Glaucoma Panel

PANEL GENE LIST

ADAMTS10, ASB10 (GLC1F), BEST1, BMP4, COL4A1, COL8A2, CREBBP, CYP1B1, FBN1, FOXC1, FOXE3, GJA1, ISPD, LMX1B, LTBP2, MAF, MYOC, NTF4, OPA1, OPA3, OPTC, OPTN, PAX6, PIK3R1, PITX2, PITX3, POMT1, PRSS56, PXDN, RPS19, RRM2B, SBF2, SH3PXD2B, SIX6, TBK1, TMEM126A, TTR, WDR36

CLINICAL FEATURES

Glaucoma is a heterogeneous neurodegenerative disorder affecting more than 60 million people worldwide.[1] It is characterized by progressive damage of retinal ganglion cells and optic nerve fibers resulting in visual field loss. Glaucoma is the leading cause of irreversible blindness when untreated.[2] It can be classified into primary and secondary types. Secondary glaucoma originates from a previous condition, trauma, or inflammation.[5] The major types of primary glaucoma include primary open-angle glaucoma (POAG), primary congenital glaucoma (PCG), primary angle closure glaucoma (PACG).

Primary open angle glaucoma

POAG is the most common form of glaucoma.[14] It is characterized by an open angle between the iris and the cornea and cupping of the optic nerve head (optic disk).[14] Progressive damage to the optic nerve results in visual field loss.[2] POAG may occur with increased or normal intraocular pressures.[1] Normal intraocular pressure is referred to as normal-tension glaucoma (NTG). POAG may have juvenile or adult onset. Juvenile onset (JOAG) is associated with high intraocular pressures, visual field loss, and optic disc damage, for which early surgical therapy is required.[1] Multiple genes have been associated with primary open angle glaucoma including *ASB10*, *CYP1B1*, *MYOC*, *NTF4*, *OPTC*, *OPTN*, *TBK1*, *WDR36*.[6-13]

Primary congenital glaucoma

PCG occurs due to developmental defects of the trabecular meshwork and anterior chamber angle.[4] It is characterized by elevated intraocular pressure and an enlarged globe (buphthalmos) due to inadequate drainage of aqueous humor.[4] PCG is present from birth and typically diagnosed within the first year. It is more commonly bilateral (70%) and occurs most often in males (65%).[4] Tearing, photophobia, corneal edema, and irritability are classic symptoms of disease. Some individuals with severe glaucoma eventually become blind while others will have excellent vision later in life.[4] Substantially better outcomes are observed in individuals with lower intraocular pressures, however, permanent vision loss may occur if untreated.[4] Variants in the *CYP1B1* gene are the most common genetic cause of PCG. The *LTBP2* gene has also been associated with PCG.[4]

Primary angle closure glaucoma

PACG occurs when disruptions in the anterior segment lead to blockage of the trabecular meshwork.[16] The closed angle between the iris and the cornea prevents appropriate drainage of the aqueous humor.[5] As a result, individuals experience elevated intraocular pressure.[5,15] Progression of PACG is preventable to some extent if the angle closure process can be stopped early.[17] Treatments including laser peripheral iridotomy and cataract extraction are recently proving to be effective.[17] While POAG is most common in Europeans and Africans, the majority (80%) of individuals with PACG are from Asia.[15,16] The molecular mechanisms and genes contributing to PACG remain poorly understood.[17] However, variants in the *PRSS56* gene have been associated with PACG.[15]

Conditions associated with glaucoma

Anterior segment dysgenesis (ASD) disorders, associated with an approximately 50% risk for glaucoma, are a group of disorders characterized by a range of congenital eye anomalies.[18] These include corneal opacity, iris hypoplasia, malformed irido-corneal angle drainage structure, posterior embryotoxon, iris hypoplasia or rupture, ectopic pupils, and irido-corneal or lens-corneal adhesion.[18] ASD can occur as an isolated ocular anomaly or as a

syndrome. In addition, certain combinations of ocular anomalies are recognized as separate diagnostic entities such as Axenfeld-Rieger syndrome, SHORT syndrome, and Peter's anomaly.[18] Genes involved in ASD and associated syndromes include *BMP4*, *CYP1B1*, *FOXC1*, *FOXE3*, *COL4A1*, *PIK3R1*, *PITX2*, *PITX3*, *PXDN*.[18-20] Many other genetic conditions associated with glaucoma exist including but not limited to Weill-Marchensani syndrome, Muscle-eye-brain disease, Walker-Warburg syndrome, Nail-patella syndrome, Marfan syndrome, and Rubenstein-Taybi syndrome.[21-24]

The glaucoma panel may clarify a clinical diagnosis or identify a genetic diagnosis for glaucoma or a glaucoma-related disorder. If a genetic diagnosis is found, genetic testing and recurrence risk information would be available for at-risk family members. In addition, having an identified genetic diagnosis may or may not impact medical management or treatment of the condition.

GENETICS

Autosomal dominant and autosomal recessive inheritance

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. For the *FOXE3* and *FOXC1* genes, sequencing but not deletion/duplication analysis is performed. 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.

CLINICAL SENSITIVITY

Primary open angle glaucoma (POAG) disease-causing genes only explain up to 10% of all cases in the general population.[14] It is likely that the hereditary aspect of most POAG cases are due to combined effects of several genes (polygenic) and environmental interactions.[2] One of the most common genes associated with POAG is *MYOC*, which accounts for 3-5% of adult-onset POAG cases.[8] It has been reported that the *CYP1B1*, *NTF4*, *OPTN*, *TBK1*, and *WDR36* genes are associated with POAG in approximately 4.6%, 1.7%, 0-6%, 1.2% and 3.7% of cases, respectively.[9,11-13] The contribution of the *OPTC* gene to POAG is unknown,[10] while variants in the *ASB10* gene are rare, having only been reported in a small subset of familes.[6,13] The genes leading to PACG remain largely unknown.[15,17]

In primary congenital glaucoma, the *CYP1B1* gene accounts for approximately 87% of familial cases and 27% of sporadic cases, though some reports have ranged from 20-100% for familial cases and 10-27% for simplex caes.[3,4] The *LTBP2* gene is reportedly responsible for up to 40% of primary congenital glaucoma cases.[4]

Genes involved in ASD and ASD-related disorders include *BMP4*, *CYP1B1*, *FOXC1*, *FOXE3 COL4A1*, *PIK3R1*, *PITX2*, *PITX3*, and *PXDN*.[18-20, 50] Variants in the *PIK3R1* seem to be the only cause of SHORT syndrome, however, a recently identified loss of function mutation in the *BMP4* gene has been associated with SHORT syndrome in one individual.[28,29] Variations in the *PITX2* and *FOXC1* have been identified in 16% and 24% of patients with ASD with or without systemic anomalies, respectively.[18] Variants in *CYP1B1*, *FOXE3*, *COL4A1*, *PITX3* are rare as they have been seen in few families with glaucoma or glaucoma related conditions.[18,19,51]

Disorders in which glaucoma is a feature or potential feature involve variants in the genes *ADAMTS10*, *BEST1*, *COL8A2*, *CREBBP*, *FBN1*, *GJA1*, *ISPD*, *LMX1B*, *LTBP2*, *MAF*, *OPA1*, *OPA3*, *PAX6, POMT1*, *PRSS56*, *RPS19*, *RRM2B*, *SBF2*, *SH3PXD2B*, *SIX6*, *TMEM126A*, *TTR*.[21,25-27,30-49] The contribution of these genes to glaucoma is generally rare and varies with the phenotype of the individual.

Gene	Protein	Inheritance	Disease Associations
ADAMTS10	A disintergrin-like and metalloproteinase with thrombospondin type 1 motif	AR	Weill-Marchensani
ASB10	Ankyrin repeat and SOCS box-containing protein 10	AD	Primary open angle glaucoma
BEST1	Bestrophin-1	AD	Bestrophinopathy, macular dystrophy, retinitis pigmentosa, vitreoretinochoroidopathy
BMP4	Bone morphogenetic protein 4	AD	SHORT syndrome, micropthalmia, orofacial cleft
COL4A1	Collagen type 4 alpha-1	AD	Walker-Warburg syndrome, muscle-eye-brain disease
COL8A2	Collagen type 8 alpha-2	AD	Fuchs endothelial corneal dystrophy, posterior polymorphous corneal dystrophy
CREBBP	Creb-binding protein	AD	Rubenstein-Taybi syndrome
CYP1B1	Cytochrome P450 subfamily 1, polypeptide 1	AR	Primary congenital glaucoma, primary open angle glaucoma, anterior segment dysgenesis
FBN1	Fibrillin	AD	Marfan syndrome, Weill-Marchesani syndrome
FOXC1	Forkhead box C1	AD	Anterior segment dysgenesis, Axenfeld-Reiger syndrome
FOXE3	Forkhead box E3	AR	Anterior segment dysgenesis, cataracts, anopthalmia
GJA1	Gap junction protein, alpha-1	AD/AR	Oculotendodigital dysplasia, palmoplantar keratoderma, hypoplastic left heart syndrome
ISPD	Isoprenoid synthase domain-containing protein	AR	Muscle-eye-brain disease, muscular dystrophy-dystroglycanopathy
LMX1B	LIM-homeobox transcription factor 1, beta	AD	Nail-Patella syndrome
LTBP2	Latent transforming growth factor-beta-binding protein 2	AR	Primary congenital glaucoma, Weill-Marchesani syndrome

Gene	Protein	Inheritance	Disease Associations
MAF	Avian musculoaponeurotic fibrosarcoma oncogene homolog	AD	Ayme-Gripp syndrome, cataracts
MYOC	Myocilin	AD	Primary open angle glaucoma
NTF4	Neurotrophin 4	AD	Primary open angle glaucoma
OPA1	Optic atrophy type 1 gene	AD	Optic atrophy, Behr syndrome
OPA3	Optic atrophy type 3 gene	AD	Optic atrophy with cataract, 3-methylglutaconic aciduria
OPTC	Opticin	AD	Primary open angle glaucoma
OPTN	Optineurin	AD	Primary open angle glaucoma
PAX6	Paired box gene 6	AD	Aniridia, Cataract, Optic nerve hypoplasia
PIK3R1	Phosphatidylinositol 3-kinase regulatory subunit 1	AD	SHORT syndrome, Immunodeficiency 36
PITX2	Paired-like homeodomain transcription factor 2	AD	Anterior segment dysgenesis, Axenfeld-Rieger syndrome
PITX3	Paired-like homeodomain transcription factor 2	AD	Anterior segment dysgenesis, cataracts
POMT1	Protein O-mannosyltransferase 1	AR	Muscle-eye brain disease, Muscular dystrophy-dystroglycanopathy, Walker-Warburg syndrome
PRSS56	Protease, serine, 56	AR	Micropthalmia, primary angle-closure glaucoma
PXDN	Peroxidasin, homolog of drosophila	AR	Anterior segment dysgenesis
RPS19	Ribosomal protein S19	AD	Diamond-Blackfan anemia
RRM2B	Ribonucleotide reductase, M2 B	AD	Progressive external opthalmoplegia, AR mtDNA depletion syndrome
SBF2	Set-binding factor 2	AR	CMT4B2
SH3PXD2B	SH3 and PXZ domains-containing protein 2B	AR	Frankt-ter Haar syndrome
SIX6	Sine oculis homeobox homolog of drosophila	AR	Optic disc anomalies, retinal and macular dystrophy
TBK1	Tank-binding kindase 1	AD	Primary open angle glaucoma, frontotemporal demential, ALS
TMEM126A	Transmembrane protein 126A	AR	Optic atrophy
TTR	Transthyretin	AD	Familial amyloidotic polyneuorpathy
WDR36	WD repeat-containing protein 36	AD	Primary open angle glaucoma

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