Cataracts Test

Test Gene List:
ABCA3, ADAMTSL4, AGK, AKR1E2, ALDH18A1, BCOR, BEST1, BFSP1, BFSP2, CHMP4B, COL11A1, COL2A1, COL4A1, COL4A2, CRYAA, CRYAB, CRYBA1, CRYBA2, CRYBA4, CRYBB1, CRYBB2, CRYBB3, CRYGB, CRYGC, CRYGD, CRYGS, CTDP1, CYP27A1, CYP51A1, EPG5, EPHA2, FAM126A, FOXC1, FOXE3, FTL, FYCO1, FZD4, GALK1, GCNT2, GFER, GJA1, GJA3, GJA8, HMX1, HSF4, JAM3, LIM2, LSS, LONP1, MAF, MIP, MIR184, MYH9, NDP, NF2, NHS, OCRL, OPA3, P3H2, PAX6, PITX2, PITX3, PXDN, RAB18, RAB3GAP1, RAB3GAP2, RECQL4, RGS6, RNLS, RRAGA, SC5D, SIL1, SIPA1L3, SIX6, SLC16A12, SLC33A1, TBC1D20, TDRD7, TFAP2A, TMEM70, UNC45B, VIM, VSX2, WDR87, WFS1, WRN

Clinical Features:
Cataracts are occlusions of the lens of the eye which block or scatter light; they result from protein buildup or a defect in the development of the lens. Cataracts are typically a fairly common cause of age-related vision loss, but can also occur congenitally or at an early age. Cataracts are often accompanied by other eye abnormalities such as microopthalmia and glaucoma, and intervention requires surgical removal of the cataracts. The exact incidence of cataracts is unknown, but has been estimated at approximately 3-6/10,000 worldwide, with the incidence being higher in undeveloped countries than in developed countries.[1,2] Only approximately 18% of congenital cataract cases have a known family history.[3]

Genetics:
Cataracts can be either isolated or syndromic; additionally, when a cataract case has a Mendelian genetic component the inheritance pattern can be recessive, dominant, or X-linked, with dominant as the most common.

The results from this test will confirm a genetic basis for cataract cases and differentiate the individual's disorder from other disorders which present with cataracts. Identification of one or more causative variants can provide the physician and family with important information regarding prognosis, treatment, and recurrence risk in future offspring. It also provides other family members the option for variant-specific carrier testing and genetic counseling.

Test Methods:
Using genomic DNA extracted from the submitted specimen, the complete coding regions and splice site junctions of the genes tested are enriched using a proprietary targeted capture system developed by GeneDx for next-generation sequencing with CNV calling (NGS-CNV). The enriched targets are simultaneously sequenced with paired-end reads on an Illumina

platform. Bi-directional sequence reads are assembled and aligned to reference sequences based on NCBI RefSeq transcripts and human genome build GRCh37/UCSC hg19. After gene specific filtering, data are analyzed to identify sequence variants and most deletions and duplications involving coding exons; however, technical limitations and inherent sequence properties effectively reduce this resolution for some genes. Alternative sequencing or copy number detection methods are used to analyze or confirm regions with inadequate sequence or copy number data by NGS. Reportable variants include pathogenic variants, likely pathogenic variants and variants of uncertain significance. Likely benign and benign variants, if present, are not routinely reported but are available upon request.

The technical sensitivity of sequencing is estimated to be >99% at detecting single nucleotide events. It will not reliably detect deletions greater than 20 base pairs, insertions or rearrangements greater than 10 base pairs, or low-level mosaicism. The copy number assessment methods used with this test cannot reliably detect copy number variants of less than 500 base pairs or mosaicism and cannot identify balanced chromosome aberrations. Assessment of exon-level copy number events is dependent on the inherent sequence properties of the targeted regions, including shared homology and exon size.

Test Sensitivity:
Past studies have traditionally observed a genetic cause for cataracts in 10-39% of patients.[1,4] However, there are studies analyzing larger gene lists which have observed a genetic cause in 58-79% of congenital nonsyndromic cases.[2,3,5] This test is designed to detect variants in the majority of genes known to be associated with cataracts to date, and as such the clinical sensitivity for such cases is expected to align with these studies involving comprehensive gene lists. The methods utilized by this panel are expected to detect over 99% of sequencing variants present in the covered regions.

Gene	Protein	Inheritance	Disease Associations
ABCA3	ATP binding cassette subfamily A member 3	AD	Cataract-microcornea syndrome
ADAMTSL4	ADAMTS-like 4	AR	Ectopia lentis et pupillae
AGK	Acylglycerol kinase	AR	Cataract; Sengers syndrome
AKR1E2	Aldo-keto reductase family 1, member E2	AR	Congenital cataract
ALDH18A1	Aldehyde dehydrogenase 18 family member A1	AD; AR	Cutis laxa and hereditary spastic paraplegia
BCOR	BCL6 corepressor	XL	Syndromic microphthalmia
BEST1	Bestrophin 1	AD; AR	MRCS syndrome

Gene	Protein	Inheritance	Disease Associations
BFSP1	Beaded filament structural protein 1	AR	Juvenile cataract
BFSP2	Beaded filament structural protein 2	AD	Congenital cataract
CHMP4B	Charged multivesicular body protein 4B	AD	Cataract
COL11A1	Collagen type X1, alpha-1	AD	Stickler and Marshall
COL2A1	Collagen type II, alpha-1	AD	Stickler (and other AD CT disorders)
COL4A1	Collagen type IV, alpha-1	AD	Schizencephaly, unilateral
COL4A2	Collagen type IV, alpha-2	AD	Porencephaly, sporadic intracerebral hemorrhage, cerebellar atrophy, hydrocephalus, focal cortical dysplasia, migraines, cataracts, and high myopia
CRYAA	Crystallin alpha A	AD	Congenital cataract
CRYAB	Crystallin alpha B	AD; AR	Congenital cataract; posterior polar cataract
CRYBA1	Crystallin beta A1	AD	Cataract, syndromic
CRYBA2	Crystallin beta A2	AD	Cataract
CRYBA4	Crystallin beta A4	AD	Congenital lamellar cataract; cataract and microphthalmia; cataract and microcornea
CRYBB1	Crystallin beta B1	AD; AR	Cataract
CRYBB2	Crystallin beta B2	AD	Cataract
CRYBB3	Crystallin beta B3	AD; AR	Cataract
CRYGB	Crystallin gamma B	AD	Congenital cataract
CRYGC	Crystallin gamma C	AD	Cataract
CRYGD	Crystallin gamma D	AD	Pediatric cataract
CRYGS	Crystallin gamma S	AD	Congenital cataract
CYP27A1	Cytochrome P450 family 27 subfamily A member 1	AR	Cerebrotendinous xanthomatosis
CYP51A1	Cytochrome P450 family 51 subfamily A member 1	AR	Cataract
EPG5	Ectopic P-granules autophagy protein 5 homolog	AR	Vici syndrome
EPHA2	EPH receptor A2	AD; AR	Pediatric cataract

Gene	Protein	Inheritance	Disease Associations
FAM126A	Family with sequence similarity 126 member A	AR	Hypomyelination and congenital cataract (HCC)
FCP1	CTD phosphatase subunit 1	AR	Congenital cataracts, facial dysmorphism, and neuropathy
FOXC1	Forkhead box C1	AD	Axenfeld-Rieger syndrome
FOXE3	Forkhead box E3	AD	Eye developmental anomalies, autosomal dominant
FTL	Ferritin light chain	AD	Hyperferritinaemia-cataract syndrome
FYCO1	FYVE and coiled-coil domain containing 1	AR	Cataracts
FZD4	Frizzled class receptor 4	AD	familial exudative vitreoretinopathy (FEVR)
GALK1	Galactokinase 1	AR	Galactokinase deficiency
GCNT2	glucosaminyl (N-acetyl) transferase 2, I-branching enzyme	AR	Congenital cataract
GFER	Growth factor, ERV1-like	AR	Progressive mitochondrial myopathy, sensorineural hearing loss, developmental delay
GJA1	Gap junction protein alpha 1	AD; AR	Oculodentodigital dysplasia
GJA3	Gap junction protein alpha 3	AD	Cataract
GJA8	Gap junction protein alpha 8	AD	Congenital cataract
HMX1	H6 family homeobox 1	AR	Oculoauricular syndrome
HSF4	Heat shock transcription factor 4	AD	Cataract, autosomal dominant
JAM3	Junctional adhesion molecule 3	AR	Hemorrhagic destruction of brain, subependymal calcification, and cataracts
LIM2	Lens intrinsic membrane protein 2	AR	Cataract
LSS	2,3-oxidosqualene-lanosterol cyclase	AR	Cataract
LONP1	Lon peptidase 1	AR	CODAS syndrome
MAF	V-maf avian musculoaponeurotic fibrosarcoma oncogene homolog	AD	Cataract

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MIP	Major intrinsic protein of lens fiber	AD	Cataract
MIR184	Micro RNA 184	AD	EDICT syndrome; keratoconus; corneal anomalies
MYH9	Myosin, heavy chain 9, non-muscle	AD	Congenital onset thrombocytopenia, giant platelets, and inclusion bodies in leukocytes with later-onset SNHL, cataracts, and proteinuric nephropathy
NDP	Norrie disease (pseudoglioma)	XL	Norrie disease
NF2	Neurofibromin 2	AD	Neurofibromatosis type 2
NHS	NHS actin remodeling regulator	XL	Nance-Horan syndrome
OCRL	Phosphatidylinositol 4,5-bisphosphate-5-phosphatase	XL	Lowe oculocerebrorenal syndrome
OPA3	Outer mitochondrial membrane lipid metabolism regulator	AD	Optic atrophy with cataract; 3-methylglutaconic aciduria, type 3
P3H2	Prolyl 3-hydroxylase-2	AR	High myopia
PAX6	Paired box 6	AD	Aniridia
PITX2	Paired-like homeodomain transcription factor 2	AD	Axenfeld-Rieger syndrome, Anterior segment dysgenesis
PITX3	Paired-like homeodomain transcription factor 3	AD; AR	Congenital cataract; anterior segment mesenchymal dysgenesis
PXDN	Peroxidasin	AR	Ocular anterior segment dysgenesis
RAB18	RAB18, member RAS oncogene family	AR	Warburg micro syndrome
RAB3GAP1	RAB3 GTPase activating protein catalytic subunit 1	AR	Warburg micro syndrome
RAB3GAP2	RAB3 GTPase activating non-catalytic protein subunit 2	AR	Martsolf syndrome; Warburg micro syndrome
RECQL4	RecQ-like helicase 4	AR	Rothmund Thompson syndrome
RGS6	Regulator of G protein signaling 6	AR	congenital cataract, mental retardation, and microcephaly

Gene	Protein	Inheritance	Disease Associations
RNLS	Renalase	AR	Cataract
RRAGA	RAS-related GTP-binding protein A	AD	Cataract
SC5D	Sterol-C5-desaturase	AR	Lathosterolosis
SIL1	SIL1 nucleotide exchange factor	AR	Marinesco Sjogren syndrome
SIPA1L3	SIPA1-like protein	AR	Cataract
SIX6	SIX homeobox 6	AR	Micropthalmia; optic disc anomalies; anopthalmia
SLC16A12	Solute carrier family 16 member 12	AD	Cataract
SLC33A1	Solute carrier family 33 member 1	AR	Congenital cataracts, hearing loss, and neurodegeneration (CCHLND)
TBC1D20	TBC1 domain family member 20	AR	Warburg micro syndrome
TDRD7	Tudor domain containing 7	AR	Congenital cataract
TFAP2A	Transcription factor AP-2 alpha	AD	Branchiooculofacial syndrome
TMEM70	Transmembrane protein 70	AR	Mitochondrial complex V (ATP synthase) deficiency
UNC45B	Unc-45 myosin chaperone B	AD	Cataract
VIM	Vimentin	AD	Congenital cataract
VSX2	Visual system homeobox 2	AR	Microphthalmia, Anophthalmia, and Coloboma spectrum (MAC spectrum)
WDR87	WD repeat domain 87	AR	Cataract
WFS1	Wolframin ER transmembrane glycoprotein	AD; AR	Wolfram syndrome
WRN	Werner syndrome RecQ-like helicase	AR	Werner syndrome

References:

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