

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, CTD1P1, 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 opacities 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 microphthalmia 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 from the submitted specimen, the complete coding regions and splice site junctions of the genes on this panel 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. Alternative sequencing or copy number detection methods are used to analyze regions with inadequate sequence or copy number data. 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
<i>ABCA3</i>	ATP binding cassette subfamily A member 3	AD	Cataract-microcornea syndrome
<i>ADAMTSL4</i>	ADAMTS-like 4	AR	Ectopia lentis et pupillae
<i>AGK</i>	Acylglycerol kinase	AR	Cataract; Sengers syndrome
<i>AKR1E2</i>	Aldo-keto reductase family 1, member E2	AR	Congenital cataract
<i>ALDH18A1</i>	Aldehyde dehydrogenase 18 family member A1	AD; AR	Cutis laxa and hereditary spastic paraplegia
<i>BCOR</i>	BCL6 corepressor	XL	Syndromic microphthalmia
<i>BEST1</i>	Bestrophin 1	AD; AR	MRCS syndrome
<i>BFSP1</i>	Beaded filament structural protein 1	AR	Juvenile cataract
<i>BFSP2</i>	Beaded filament structural protein 2	AD	Congenital cataract

<i>CHMP4B</i>	Charged multivesicular body protein 4B	AD	Cataract
<i>COL11A1</i>	Collagen type X1, alpha-1	AD	Stickler and Marshall
<i>COL2A1</i>	Collagen type II, alpha-1	AD	Stickler (and other AD CT disorders)
<i>COL4A1</i>	Collagen type IV, alpha-1	AD	Schizencephaly, unilateral
<i>COL4A2</i>	Collagen type IV, alpha-2	AD	Porencephaly, sporadic intracerebral hemorrhage, cerebellar atrophy, hydrocephalus, focal cortical dysplasia, migraines, cataracts, and high myopia
<i>CRYAA</i>	Crystallin alpha A	AD	Congenital cataract
<i>CRYAB</i>	Crystallin alpha B	AD; AR	Congenital cataract; posterior polar cataract
<i>CRYBA1</i>	Crystallin beta A1	AD	Cataract, syndromic
<i>CRYBA2</i>	Crystallin beta A2	AD	Cataract
<i>CRYBA4</i>	Crystallin beta A4	AD	Congenital lamellar cataract; cataract and microphthalmia; cataract and microcornea
<i>CRYBB1</i>	Crystallin beta B1	AD; AR	Cataract
<i>CRYBB2</i>	Crystallin beta B2	AD	Cataract
<i>CRYBB3</i>	Crystallin beta B3	AD; AR	Cataract
<i>CRYGB</i>	Crystallin gamma B	AD	Congenital cataract
<i>CRYGC</i>	Crystallin gamma C	AD	Cataract
<i>CRYGD</i>	Crystallin gamma D	AD	Pediatric cataract
<i>CRYGS</i>	Crystallin gamma S	AD	Congenital cataract
<i>CTDP1</i>	CTD phosphatase subunit 1	AR	Congenital cataracts, facial dysmorphism, and neuropathy
<i>CYP27A1</i>	Cytochrome P450 family 27 subfamily A member 1	AR	Cerebrotendinous xanthomatosis
<i>CYP51A1</i>	Cytochrome P450 family 51 subfamily A member 1	AR	Cataract
<i>EPG5</i>	Ectopic P-granules autophagy protein 5 homolog	AR	Vici syndrome
<i>EPHA2</i>	EPH receptor A2	AD; AR	Pediatric cataract
<i>FAM126A</i>	Family with sequence similarity 126 member A	AR	Hypomyelination and congenital cataract (HCC)
<i>FOXC1</i>	Forkhead box C1	AD	Axenfeld-Rieger syndrome

<i>FOXE3</i>	Forkhead box E3	AD	Eye developmental anomalies, autosomal dominant
<i>FTL</i>	Ferritin light chain	AD	Hyperferritinaemia-cataract syndrome
<i>FYCO1</i>	FYVE and coiled-coil domain containing 1	AR	Cataracts
<i>FZD4</i>	Frizzled class receptor 4	AD	familial exudative vitreoretinopathy (FEVR)
<i>GALK1</i>	Galactokinase 1	AR	Galactokinase deficiency
<i>GCNT2</i>	glucosaminyl (N-acetyl) transferase 2, I-branching enzyme	AR	Congenital cataract
<i>GFER</i>	Growth factor, ERV1-like	AR	Progressive mitochondrial myopathy, sensorineural hearing loss, developmental delay
<i>GJA1</i>	Gap junction protein alpha 1	AD; AR	Oculodentodigital dysplasia
<i>GJA3</i>	Gap junction protein alpha 3	AD	Cataract
<i>GJA8</i>	Gap junction protein alpha 8	AD	Congenital cataract
<i>HMX1</i>	H6 family homeobox 1	AR	Oculoauricular syndrome
<i>HSF4</i>	Heat shock transcription factor 4	AD	Cataract, autosomal dominant
<i>JAM3</i>	Junctional adhesion molecule 3	AR	Hemorrhagic destruction of brain, subependymal calcification, and cataracts
<i>LIM2</i>	Lens intrinsic membrane protein 2	AR	Cataract
<i>LSS</i>	2,3-oxidosqualene-lanosterol cyclase	AR	Cataract
<i>LONP1</i>	Lon peptidase 1	AR	CODAS syndrome
<i>MAF</i>	V-maf avian musculoaponeurotic fibrosarcoma oncogene homolog	AD	Cataract
<i>MIP</i>	Major intrinsic protein of lens fiber	AD	Cataract
<i>MIR184</i>	Micro RNA 184	AD	EDICT syndrome; keratoconus; corneal anomalies

<i>MYH9</i>	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
<i>NDP</i>	Norrie disease (pseudoglioma)	XL	Norrie disease
<i>NF2</i>	Neurofibromin 2	AD	Neurofibromatosis type 2
<i>NHS</i>	NHS actin remodeling regulator	XL	Nance-Horan syndrome
<i>OCRL</i>	Phosphatidylinositol 4,5-bisphosphate-5-phosphatase	XL	Lowe oculocerebrorenal syndrome
<i>OPA3</i>	Outer mitochondrial membrane lipid metabolism regulator	AD	Optic atrophy with cataract; 3-methylglutaconic aciduria, type 3
<i>P3H2</i>	Prolyl 3-hydroxylase-2	AR	High myopia
<i>PAX6</i>	Paired box 6	AD	Aniridia
<i>PITX2</i>	Paired-like homeodomain transcription factor 2	AD	Axenfled-Rieger syndrome, Anterior segment dysgenesis
<i>PITX3</i>	Paired-like homeodomain transcription factor 3	AD; AR	Congenital cataract; anterior segment mesenchymal dysgenesis
<i>PXDN</i>	Peroxidasin	AR	Ocular anterior segment dysgenesis
<i>RAB18</i>	RAB18, member RAS oncogene family	AR	Warburg micro syndrome
<i>RAB3GAP1</i>	RAB3 GTPase activating protein catalytic subunit 1	AR	Warburg micro syndrome
<i>RAB3GAP2</i>	RAB3 GTPase activating non-catalytic protein subunit 2	AR	Martsof syndrome; Warburg micro syndrome
<i>RECQL4</i>	RecQ-like helicase 4	AR	Rothmund Thompson syndrome
<i>RGS6</i>	Regulator of G protein signaling 6	AR	congenital cataract, mental retardation, and microcephaly
<i>RNLS</i>	Renalase	AR	Cataract
<i>RRAGA</i>	RAS-related GTP-binding protein A	AD	Cataract
<i>SC5D</i>	Sterol-C5-desaturase	AR	Lathosterolosis

<i>SIL1</i>	SIL1 nucleotide exchange factor	AR	Marinesco Sjogren syndrome
<i>SIPA1L3</i>	SIPA1-like protein	AR	Cataract
<i>SIX6</i>	SIX homeobox 6	AR	Microphthalmia; optic disc anomalies; anophthalmia
<i>SLC16A12</i>	Solute carrier family 16 member 12	AD	Cataract
<i>SLC33A1</i>	Solute carrier family 33 member 1	AR	Congenital cataracts, hearing loss, and neurodegeneration (CCHLND)
<i>TBC1D20</i>	TBC1 domain family member 20	AR	Warburg micro syndrome
<i>TDRD7</i>	Tudor domain containing 7	AR	Congenital cataract
<i>TFAP2A</i>	Transcription factor AP-2 alpha	AD	Branchiooculofacial syndrome
<i>TMEM70</i>	Transmembrane protein 70	AR	Mitochondrial complex V (ATP synthase) deficiency
<i>UNC45B</i>	Unc-45 myosin chaperone B	AD	Cataract
<i>VIM</i>	Vimentin	AD	Congenital cataract
<i>VSX2</i>	Visual system homeobox 2	AR	Microphthalmia, Anophthalmia, and Coloboma spectrum (MAC spectrum)
<i>WDR87</i>	WD repeat domain 87	AR	Cataract
<i>WFS1</i>	Wolframin ER transmembrane glycoprotein	AD; AR	Wolfram syndrome
<i>WRN</i>	Werner syndrome RecQ-like helicase	AR	Werner syndrome

References:

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