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Retinitis Pigmentosa/Leber Congenital Amaurosis Panel

Retinitis pigmentosa (RP) is a heterogeneous group of disorders affecting the photoreceptors (rods and cones) and retinal pigment epithelium, leading to visual deterioration. Leber congenital amaurosis (LCA) is a severe retinal dystrophy, with onset in the first year of life. Genetic sequencing and deletion/duplication testing is preferred to confirm a diagnosis of inherited retinal diseases, including RP, LCA, Stargardt disease, and cone-rod dystrophy.

TESTS TO CONSIDER

Retinitis Pigmentosa/Leber Congenital Amaurosis Panel, Sequencing and Deletion/Duplication 2007085
Method: Massively Parallel Sequencing/Exonic Oligonucleotide-based CGH Microarray

Recommended test for confirming a diagnosis of inherited retinal disease, including RP, LCA, Stargardt disease, and cone-rod dystrophy

Familial Mutation, Targeted Sequencing 2001961
Method: Polymerase Chain Reaction/Sequencing

- Recommended test if there is a known familial sequence variant previously identified in a family member.
- A copy of the family member's lab report documenting the known familial variant is required.

DISEASE OVERVIEW

Symptoms

Retinitis Pigmentosa

- Most common clinical features:
  - Decreased visual acuity, high myopia, astigmatism
  - Night blindness; onset in childhood
  - Tunnel vision
  - Progressive loss of central vision; usually occurs in third decade of life
  - Various abnormalities on ophthalmic examination
  - Mild hearing loss
- Individuals with autosomal dominant RP generally have milder disease than those with autosomal recessive or X-linked RP

Leber Congenital Amaurosis

- Most common clinical features:
  - Initial symptom, poor visual acuity in first year of life
  - Severe retinal dystrophy
  - Congenital nystagmus
  - Poor to near-absent pupillary response
  - Photophobia

Incidence

- RP – 1/3,500-4,000
- LCA – ~1/33,000-50,000

Prevalence

Accounts for >5% of all inherited retinopathies

Inheritance

- RP – autosomal dominant, autosomal recessive, or X-linked recessive; digenic rarely reported
- LCA – autosomal recessive; autosomal dominant rare

TEST DESCRIPTION

See Genes Tested table for genes included in the panel.

Clinical Sensitivity

Variable, dependent on phenotype/condition

Limitations

- A negative result does not exclude a heritable form of RP or LCA.
- Diagnostic errors can occur due to rare sequence variations.
- Interpretation of this test result may be impacted if the individual has had an allogeneic stem cell transplantation.

- The following will not be evaluated:
  - Variants outside the coding regions and intron-exon boundaries of the targeted genes
  - Regulatory region variants and deep intronic variants
  - Breakpoints of large deletions/duplications
  - Deletions/duplications in *C8orf37, CHM, CLRN1, FAM161A, IMPG2, IQCB1, KIZ, MAK, NMNAT1, USH1C*
  - Noncoding transcripts
  - The following regions are not sequenced due to technical limitations of the assay:
    - *CNGA1* (NM_001142564) exon(s) 2
    - *CHM* (NM_001145414) exon(s) 5
    - *RPGR* (NM_001034853) exon 15b, also known as amino acids 737-998 or ORF15
- The following may not be detected:
  - Deletions/duplications/insertions of any size by massively parallel sequencing
  - Deletions/duplications less than 1kb in the targeted genes by array
  - Some variants due to technical limitations in the presence of pseudogenes, repetitive, or homologous regions
  - Low-level somatic variants
  - Single exon deletions/duplications in the following exons:

Gene	Exon(s)
CDHR1	(NM_033100) 1
CEP290	(NM_025114) 52
CNGA1	(NM_001142564) 2
CNGB1	(NM_001135639) 13
CNGB1	(NM_001297) 10, 14, 24, 30
FSCN2	(NM_001077182) 2, 4, 5
FSCN2	(NM_012418) 4
GUCY2D	(NM_000180) 11, 16
IMPDH1	(NM_000883) 1, 4, 7, 10
IMPDH1	(NM_001142574) 4
KLHL7	(NM_001031710) 1
MERTK	(NM_006343) 1
PROM1	(NM_006017) 26
PRPF3	(NM_004698) 9
PRPF31	(NM_015629) 11
RPGR	(NM_000328) 1, 2
RPGRIP1	(NM_020366) 10
SAG	(NM_000541) 13
SNRNP200	(NM_014014) 1, 43
SPATA7	(NM_018418) 4
TTC8	(NM_001288781) 8
TTC8	(NM_001288782) 6
TTC8	(NM_198309) 2
TULP1	(NM_003322) 3, 4, 5

Analytical Sensitivity

For massively parallel sequencing:

Variant Class	Analytical Sensitivity (PPA) Estimate[a] (%)	Analytical Sensitivity (PPA) 95% Credibility Region[a] (%)
SNVs	99.2	96.9-99.4
Deletions 1-10 bp	93.8	84.3-98.2
Deletions 11-44 bp	100	87.8-100
Insertions 1-10 bp	94.8	86.8-98.5
Insertions 11-23 bp	100	62.1-100

[a]Genes included on this test are a subset of a larger methods-based validation from which the PPA values are derived.

bp, base pairs; PPA, positive percent agreement; SNVs, single nucleotide variants

Genes Tested

Gene	MIM Number	Disorder	Inheritance
ABCA4	601691	Age-related macular degeneration 2	AD

Gene	MIM Number	Disorder	Inheritance
		Stargardt disease 1 Retinitis pigmentosa 19 Cone rode dystrophy 3	AR
AIPL1	604392	Retinitis Pigmentosa Leber congenital amaurosis 4	AR
BEST1	607854	Macular dystrophy vitelliform 2 Vitreoretinochoroidopathy Retinitis pigmentosa 50	AD
		Bestrophinopathy, autosomal recessive	AR
C8orf37	614477	Cone-rod dystrophy 16	AR
CA4	114760	Retinitis pigmentosa 17	AD
CDHR1	609502	Cone-rod dystrophy 15 Retinitis Pigmentosa 65	AR
CEP290	610142	Senior-Loken Syndrome 6 Leber congenital amaurosis 10	AR
CERKL	608381	Retinitis pigmentosa 26	AR
CHM	300390	Choroideremia	XLD
CLRN1	606397	Usher syndrome, type IIIA Retinitis pigmentosa 61	AR
CNGA1	123825	Retinitis pigmentosa 49	AR
CNGB1	600724	Retinitis pigmentosa 45	AR
CRB1	604210	Pigmented paravenous chorioretinal atrophy	AD
		Retinitis pigmentosa 12 Leber congenital amaurosis 8	AR
CRX	602225	Cone-rod dystrophy 2	AD
		Leber congenital amaurosis 7	AD, AR
DHDDS	608172	Retinitis pigmentosa 59	AR
		Developmental delay and seizures with or without movement abnormalities	AD
EYS	612424	Retinitis pigmentosa 25	AR
FAM161A	613596	Retinitis pigmentosa 28	AR
FSCN2	607643	Retinitis pigmentosa 30	AD
GUCY2D	600179	Leber congenital amaurosis 1	AR
		Cone-rod dystrophy 6	AD, AR
IDH3B	604526	Retinitis pigmentosa 46	AR
IMPDH1	146690	Retinitis pigmentosa 10 Leber congenital amaurosis 11	AD
IMPG2	607056	Retinitis pigmentosa 56	AR
		Macular dystrophy vitelliform, 5	AD
IQCB1	609237	Senior-Loken syndrome 5	AR
KIZ	615757	Retinitis pigmentosa 69	AR
KLHL7	611119	Retinitis pigmentosa 42	AD
		Crisponi/cold-induced sweating syndrome 3	AR
LCA5	611408	Leber congenital amaurosis 5	AR

Gene	MIM Number	Disorder	Inheritance
LRAT	604863	Leber congenital amaurosis 14 Juvenile retinitis pigmentosa	AR
MAK	154235	Retinitis pigmentosa 62	AR
MERTK	604705	Retinitis pigmentosa 38	AR
NMNAT1	608700	Leber congenital amaurosis 9	AR
NR2E3	604485	Enhanced S-cone syndrome	AR
		Retinitis pigmentosa 37	AD, AR
NRL	162080	Retinitis pigmentosa 27	AD
PCARE	613425	Retinitis pigmentosa 54	AR
PDE6A	180071	Retinitis pigmentosa 43	AR
PDE6B	180072	Night blindness, congenital stationary, autosomal dominant 2	AD
		Retinitis pigmentosa 40	AR
PRCD	610598	Retinitis pigmentosa 36	AR
PROM1	604365	Stargardt disease 4 Macular dystrophy, retinal, 2	AD
		Retinitis pigmentosa 41	AR
		Cone-rod dystrophy 12	AD, AR
PRPF3	607301	Retinitis pigmentosa 18	AD
PRPF31	606419	Retinitis pigmentosa 11	AD
PRPF8	607300	Retinitis pigmentosa 13	AD
PRPH2	179605	Retinitis fundus albipunctatus	AD, AR
		Macular dystrophy, patterned, 1 Macular dystrophy, vitelliform, 3 Choroidal dystrophy, central areolar 2	AD
		Retinitis pigmentosa 7	AD, AR, digenic
RDH12	608830	Leber congenital amaurosis13	AD, AR
RGR	600342	Retinitis pigmentosa 44	AD, AR
RHO	180380	Fundus albipunctatus	AD, AR
		Night blindness, congenital stationary, autosomal dominant 1	AD
		Retinitis pigmentosa 4	AD, AR rarely
RLBP1	180090	Fundus albipunctatus	AD, AR
		Bothnia retinal dystrophy Newfoundland rod-cone dystrophy	AR
ROM1	180721	Retinitis pigmentosa 7	AD
RP1	603937	Retinitis pigmentosa 1	AD, AR
RP2	300757	Retinitis pigmentosa 2	XL
RPE65	180069	Leber congenital amaurosis 2 Retinitis pigmentosa 20	AR
RPGR	312610	Retinitis pigmentosa 3 Retinitis pigmentosa, X-linked, and sinorespiratory infections, with or without deafness Macular degeneration, X-linked atrophic Cone-rod dystrophy, X-linked, 1	XL
RPGRIP1	605446	Cone-rod dystrophy 13 Leber congenital amaurosis 6	AR

Gene	MIM Number	Disorder	Inheritance
SAG	181031	Oguchi disease 1 Retinitis pigmentosa 47	AR
SEMA4A	607292	Retinitis pigmentosa 35	AD, AR
		Cone-rod dystrophy 10	AR
SNRNP200	601664	Retinitis pigmentosa 33	AD
SPATA7	609868	Leber congenital amaurosis 3 Juvenile retinitis pigmentosa	AR
TOPORS	609507	Retinitis pigmentosa 31	AD
TTC8	608132	Retinitis pigmentosa 51	AR
TULP1	602280	Retinitis pigmentosa 14 Leber congenital amaurosis 15	AR
USH1C	605242	Usher syndrome, type IC Deafness, autosomal recessive 18A	AR
USH2A	608400	Usher syndrome, type IIA Retinitis pigmentosa 39	AR

AD, autosomal dominant; AR, autosomal recessive; XL, X-linked recessive; XLD, X-linked dominant

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