Cataract Panel

PANEL GENE LIST:

ABCA3, ABHD5, 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, EBP, EPG5, EPHA2, ERCC2, ERCC5, ERCC6, ERCC8, EYA1, FAM126A, FOXC1, FOXE3, FTL, FYCO1, FZD4, GALK1, GALT, GCNT2, GFER, GJA1, GJA3, GJA8, HMX1, HSF4, JAM3, LIM2, LONP1, LSS, MAF, MAN2B1, MIP, MIR184, MYH9, NDP, NF2, NHS, OCRL, OPA3, PAX6, PEX11B, PEX7, 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 a fairly common cause of agerelated vision loss, but can also occur congenitally or at an early age. Cataracts are often accompanied by other eye abnormalities, such as micropthalmia and glaucoma, and intervention requires surgical removal of the cataracts. The exact incidence of cataracts is unknown, but it has been estimated to be approximately 3-6/10,000 worldwide, with a higher incidence in undeveloped countries.[1,2] Only approximately 18% of congenital cataract cases have a known family history.[3]

GENETICS:

Cataracts can occur as an isolated finding or are part of a genetic syndrome. Mendelian forms of cataract may be inherited as autosomal recessive, autosomal dominant, or X-linked traits, with autosomal dominant inheritance being the most common.

Genetic testing may provide the underlying genetic causes of cataract 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. For the *CRYBB2* gene, only whole gene deletions/duplications are reported. For the *EBP, ERCC8, FOXC1, FOXE3, HMX1, MAF* and *RECQL4* genes sequencing but not deletion/duplication analysis is performed.

CLINICAL SENSITIVITY:

Genetic studies have established a genetic cause for cataracts in 10-39% of patients.[1,4] However, when analyzing larger gene lists, a genetic cause may be identified in 58-79% of individuals with congenital non-syndromic cataract.[2,3,5] This test is designed to detect variants in the majority of genes known to be associated with non-syndromic cataracts and common forms of syndromic cataract. The clinical test sensitivity depends on a patient's specific diagnosis (see table below). The methods utilized by this panel are expected to detect over 99% of sequencing variants within the regions covered by the test.

Gene	Protein	Inheritance	Disease Associations
ABCA3	ATP binding cassette subfamily A member 3	AD	Cataract-Microcornea syndrome
ABHD5	Lysophosphatidic acid acyltransferase	AR	Chanarin-Dorfman syndrome (Neutral lipid storage disease with ichthyosis)
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
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
CTDP1	CTD phosphatase subunit 1	AR	Congenital cataracts facial dysmorphism and neuropathy syndrome (CCFDN)
CYP27A1	Cytochrome P450 family 27 subfamily A member 1	AR	Cerebro-ttendinous xanthomatosis
CYP51A1	Cytochrome P450 family 51 subfamily A member 1	AR	Cataract
EBP	EBP cholestenol delta-isomerase	XL	Chondrodysplasia punctata, X-linked dominant

EPG5	Ectopic P-granules autophagy protein 5 homolog	AR	Vici syndrome
EPHA2	EPH receptor A2	AD;AR	Pediatric cataract
ERCC2	ERCC excision repair 2, TFIIH core complex helicase subunit	AR	Cerebro-oculo-facio-skeletal syndrome 2
ERCC5	ERCC excision repair 5, endonuclease	AR	Xeroderma pigmentosum, group G
ERCC6	ERCC excision repair 6, chromatin remodeling factor	AD;AR	Cockayne syndrome, type B
ERCC8	ERCC excision repair 8, CSA ubiquitin ligase complex subunit	AR	Cockayne syndrome, type A
EYA1	EYA transcriptional coactivator and phosphatase 1	AD	Branchio-oto-renal syndrome 1, anterior segment anomalies, with or without cataracts
FAM126A	Family with sequence similarity 126 member A	AR	Hypomyelination and congenital cataract (HCC)
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 coiledcoil domain containing 1	AR	Cataracts
FZD4	Frizzled class receptor 4	AD	Familial Exudative Vitreoretinopathy (FEVR)
GALK1	Galactokinase 1	AR	Galactokinase deficiency
GALT	Galactose-1phosphate uridylyltransferase	AR	Galactosemia

GCNT2	Glucosaminyl (Nacetyl) 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	Oculo-dento-digital dysplasia
GJA3	Gap junction protein alpha 3	AD	Cataract
GJA8	Gap junction protein alpha 8	AD	Cataract 1, with or without micorcornea
HMX1	H6 family homeobox 1	AR	Oculoauricular syndrome
HSF4	Heat shock transcription factor 4	AD;AR	Cataract 5
JAM3	Junctional adhesion molecule 3	AR	Hemorrhagic destruction of the brain, subependymal calcification, and cataracts
LIM2	Lens intrinsic membrane protein 2	AR	Cataract 19
LONP1	Ion peptidase 1, mitochondrial	AR;AD	CODAS syndrome
LSS	Lanosterol synthase	AR	LSS-related neuroectodermal disorder
MAF	MAF bZIP transcription factor	AD	Cataract 21
MAN2B1	Mannosidase alpha class 2B member 1	AR	Mannosidosis, alpha I and II
MIP	Major intrinsic protein of lens fiber	AD	Cataract 15
MIR184	MicroRNA 184	AD	EDICT syndrome
MYH9	Myosin heavy chain 9	AD	MYH9-related disorder
NDP	Norrin cystine knot growth factor NDP	XL	Norrie disease; Exudative vitreoretinopathy 2, Xlinked
NF2	Neurofibromin 2	AD	Neurofibromatosis, type 2

NHS	NHS actin remodeling regulator	XL	Cataract 40, X-linked
OCRL	OCRL inositol polyphosphate-5phosphatase	XL	Lowe syndrome
OPA3	Outer mitochondrial membrane lipid metabolism regulator OPA3	AD;AR	Optic atrophy 3 with cataract
PAX6	Paired box 6	AD	PAX6-related disorder
PEX11B	Peroxisomal biogenesis factor 11 beta	AR	Peroxisome biogenesis disorder 14B
PEX7	Peroxisomal biogenesis factor 7	AR	Rhizomelic chondrodysplasia punctata, type 1
PITX2	Paired like homeodomain 2	AD	Axenfeld-Rieger syndrome type 1
PITX3	Paired like homeodomain 3	AD;AR	PITX3-associated cataract with or without anterior segment mesenchymal dysgenesis
PXDN	Peroxidasin	AR	Anterior segment dysgenesis 7, with sclerocornea
RAB18	RAB18, member RAS oncogene family	AR	Warburg micro syndrome 3
RAB3GAP1	RAB3 GTPase activating protein catalytic subunit 1	AR	Warburg micro syndrome 1
RAB3GAP2	RAB3 GTPase activating noncatalytic protein subunit 2	AR	Warburg micro syndrome 2
RECQL4	RecQ like helicase 4	AR	Rothmund-Thomson syndrome, type 2
RGS6	Regulator of G protein signaling 6	AR	RGS6-related disorder
RNLS	Renalase, FAD dependent amine oxidase	AR	RNLS-related disorder
RRAGA	Ras related GTP binding A	AD	RRAGA-related disorder

SC5D	Sterol-C5desaturase	AR	Lathosterolosis
SIL1	SIL1 nucleotide exchange factor	AR	Marinesco-Sjogren syndrome
SIPA1L3	Signal induced proliferation associated 1 like 3	AR	Cataract 45
SIX6	SIX homeobox 6	AD;AR	Microphthalmia, optic disc anomalies, retinal dystrophy and/or macular dystrophy; SIX6-related micro/anphthalmia
SLC16A12	Solute carrier family 16 member 12	AD	Cataract 47, juvenile, with microcornea
SLC33A1	Solute carrier family 33 member 1	AR;AD	Congenital cataracts, hearing loss, and neurodegeneration
TBC1D20	TBC1 domain family member 20	AR	Warburg micro syndrome 4
TDRD7	Tudor domain containing 7	AR	Cataract 36
TFAP2A	Transcription factor AP-2 alpha	AD	Branchio-oculo-facial syndrome
TMEM70	Transmembrane protein 70	AR	Mitochondrial complex V (ATP synthase) deficiency, nuclear type 2
UNC45B	Unc-45 myosin chaperone B	AD;AR	Cataract 43
VIM	Vimentin	AD	Cataract 30
VSX2	Visual system homeobox 2	AR	VSX2-related MAC spectrum disorder
WDR87	WD repeat domain 87	AR	WDR87-related disorder
WFS1	Wolframin ER transmembrane glycoprotein	AD;AR	Cataract 41
WRN	WRN RecQ like helicase	AR	Werner syndrome

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