis pigmentosa	AR	11	22
MERTK	Retinitis pigmentosa	AR	25	75
MFRP	Microphthalmia, isolated 5, Nanophthalmos 2, Retinitis pigmentosa, autosomal recessive	AR	27	30
MT-ATP6	Neuropathy, ataxia, and retinitis pigmentosa, Leber hereditary optic neuropathy, Ataxia and polyneuropathy, adult-onset, Cardiomyopathy, infantile hypertrophic, Leigh syndrome, Striatonigral degeneration, infantile, mitochondrial	Mitochondrial	19	
MT-ATP8	Cardiomyopathy, apical hypertrophic, and neuropathy, Cardiomyopathy, infantile hypertrophic	Mitochondrial	4	
MT-CO1	Myoglobinuria, recurrent, Leber hereditary optic neuropathy, Sideroblastic anemia, Cytochrome C oxidase deficiency	Mitochondrial	17	
MT-CO2	Cytochrome c oxidase deficiency	Mitochondrial	8	
MT-CO3	Cytochrome c oxidase deficiency, Leber hereditary optic neuropathy	Mitochondrial	9	
MT-CYB	Leber hereditary optic neuropathy	Mitochondrial	69	

MT-ND1	Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes, Leber hereditary optic neuropathy, Leber optic atrophy and dystonia	Mitochondrial	21
MT-ND2	Leber hereditary optic neuropathy, Mitochondrial complex I deficiency	Mitochondrial	6
MT-ND3	Leber optic atrophy and dystonia, Mitochondrial complex I deficiency	Mitochondrial	7
MT-ND4	Leber hereditary optic neuropathy, Leber optic atrophy and dystonia, Mitochondrial complex I deficiency	Mitochondrial	11
MT-ND4L	Leber hereditary optic neuropathy	Mitochondrial	2
MT-ND5	Myoclonic epilepsy with ragged red fibers, Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes, Leber hereditary optic neuropathy, Mitochondrial complex I deficiency	Mitochondrial	19
MT-ND6	Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes, Oncocytoma, Leber hereditary optic neuropathy, Leber optic atrophy and dystonia, Mitochondrial complex I deficiency	Mitochondrial	16
MT-RNR1	Deafness, mitochondrial	Mitochondrial	3
MT-RNR2	Chloramphenicol toxicity/resistance	Mitochondrial	2
MT-TA	Leber hereditary optic neuropathy, Mitochondrial multisystemic disorder, Progressive external ophthalmoplegia, Dilated cardiomyopathy (DCM)	Mitochondrial	4
MT-TC	Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes	Mitochondrial	3
MT-TD	Mitochondrial multisystemic disorder	Mitochondrial	1
MT-TE	Diabetes-deafness syndrome, Mitochondrial myopathy, infantile, transient, Mitochondrial myopathy with diabetes	Mitochondrial	5
MT-TF	Myoclonic epilepsy with ragged red fibers, Nephropathy, tubulointerstitial, Encephalopathy, mitochondrial, Epilepsy, mitochondrial, Myopathy, mitochondrial, Mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes	Mitochondrial	7
MT-TG	Hypertrophic cardiomyopathy, Encephalopathy, Myopathy	Mitochondrial	3
MT-TH	Mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes	Mitochondrial	4
MT-TI	Progressive external ophthalmoplegia	Mitochondrial	7
MT-TK	Myoclonic epilepsy with ragged red fibers	Mitochondrial	5
MT-TL1	Cytochrome c oxidase deficiency, Myoclonic epilepsy with ragged red fibers, Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes, Diabetes-deafness syndrome, Cyclic vomiting syndrome, SIDS, susceptibility to	Mitochondrial	14
MT-TL2	Progressive external ophthalmoplegia, Mitochondrial multisystemic disorder	Mitochondrial	5
MT-TM	Mitochondrial Myopathy, Leigh syndrome, Mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes	Mitochondrial	1

MT-TN	Progressive external ophthalmoplegia	Mitochondrial	3	
MT-TP	Mitochondrial multisystemic disorder	Mitochondrial	2	
MT-TQ	Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes, Encephalopathy	Mitochondrial	2	
MT-TR	Dilated cardiomyopathy (DCM)	Mitochondrial	2	
MT-TS1	Myoclonic epilepsy with ragged red fibers, Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes	Mitochondrial	10	
MT-TS2	Mitochondrial multisystemic disorder	Mitochondrial	2	
MT-TT		Mitochondrial	5	
MT-TV	Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes	Mitochondrial	3	
MT-TW	Leigh syndrome, Mitochondrial Myopathy	Mitochondrial	8	
MT-TY		Mitochondrial	4	
MVK	Mevalonic aciduria, Hyper-IgD syndrome, Porokeratosis 3, multiple types	AD/AR	35	181
NEK2	Retinitis pigmentosa 67	AR	1	1
NMNAT1	Leber congenital amaurosis	AR	20	74
NR2E3	Retinitis pigmentosa, Enhanced S-cone syndrome	AD/AR	19	77
NRL	Retinitis pigmentosa, Clumped pigmentary retinal degeneration	AD/AR	11	25
OAT	Gyrate atrophy of choroid and retina	AR	67	71
OFD1	Simpson-Golabi-Behmel syndrome, Retinitis pigmentosa, Orofaciodigital syndrome, Joubert syndrome	XL	153	160
PDE6A	Retinitis pigmentosa	AR	16	49
PDE6B	Retinitis pigmentosa, Night blindness, congenital stationary	AD/AR	35	125
PDE6G	Retinitis pigmentosa	AR	1	2
PEX1	Heimler syndrome, Peroxisome biogenesis factor disorder 1A, Peroxisome biogenesis factor disorder 1B	AR	112	134
PEX2	Zellweger syndrome, Peroxisome biogenesis disorder	AR	16	18
PEX7	Refsum disease, Rhizomelic CDP type 1	AR	44	53
PHYH	Refsum disease	AR	12	36
PITPNM3	Cone-rod dystrophy 5	AD	1	5
PLA2G5	Fleck retina, familial benign	AR	1	7
POMGNT1	Muscular dystrophy-dystroglycanopathy	AR	96	88
PRCD	Retinitis pigmentosa	AR	2	7

PROM1#	Stargardt disease, Retinitis pigmentosa, Cone rod dystrophy, Macular dystrophy, retinal,	AD/AR	22	80
PRPF3	Retinitis pigmentosa	AD	3	7
PRPF31	Retinitis pigmentosa	AD	36	165
PRPF4	Retinitis pigmentosa 70	AD	2	4
PRPF6	Retinitis pigmentosa 60	AD	4	11
PRPF8	Retinitis pigmentosa	AD	13	46
PRPH2	Choriodal dystrophy, central areolar, Macular dystrophy, vitelliform, Retinitis pigmentosa, Retinitis punctata albescens, Macula dystrophy, patterned	AD/AR	48	176
RBP3	Retinitis pigmentosa	AR	5	17
RBP4	Retinal dystrophy, iris coloboma, and comedogenic acne syndrome, Microphthalmia, isolated, with coloboma 10	AD/AR	8	7
RCBTB1	Retinal dystrophy with or without extraocular anomalies (RDEOA), Familial exudative vitreoretinopathy	AR	6	9
RDH12	Retinitis pigmentosa, Leber congenital amaurosis	AD/AR	23	102
RDH5	Fundus albipunctatus	AR	11	51
REEP6	Retinitis pigmentosa 77	AR	4	8
RGR	Retinitis pigmentosa	AD/AR	2	11
RHO	Retinitis pigmentosa, Night blindness, congenital stationary, Retinitis punctata albescens	AD/AR	58	212
RIMS1	Cone-rod dystrophy 7	AD	3	12
RLBP1	Newfoundland rod-cone dystrophy, Fundus albipunctatus, Bothnia retinal dystrophy, Retinitis punctata albescens	AR	9	37
ROM1	Retinitis pigmentosa 7, digenic	AD/AR	3	18
RP1	Retinitis pigmentosa	AD/AR	45	181
RP2	Retinitis pigmentosa	XL	26	118
RPE65	Retinitis pigmentosa, Leber congenital amaurosis	AR	31	197
RPGR	Retinitis pigmentosa, Cone-rod dystrophy, X-linked, 1, Macular degeneration, X-linked atrophic, Retinitis pigmentosa 3	XL	79	218
RPGRIP1	Cone rod dystrophy, Leber congenital amaurosis	AR	44	145
RS1	Retinoschisis	XL	44	262
SAG	Retinitis pigmentosa, Oguchi disease	AD/AR	6	15
SAMD11	Retinitis pigmentosa	AR	2	5

SCAPER	Retinal dystrophy, Retinitis pigmentosa, Intellectual disability, Bardet-Biedl syndrome	AR	4	7
SCLT1	Senior-Loken syndrome, Retinal dystrophy			3
SEMA4A	Retinitis pigmentosa, Cone rod dystrophy	AR	4	14
SLC7A14	Retinitis pigmentosa 68	AR	4	8
SNRNP200	Retinitis pigmentosa	AD	6	34
SPATA7	Leber congenital amaurosis, Retitinitis pigmentosa	AR	15	39
SPP2	Retinitis pigmentosa	AD	1	2
TOPORS	Retinitis pigmentosa	AD	7	22
TTC8	Bardet-Biedl syndrome, Retinitis pigmentosa	AR	5	16
TTPA	Ataxia with isolated vitamin E deficiency	AR	29	30
TUB	Retinal dystrophy and obesity	AR	1	2
TULP1	Retinitis pigmentosa, Leber congenital amaurosis	AR	24	74
USH1C	Deafness, Usher syndrome, type IC	AR	45	51
USH2A	Retinitis pigmentosa 39, Usher syndrome, type 2A	AR	401	1169
VPS13B	Cohen syndrome	AR	351	203
WDR19	Retinitis pigmentosa, Nephronophthisis, Short -rib thoracic dysplasia with or without polydactyly, Senior-Loken syndrome, Cranioectodermal dysplasia (Levin-Sensenbrenner) type 1, Cranioectodermal dysplasia (Levin-Sensenbrenner) type 2, Asphyxiating thoracic dysplasia (ATD; Jeune)	AR	33	43
ZNF408	Exudative vitreoretinopathy 6, Retinitis pigmentosa 72	AD/AR	3	9
ZNF513	Retinitis pigmentosa	AR	1	3

*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

ABCA4	Chr1:94461770	c.6730-19G>A	NM_000350.2	rs375179475
ABCA4	Chr1:94468019	c.6148-471C>T	NM_000350.2	
ABCA4	Chr1:94481967	c.5197–557G>T	NM_000350.2	
ABCA4	Chr1:94484001	c.5196+1137G>A	NM_000350.2	rs778234759
ABCA4	Chr1:94484001	c.5196+1137G>T	NM_000350.2	
ABCA4	Chr1:94484082	c.5196+1056A>G	NM_000350.2	
ABCA4	Chr1:94492936	c.4539+2065C>G	NM_000350.2	
ABCA4	Chr1:94492937	c.4539+2064C>T	NM_000350.2	
ABCA4	Chr1:94492973	c.4539+2028C>T	NM_000350.2	rs869320785
ABCA4	Chr1:94493000	c.4539+2001G>A	NM_000350.2	
ABCA4	Chr1:94493073	c.4539+1928C>T	NM_000350.2	
ABCA4	Chr1:94493272	c.4539+1729G>T	NM_000350.2	
ABCA4	Chr1:94493895	c.4539 +1106C>T	NM_000350.2	
ABCA4	Chr1:94493901	c.4539+1100A>G	NM_000350.2	
ABCA4	Chr1:94496509	c.4253+43G>A	NM_000350.2	
ABCA4	Chr1:94508465	c.3191–11T>A	NM_000350.2	
ABCA4	Chr1:94509047	c.3051-16T>A	NM_000350.2	
ABCA4	Chr1:94509799	c.3050+370C>T	NM_000350.2	
ABCA4	Chr1:94510683	c.2919-383C>T	NM_000350.2	
ABCA4	Chr1:94525509	c.2160+584A>G	NM_000350.2	
ABCA4	Chr1:94526934	c.1938-619A>G	NM_000350.2	
ABCA4	Chr1:94527698	c.1937+435C>G	NM_000350.2	
ABCA4	Chr1:94528120	c.1937+13T>G	NM_000350.2	
ABCA4	Chr1:94546780	c.859-506G>C	NM_000350.2	
ABCA4	Chr1:94546814	c.859–540C>G	NM_000350.2	
ABCA4	Chr1:94549781	c.769–784C>T	NM_000350.2	
ABCA4	Chr1:94561127	c.768+3223C>T	NM_000350.2	
ABCA4	Chr1:94566773	c.570+1798A>G	NM_000350.2	
ABCA4	Chr1:94576926	c.302+68C>T	NM_000350.2	rs761188244
ABCA4	Chr1:94577158	c.161–23T>G	NM_000350.2	
ABCA4	Chr1:94578638	c.67-16T>A	NM_000350.2	

BBS1	Chr11:66291105	c.951+58C>T	NM_024649.4	
BEST1	Chr11:61717900	c.-29+1G>T	NM_001139443.1	
BEST1	Chr11:61717904	c.-29+5G>A	NM_001139443.1	
C21ORF2	Chr21:45750232	c.1000-23A>T	NM_001271441.1	
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	
CHM	ChrX:85220593	c.315-1536A>G	NM_000390.2	
CHM	ChrX:85223644	c.315-4587T>A	NM_000390.2	
CHM	ChrX:85302626		NM_000390.2	
CHM	ChrX:85302634		NM_000390.2	
CHM	ChrX:85302634		NM_000390.2	
CHM	ChrX:85302644		NM_000390.2	
CLN3	Chr16:28493392	c.1056+34C>A	NM_000086.2	
CLN3	Chr16:28497984	c.461-13G>C	NM_000086.2	rs386833721
CLRN1	Chr3:150660197	c.254-649T>G	NM_001195794.1	rs976853535
DHDDS	Chr1:26774026	c.441-24A>G	NM_024887.3	rs764831063
EYS	Chr6:66417023	c.-448+5G>A	NM_001142800.1	
GNPTG	Chr16:1412562	c.610-16_609+28del	NM_032520.4	rs193302853
GUCY2D	Chr17:7906220	c.-9-137T>C	NM_000180.3	
HGSNAT	Chr8:43028824	c.821-28_821-10delTTGCTTATGCTTTGTACTT	NM_152419.2	
HK1	Chr10:71038447	c.-390-3838G>C	NM_033500.2	rs797044964
HK1	Chr10:71038467	c.-390-3818G>C	NM_033500.2	rs397514654
HK1	Chr10:71075518	c.27+14901A>G	NM_033500.2	rs187500777
IFT140	Chr16:1576595	c.2577+25G>A	NM_014714.3	rs1423102192
LRAT	Chr4:155670121	c.541-15T>G	NM_004744.3	rs779487944
MVK	Chr12:110029032	c.769-7dupT	NM_000431.2	rs104895348
NMNAT1	Chr1:10003560	c.-70A>T	NM_022787.3	
NMNAT1	Chr1:10003561	c.-69C>T	NM_022787.3	
NMNAT1	Chr1:10003580	c.-57+7T>G	NM_022787.3	

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	
PEX7	Chr6:137143759	c.-45C>T	NM_000288.3	rs267608252
PROM1	Chr4:15989860	c.2077-521A>G	NM_006017.2	rs796051882
PRPF31	Chr19:54631586	c.1073+20_1073+36delCGGTAGGCATGGGGGTC	NM_015629.3	
PRPF31	Chr19:54633399	c.1374+654C>G	NM_015629.3	
PRPF4	Chr9:116037909		NM_004697.4	rs541873609
RDH5	Chr12:56114302	c.-33+2dupT	NM_002905.3	
RPE65	Chr1:68910577	c.246-11A>G	NM_000329.2	
RPGR	ChrX:38128234		NM_000328.2	
RPGR	ChrX:38160137	c.1059+363G>A	NM_001034853.1	
RPGRIP1	Chr14:21789155	c.1468-263G>C	NM_020366.3	
RPGRIP1	Chr14:21789588	c.1611+27G>A	NM_020366.3	
RPGRIP1	Chr14:21793563	c.2367+23delG	NM_020366.3	rs781728563
RPGRIP1	Chr14:21793564	c.2367+23delG	NM_020366.3	
RPGRIP1	Chr14:21795769	c.2711-13G>T	NM_020366.3	rs369991630
USH2A	Chr1:215821092	c.14583-20C>G	NM_206933.2	
USH2A	Chr1:215967783	c.9959-4159A>G	NM_206933.2	
USH2A	Chr1:216039721	c.8845+628C>T	NM_206933.2	
USH2A	Chr1:216064540	c.7595-2144A>G	NM_206933.2	rs786200928
USH2A	Chr1:216247476	c.5573-834A>G	NM_206933.2	
USH2A	Chr1:216592035	c.486-14G>A	NM_206933.2	rs374536346
USH2A	Chr1:216596610	c.-259G>T	NM_206933.2	

Test Strengths

The majority of the X-linked RP is caused by mutations in the*RPGR* gene, which contains a mutational hotspot at a unique 567-aa exon called ORF15 accounting for two-thirds of all disease-causing mutations. The exon ORF15, however, includes a highly repetitive, purine-rich sequence, which generally performs poorly in NGS-based assays. Blueprint Genetics custom assay has good coverage (>20x) with high mapping rates (mapping quality >20) for 100.0% of the target regions in *RPGR* gene. Our validation showed high mean coverage of 139X for the *RPGR* gene. Thus, our NGS Panel is not expected to have major limitations in detecting variants in *RPGR* gene including ORF15 exon.

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: *CHM* (NM_001145414:5), *CNGA1* (NM_001142564:2), *HK1* (NM_001322365:5), *NEK2* (NM_001204182:8), *NMNAT1* (NM_001297779:5), *SCLT1* (NM_001300898:6). Genes with suboptimal coverage in our assay are marked with number sign (#) and genes with partial, or whole gene, segmental duplications in the human genome are marked with an asterisk (*) if they overlap with the UCSC pseudogene regions. Gene is considered to have suboptimal coverage when >90% of the gene's target nucleotides are not covered at >20x with mapping quality score (MQ>20) reads. The technology may have limited sensitivity to detect variants in genes marked with these symbols (please see the Panel content table above).

This test does not detect the following:

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

This test may not reliably detect the following:

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

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

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

Test performance

The Blueprint Genetics retinitis pigmentosa panel covers classical genes associated with Stargardt disease, x-linked

retinoschisis, retinitis pigmentosa, choroideremia and gyrate atrophy of choroid and retina. The genes on the panel have been carefully selected based on scientific literature, mutation databases and our experience.

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

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

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

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

	Sensitivity % (TP/(TP+FN)	**Specificity %**
Single nucleotide variants	99.89% (99,153/99,266)	>99.9999%
Insertions, deletions and indels by sequence analysis		
1-10 bps	96.9% (7,563/7,806)	>99.9999%
11-50 bps	99.13% (2,524/2,546)	>99.9999%
Copy number variants (exon level dels/dups)		
1 exon level deletion (heterozygous)	100% (20/20)	NA
1 exon level deletion (homozygous)	100% (5/5)	NA
1 exon level deletion (het or homo)	100% (25/25)	NA
2-7 exon level deletion (het or homo)	100% (44/44)	NA
1-9 exon level duplication (het or homo)	75% (6/8)	NA
Simulated CNV detection		
5 exons level deletion/duplication	98.7%	100.00%
Microdeletion/-duplication sdrs (large CNVs, n=37))		
Size range (0.1-47 Mb)	100% (37/37)	
The performance presented above reached by Blueprint Genetics high-quality, clinical grade NGS sequencing assay with the following coverage metrics		
Mean sequencing depth	143X	
Nucleotides with >20x sequencing coverage (%)	99.86%	

Performance of Blueprint Genetics Mitochondrial Sequencing Assay.

	Sensitivity %	Specificity %
ANALYTIC VALIDATION (NA samples; n=4)		
Single nucleotide variants		
Heteroplasmic (45-100%)	100.0% (50/50)	100.0%
Heteroplasmic (35-45%)	100.0% (87/87)	100.0%
Heteroplasmic (25-35%)	100.0% (73/73)	100.0%
Heteroplasmic (15-25%)	100.0% (77/77)	100.0%
Heteroplasmic (10-15%)	100.0% (74/74)	100.0%
Heteroplasmic (5-10%)	100.0% (3/3)	100.0%
Heteroplasmic (<5%)	50.0% (2/4)	100.0%
CLINICAL VALIDATION (n=76 samples)		
All types		
Single nucleotide variants n=2026 SNVs		
Heteroplasmic (45-100%)	100.0% (1940/1940)	100.0%
Heteroplasmic (35-45%)	100.0% (4/4)	100.0%
Heteroplasmic (25-35%)	100.0% (3/3)	100.0%
Heteroplasmic (15-25%)	100.0% (3/3)	100.0%
Heteroplasmic (10-15%)	100.0% (9/9)	100.0%
Heteroplasmic (5-10%)	92.3% (12/13)	99.98%
Heteroplasmic (<5%)	88.9% (48/54)	99.93%
Insertions and deletions by sequence analysis n=40 indels		
Heteroplasmic (45-100%) 1-10bp	100.0% (32/32)	100.0%
Heteroplasmic (5-45%) 1-10bp	100.0% (3/3)	100.0%
Heteroplasmic (<5%) 1-10bp	100.0% (5/5)	99,997%
SIMULATION DATA /(mitomap mutations)		
Insertions, and deletions 1-24 bps by sequence analysis; n=17		
Homoplasmic (100%) 1-24bp	100.0% (17/17)	99.98%
Heteroplasmic (50%)	100.0% (17/17)	99.99%
Heteroplasmic (25%)	100.0% (17/17)	100.0%
Heteroplasmic (20%)	100.0% (17/17)	100.0%
Heteroplasmic (15%)	100.0% (17/17)	100.0%

Heteroplasmic (10%)	94.1% (16/17)	100.0%
Heteroplasmic (5%)	94.1% (16/17)	100.0%
Copy number variants (separate artifical mutations; n=1500)		
Homoplasmic (100%) 500 bp, 1kb, 5 kb	100.0%	100.0%
Heteroplasmic (50%) 500 bp, 1kb, 5 kb	100.0%	100.0%
Heteroplasmic (30%) 500 bp, 1kb, 5 kb	100.0%	100.0%
Heteroplasmic (20%) 500 bp, 1kb, 5 kb	99.7%	100.0%
Heteroplasmic (10%) 500 bp, 1kb, 5 kb	99.0%	100.0%
The performance presented above reached by following coverage metrics at assay level (n=66)		
	Mean of medians	Median of medians
Mean sequencing depth MQ0 (clinical)	18224X	17366X
Nucleotides with >1000x MQ0 sequencing coverage (%) (clinical)	100%	
rho zero cell line (=no mtDNA), mean sequencing depth	12X	

Bioinformatics

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

Clinical interpretation

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

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

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

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

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

Our interpretation team analyzes millions of variants from thousands of individuals with rare diseases. Thus, our database, and our understanding of variants and related phenotypes, is growing by leaps and bounds. Our laboratory is therefore well positioned to re-classify previously reported variants as new information becomes available. If a variant previously reported by Blueprint Genetics is re-classified, our laboratory will issue a follow-up statement to the original ordering health care provider at no additional cost.

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ICD codes

Commonly used ICD-10 codes when ordering the Retinitis Pigmentosa Panel

ICD-10	Disease
F84.2	Rett syndrome
H35.50	Stargardt disease
Q14.1	X-linked retinoschisis
H49.40	Progressive external ophthalmoplegia
H35.50	Retinitis pigmentosa
H31.21	Choroideremia
E72.4	Gyrate atrophy of choroid and retina
G11.9	Hereditary ataxia
C94.2	Acute Megakaryoblastic Leukemia
K59.8	Chronic Intestinal Pseudoobstruction
T36.5	Adverse effect of aminoglycosides

G93.41	Metabolic Encephalopathy
H49.81	Kearns Sayre Syndrome
E88.42	MERFF Syndrome
H47.013	Nonarteritic Anterior Ischemic Optic Neuropathy
G60.2	Neuropathy in association with hereditary ataxia
G30	Alzheimer's Disease
G25.5	Chorea
G40	Epilepsy and recurrent seizures
I42	Cardiomyopathy
N26.9	Focal Segmental Glomerulosclerosis
G31.82	Leigh's Disease
H47.2	Leber's hereditary optic neuropathy
G71.3	Mitochondrial Myopathy
I42.1	Hypertrophic Cardiomyopathy
E11.9	Non-Insulin Dependent Diabetes Mellitus
Z86.74	Personal history of sudden cardiac arrest
H90.3	Sensorineural Hearing Loss

Accepted sample types

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

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

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

Resources

- Choroideremia Research Foundation
- Fighting Blindness - Retinitis Pigmentosa
- Fighting Blindness - Retinitis Pigmentosa
- GeneReviews - Retinitis Pigmentosa
- GeneReviews - X-linked Retinoschisis
- GeneReviews - X-linked retinoschisis
- NORD - Choroideremia
- Retina International - Stargardt Disease
- Royal National Institute of Blind People - Retinitis Pigmentosa
- Royal National Institute of Blind People - Stargardt Disease