Retinitis Pigmentosa/Leber Congenital Amaurosis Panel, 53 Genes

Indications for Ordering

- Individuals with a clinical diagnosis of
  - Retinitis pigmentosa (RP)
  - Leber congenital amaurosis (LCA)
  - Cone-rod dystrophy
  - Another related disorder of retinal function

Test Description

Massively parallel sequencing/exonic oligonucleotide-based comparative genomic hybridization (CGH) microarray

Tests to Consider

Primary tests

Retinitis Pigmentosa/Leber Congenital Amaurosis Panel, Sequencing and Deletion/Duplication, 53 Genes 2007085

- Preferred panel for confirming diagnosis of congenital retinal diseases

Related test

Familial Mutation, Targeted Sequencing 2001961

- Useful when a pathogenic familial variant identifiable by sequencing is known

Disease Overview

Incidence

- RP – 1/3,000-5,000
- LCA – ~1/30,000-81,000

Prevalence – accounts for >5% of all inherited retinopathies

Symptoms

RP

- Heterogeneous group of disorders
- Most common clinical features
  - Decreased visual acuity, high myopia, astigmatism
  - Night blindness
    - Typically occurs in childhood
- Tunnel vision
- Progressive loss of central vision
  - Typically occurs in third decade
- Ophthalmic examination
  - Dark pigmentary changes to the fundus
  - Attenuated retinal vessels
  - Cystoid macular edema
  - Waxy appearance to the optic disc pallor
  - Fine pigmented vitreous cells
  - Posterior subcapsular cataracts (39-72%)
  - Keratoconus
- Mild hearing loss
- Individuals with autosomal dominant RP generally have milder disease than those with autosomal recessive or X-linked RP

LCA

- 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
  - Keratoconus
  - High hyperopia (vision usually 20/400 or less)
  - Characteristic rubbing and poking of the eye (Franceschetti's oculo-digital sign)

Genetics

Genes – See table

Inheritance

- RP and LCA
  - Autosomal recessive
  - Autosomal dominant
  - X-linked – *RPGR*, *RP2*
  - Digenic (rare) – *PRPH2* , *ROM1*

Test Interpretation

Clinical sensitivity – unknown

Results

- Positive
  - Pathogenic variant detected
    - Diagnosis of suspected disorder confirmed
- Negative
  - No pathogenic variant detected
    - Risk of being affected with RP or LCA reduced but not eliminated
- Inconclusive
  - Sequencing and deletion/duplication may detect variants of unknown clinical significance

Limitations

- Only genes listed in table below will be analyzed
- Not evaluated/detected
  - Deep intronic variants
  - Regulatory region variants
  - Breakpoints of large deletions and/or duplications
  - Copy number variants smaller than 1 kb (1,000 base pairs) by deletion/duplication analysis
  - Variants in genes not in table below
  - The first exon of each gene with deletion/duplication analysis
  - Amino acids 737-998 (ORF15) of the *RPGR* gene
- Polymorphisms in RNA bait-binding site may compromise analytical specificity

Gene Symbol	Gene Name	NM #	OMIM #	Inherited		Proportion of RP or LCA Due to Variant	Variants in This Gene Have Been Associated With
				RP	LCA		
ABCA4	ATP-binding cassette, subfamily A (ABC1), member 4	000350	601691	AR		arRP – 2-5%	AR Stargardt disease; cone-rod dystrophy
AIPL1	Aryl hydrocarbon receptor interacting protein-like 1	014336	604392	AD	AR	adRP – rare LCA4 – 4-8%	Cone-rod dystrophy; AD retinopathy
BEST1	Bestrophin 1	004183	607854	AD		adRP – rare arRP – ≤1%	
C2ORF71	Chromosome 2 open reading frame 71	001029883	613425	AR		arRP – ≤1%	
CA4	Carbonic anhydrase 4	000717	600852	AD		adRP – rare	
CDHR1	Cadherin-related family member 1	033100	609502	AR			
CEP290	Centrosomal protein 290kDa	025114	610142		AR	LCA – ≤20%	Joubert syndrome; nephronophthisis; Meckel-Gruber syndrome
CERKL	Ceramide kinase-like	001030311	608381	AR		arRP – 3-4% in Spain	
CNGA1	Cyclic nucleotide gated channel alpha 1	001142564	123825	AR		arRP – 1-2%	
CNGB1	Cyclic nucleotide gated channel beta 1	001297	600724	AR		arRP – ≤1%	
CRB1	Crumbs homolog 1 (Drosophila)	201253	600105	AR	AR	arRP – 6-7% in Spain LCA – unknown	RP with Coats-like vasculopathy; RP with preserved para-arteriolar RPE (PPRPE)
CRX	Cone-rod homeobox	000554	120970	AD	AR AD	adRP – 1% LCA – ~3%	Cone-rod dystrophy
DHDDS	Dehydrodolichyl diphosphate synthase	024887	608172	AR		arRP – ≤1%	
EYS	Eyes shut homolog (Drosophila)	001142800	602772	AR		arRP – 10-30% in Spain; common in China	
FSCN2	Fascin homolog 2, actin-bundling protein, retinal (Strongylocentrotus purpuratus)	001077182	607643	AD		adRP – 3% in Japan; otherwise rare	
GUCA1B	Guanylate cyclase activator 1B (retina)	002098	602275	AD		adRP – 4-5% in Japan; rare in UK	
GUCY2D	Guanylate cyclase 2D, membrane (retina-specific)	000180	600179		AR	LCA – 6-21%	AD cone-rod dystrophy
IDH3B	Socitrate dehydrogenase 3 (NAD+) beta	006899	604526	AR		arRP – ≤1%	

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IMPDH1	(inosine 5'-monophosphate) dehydrogenase 1	000883	146690	AD	AR	adRP – 2-3% LCA – rare	
KLHL7	Kelch-like family member 7	001031710	611119	AD		adRP – 1-2%	
LCA5	Leber congenital amaurosis 5	181714	611408		AR	LCA – ~1-2%	
LRAT	Lecithin retinol acyltransferase (phosphatidylcholine – retinol O-acyltransferase)	004744	604863	AR	AR	arRP – ≤1% LCA – unknown	
MERTK	c-mer proto-oncogene tyrosine kinase	006343	604705	AR		arRP – ≤1%	
NR2E3	Nuclear receptor subfamily 2, group E, member 3	014249 *NR2E3*	604485	AD AR		adRP – 1-2% arRP – rare; found in Sephardic Jews in Portugal	AR enhanced S-cone syndrome
NRL	Neural retina leucine zipper	006177	162080	AD AR		adRP – rare arRP – rare	
PDE6A	Phosphodiesterase 6A, cGMP-specific, rod, alpha	000440	180071	AR		arRP – 2-5%	
PDE6B	Phosphodiesterase 6B, cGMP-specific, rod, beta	000283	180072	AR		arRP – 2-5%	
PRCD	Progressive rod-cone degeneration	001077620	610598	AR		arRP – ≤1%	
PROM1	Prominin 1	006017	604365	AR		arRP – ≤1	
PRPF3	Pre-mRNA processing factor 3	004698	601414	AD		adRP – 1% several families	
PRPF31	Pre-mRNA processing factor 31	015629	600138	AD		adRP – 5-10%	
PRPF8	Pre-mRNA processing factor 8	006445	600059	AD		adRP – 2-3%	
RD3	Retinal degeneration 3	183059	180040		AR	LCA – unknown	
RDH12	Retinol dehydrogenase 12 (all-trans/9-cis/11-cis)	152443	608830	AD	AR	adRP – unknown LCA – ~4%	Severe, progressive cone-rod dystrophy
PRPH2	PRPH2 peripherin 2 (retinal degeneration, slow)	000322	179605	AD		adRP – 5-10%	adMD; AD adult vitelliform MD; digenic RP with *ROM1*
RGR	Retinal G protein-coupled receptor	002921	600342	AR		arRP – ≤1%	AD coroidal sclerosis
RHO	Rhodopsin	000539	180380	AD AR		adRP – 20-30% adRP – ≤1T	AD CSNB
RLBP1	Retinaldehyde binding protein 1	000326	180090	AR		arRP – ≤1%	AR Bothnia dystrophy; AR retinitis punctata albescans; AR Newfoundland rod-cone dystrophy
ROM1	Retinal outer segment membrane protein 1	000327	180721	AD		Rare	Digenic RP with *PRPH2*
RP1	Retinitis pigmentosa 1 (autosomal dominant)	006269	180100	AD AR		adRP – 3-4% arRP – ≤1%	
RP2	Retinitis pigmentosa 2 (X-linked recessive)	006915	300757	XL		10-20%	Peripapillary and macular atrophy
RP9	Retinitis pigmentosa 9 (autosomal dominant)	203288	180104	AD		Rare	
RPE65	Retinal pigment epithelium-specific protein 65kDa	000329	180069	AR	AR	adRP – rare arRP – 2-5% LCA – 3-16%	

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RPGR	Retinitis pigmentosa GTPase regulator	000328	300029	XL		70-90%	XL CSNB; XL cone dystrophy 1; XLR atrophic MD; RP plus sensorineural hearing loss and recurrent sinopulmonary infection
RPGRIP1	Retinitis pigmentosa GTPase regulator interacting protein 1	020366	605446		AR	LCA – ~5%	AR cone-rod dystrophy
SAG	S-antigen; retina and pineal gland (arrestin)	000541	181031	AR		Rare arRP – 2-3% in Japan	AR Oguchi disease
SEMA4A	Sema domain, immunoglobulin domain (Ig), transmembrane domain (TM) and short cytoplasmic domain, (semaphorin) 4A	022367	607292	AD		adRP – 3-4% in Pakistan	
SNRNP200	Small nuclear ribonucleoprotein, 200–kd	014014	601664	AD		adRP – unknown	
SPATA7	Spermatogenesis associated 7	018418	604232	AR	AR	arRP – ≤1% LCA – unknown	
TOPORS	Topoisomerase I binding, arginine/serine-rich, E3 ubiquitin protein ligase	005802	609507	AD		adRP – 1%	
TTC8	Tetratricopeptide repeat domain 8	144596	608132	AR		arRP – ≤1%	
TULP1	Tubby like protein 1	003322	600132	AR	AR	arRP – ≤1% LCA – unknown	
USH2A	Usher syndrome 2A (autosomal recessive, mild)	206933	608400	AR		arRP – 10-15%	Usher syndrome, type 2
AD = autosomal dominant, AR = autosomal recessive, XL = X-linked							