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Molecular Genetics in Glaucoma

Yutao Liu, M.D. & PhD[1,2] and **R. Rand Allingham, M.D.**[3]

[1]Center for Human Genetics, Duke University Medical Center, Durham, North Carolina, USA

[2]Department of Medicine, Duke University Medical Center, Durham, North Carolina, USA

[3]Duke University Eye Center, Duke University Medical Center, Durham, North Carolina, USA

Abstract

Glaucoma is a family of diseases whose pathology is defined by the progressive loss of retinal ganglion cells. Clinically, glaucoma presents as a distinctive optic neuropathy with associated visual field loss. Primary open-angle glaucoma (POAG), chronic angle closure glaucoma (ACG), and exfoliation glaucoma (XFG) are the most prevalent forms of glaucoma globally and are the most common causes of glaucoma-related blindness worldwide. A host of genetic and environmental factors contribute to glaucoma phenotypes. This review examines the current status of genetic investigations of POAG, ACG, XFG, including the less common forms of glaucoma primary congenital glaucoma (PCG), the developmental glaucomas, and pigment dispersion glaucoma.

Introduction

Glaucoma is the most common cause of irreversible blindness worldwide (Quigley and Broman, 2006). It is a heterogeneous group of disorders. There are many types, but the major forms of glaucoma include primary open-angle glaucoma (POAG), chronic angle-closure glaucoma (ACG), and exfoliation glaucoma (XFG) (Allingham and Shields, 2011). Glaucoma is defined as the progressive loss of retinal ganglion cells that leads to a characteristic optic neuropathy with associated visual field loss. Genetic factors are considered to be major contributors to the pathogenesis of most forms of glaucoma. Many genes and chromosomal loci have been identified that are associated or, less commonly, causal for glaucoma. What follows is a comprehensive discussion of the genetic contribution in this group of ocular diseases.

Genetic Approaches to Glaucoma Research

Several approaches have been utilized to identify genetic factors that are associated with glaucoma. Genetic linkage analysis has been widely used to localize genes that are inherited

Correspondence to: R. Rand Allingham.

as a Mendelian trait (Fan et al., 2006). This method relies on the availability of families with multiple affected individuals. After the identification of a linkage locus, potential disease-associated genetic variants are examined within the chromosomal region of linkage. With the recent development in high-throughput DNA sequencing, it is now feasible to sequence all the coding regions in the linkage locus or the whole coding region of the genome (exome), an approach known as whole exome sequencing (Teer and Mullikin, 2010). However, whole exome sequencing is limited to protein-coding regions only and does not cover untranslated regions of the genome. Due to sequence capturing technology, a small portion of the coding region is not covered in whole exome sequencing. Whole exome sequencing has been used successfully to identify causal mutations or genetic variants for a variety of rare Mendelian diseases including Miller syndrome, congenital chloride-losing diarrhea, and Schinzel-Giedion syndrome (Bilguvar et al., 2010; Hoischen et al., 2010; Ng et al., 2010). The process of identifying rare causal variants using this technology offers a powerful approach to improve our understanding of specific mechanisms of disease.

To study common and complex disorders, several approaches including the genome-wide association study (GWAS) and admixture mapping are widely used. GWAS integrates a massive number of genetic markers (single nucleotide polymorphisms (SNPs)) with large case/control datasets, typically containing thousands of cases and controls (Manolio, 2010). GWAS is a powerful method used to identify common genetic variants that are associated with the specific diseases or phenotypes. Although the underlying mechanisms remain unclear and the findings from GWAS explain only a limited amount of heritability, this approach has led to the identification of disease-associated genetic variants in a wide range of human diseases and/or traits (GWAS catalog www.genome.gov/gwastudies) (Hindorff et al., 2009), including age-related macular degeneration (AMD), POAG and XFG (Burdon et al., 2011; Chen et al., 2010b; Klein et al., 2005; Neale et al., 2010; Thorleifsson et al., 2007; Thorleifsson et al., 2010; Yu et al., 2011). Admixture mapping is based on the disease prevalence difference across populations to localize disease-associated variants. Disease prevalence differences across populations are due in part to allele frequency differences in disease-causing genetic variants, which enables the localization of a trait to a specific genomic location (Winkler et al., 2010). This approach is currently being employed by researchers investigating the genetic etiology of POAG in African Americans (personal communication, Michael Hauser, Ph.D.). A growing area of interest is the influence of DNA copy number variants and genetic imprinting on inherited disorders. Altogether, these innovative approaches are expanding our understanding of glaucoma, in particular POAG.

Primary Open-Angle Glaucoma (POAG)

POAG is the most common type of glaucoma and is characterized by the presence of glaucomatous optic neuropathy without an identifiable secondary cause (Allingham et al., 2009). Abnormally elevated intraocular pressure (IOP) is often associated with POAG and is a major risk factor for this disease (Libby et al., 2005). A number of studies indicate the familial nature of POAG and support the presence of genetic factors in the pathogenesis of POAG. At least 14 linkage loci have been identified and are designated as GLC1A through GLC1N (Allingham et al., 2009). Several genes have been identified within these loci,

including myocilin, optineurin, and WD repeat domain 36 (*WDR36*) (Allingham et al., 2009; Kwon et al., 2009).

Myocilin

Myocilin (*MYOC*), located on chromosome 1, was the first gene identified for POAG in the GLC1A locus (Sheffield et al., 1993; Stone et al., 1997). Myocilin was also known as trabecular meshwork inducible-glucocorticoid response protein (TIGR) (Polansky et al., 1997). *MYOC*-associated glaucoma is transmitted as an autosomal dominant Mendelian trait. Mutations in *MYOC* are primarily found in patients with juvenile or early-adult forms of POAG. These patients often have a severe clinical phenotype that includes highly elevated IOP and the frequent need for surgical management (Fingert et al., 1999). *MYOC* mutations account for 3-5% of POAG patients worldwide (Allingham et al., 2009; Resch and Fautsch, 2009). The *MYOC* gene has three exons. Most mutations are found in the third exon which encodes the olfactomedin-like domain. Although myocilin is expressed in most ocular and non-ocular tissues throughout the body, open angle glaucoma is the only reported phenotype (Kwon et al., 2009). Among more than 70 reported mutations (Hewitt et al., 2008), the most common mutation is Q368X. This mutation encodes a stop codon that causes premature termination of the translated protein, it is associated with a later adult-onset form of POAG while other mutations are generally associated with a juvenile-onset form (Allingham et al., 1998; Alward et al., 1998).

How *MYOC* mutations lead to elevated IOP and open angle glaucoma remains unclear. It appears that *MYOC* mutations do not cause glaucoma via haploinsufficiency or overexpression (Kwon et al., 2009; Resch and Fautsch, 2009). Animal models where MYOC expression is either reduced or overexpressed do not appear to produce glaucoma. *MYOC* mutations may alter protein function and cause elevated IOP and loss of retinal ganglion cells. However, studies using the transgenic mouse model with the Tyr437His mutation have produced conflicting results: one group reported normal phenotype while another reported glaucoma phenotype of elevated IOP and loss of retinal ganglion cells (Gould et al., 2006; Kim et al., 2001; Kwon et al., 2009; Senatorov et al., 2006; Zhou et al., 2008).

MYOC protein is normally released into the aqueous humor from inside of the cells (Resch and Fautsch, 2009; Resch et al., 2010), which occurs in a Golgi-independent manner. Release of MYOC into the extracellular space in the presence of glaucoma-associated mutations is markedly reduced (Jacobson et al., 2001). It has recently been reported that MYOC release into the aqueous humor is associated with shedding of small vesicles called exosomes (Hoffman et al., 2009; Resch et al., 2010; Stamer et al., 2011). Exosomes contain ligands involved in autocrine and paracrine signaling. These ligands may play a role in the homeostasis of trabecular meshwork. Mutated MYOC could lead to trabecular meshwork dysfunction and elevated IOP/glaucoma. Other studies suggest that mutated MYOC protein may interfere with protein trafficking and result in the intracellular accumulation of mis-folded MYOC protein and IOP increase (Kwon et al., 2009).

OPTN

OPTN, located on chromosome 10, was the second gene identified for POAG (Rezaie et al., 2002). In contrast to the elevated IOP found in *MYOC*-associated POAG, *OPTN*-associated glaucoma is characterized with normal or only moderately elevated IOP seen in patients with normal tension glaucoma (NTG) (Rezaie et al., 2002). NTG is common in many populations and comprises approximately 15-20% of POAG cases in the Baltimore Eye Survey (Sommer et al., 1991). Among all *OPTN* mutations, E50K has the strongest evidence for a causal role in POAG (Allingham et al., 2009; Libby et al., 2005). NTG patients carrying E50K mutations have more severe glaucoma phenotypes, including an earlier onset, more advanced optic nerve cupping, and requirement of more frequent surgical intervention (Aung et al., 2005). Mutations of *OPTN* have recently been identified in patients with amyotrophic lateral sclerosis and Paget disease of bone (Albagha et al., 2010; Maruyama et al., 2010).

The molecular mechanism related to the E50K mutation is unclear. OPTN interacts with RAB8 (Rab-protein 8), myosin VI, and transferrin receptor (Sahlender et al., 2005). OPTN negatively regulates *TNFα*-induced NF-κB activation and affects the apoptotic threshold (Zhu et al., 2007). OPTN with the E50K mutation increases binding to TBK1 (TANK-binding kinase 1). This forms a complex that regulates TNFα along with its pro-apoptotic effects (Morton et al., 2008). Studies by De Marco et al suggest that over-expression of OPTN with E50K mutation in retinal ganglion cells inhibits the translocation of OPTN to the nucleus and compromises mitochondrial membrane integrity, leading to apoptosis under the influence of external stressors (De Marco et al., 2006). Overexpressing E50K OPTN also results in a pronounced impairment of transferrin uptake in human retinal pigment epithelial cells and in the RGC5 cell line, indicating defective protein trafficking (Park et al., 2010). Transgenic mice with the E50K mutation develop apoptosis and retinal degeneration which reduces retinal thickness by approximately 28% (Chi et al., 2010a). OPTN is also reported to be involved in the ubiquitin-proteasome pathway and autophagy. The E50K mutation decreases the level of the proteasome regulatory β35 subunit and proteasome activity and enhances autophagy in retinal ganglion cells (Shen et al., 2011).

In summary, OPTN may exert its primary effect on retinal ganglion cells by increasing their susceptibility to premature cell death. This contrasts with *MYOC* that mediates its effect through increased IOP which secondarily causes loss of retinal ganglion cells. How different mutations in *OPTN* cause different diseases remains unclear.

WDR36

WDR36 contains 23 exons and is located on chromosome 5 (Monemi et al., 2005). It is ubiquitously expressed in the eye and other tissues of the body. Although the original study reported the prevalence of *WDR36* disease variants in POAG patients ranged from 1.6-17%, subsequent studies failed to identify genetic mutations in *WDR36* as the causal agent (Allingham et al., 2009). Hauser et al reported that POAG patients with *WDR36* sequence variants are associated with a more severe disease phenotype than those without. This suggests that *WDR36* sequence variants may influence susceptibility to POAG rather than causality (Hauser et al., 2006). WDR36 is involved in rRNA processing, which is critical for

ribosome biogenesis. It interacts with the *p53* mediated stress response pathway (Footz et al., 2009). Chi et al reported that *WDR36* mutations may directly affect axon growth of the retinal ganglion cells and lead to progressive retinal degeneration at the peripheral retina with normal IOP in transgenic mice (Chi et al., 2010b). Lack of WDR36 in human trabecular meshwork cells may delay the formation of 18S rRNA and cause apoptotic cell death (Gallenberger et al., 2011).

Neurotrophin 4 (*NTF4*)

Recently mutations in *NTF4* were reported in 1.7% of POAG patients in the European population (Pasutto et al., 2009). It was hypothesized that *NTF4* mutations would affect either NTF4 dimer stability or the interaction between NTF4 dimer and its receptor TrkB. However, other studies failed to corroborate this association. In a study of cases of European ancestry there were more non-synonymous coding changes in controls than cases (Liu et al., 2010). Similar findings were reported by another study conducted in India (Rao et al., 2010). Although a recent study suggests *NTF4* mutations as a rare cause (0.6%) of POAG (Vithana et al., 2010), the role of *NTF4* in POAG remains unclear.

Association Studies in POAG

Major new genetic associations with POAG have been identified since our last major review of POAG genetics (Allingham et al., 2009). Although over 20 candidate genetic associations with POAG have been reported, most have not been replicated. The advent of studies that have utilized larger datasets and have harnessed the power of GWAS are now demonstrating new compelling genetic associations in POAG.

The first POAG GWAS was performed in a Japanese POAG dataset containing 827 POAG cases and 748 controls, but no genetic association reached genome-wide significance (Nakano et al., 2009). A second GWAS in a Japanese normal tension glaucoma (NTG) dataset that contained 305 NTG patients and 355 controls found an association with the intronic SNP rs3213787 in the gene of *SRBD1* (S1 RNA binding domain 1) on chromosome 2 (Meguro et al., 2010). These findings have recently been replicated in an independent Japanese NTG dataset by Mabuchi et al (Mabuchi et al., 2011), suggesting a role of SRBD1 in NTG.

Caveolin 1 and 2 (*CAV1/CAV2*)

In a major GWAS of POAG datasets of European descent, Thorleifsson and coworkers identified a significant association with SNP rs4236601 on chromosome 7q31 with POAG (Thorleifsson et al., 2010). This association was replicated in a second Caucasian population and an Asian (Chinese) population. The OR (odds ratio) was smaller in the replicated Caucasian dataset (1.18) than the original Icelandic population (1.36). The risk allele frequency of rs4236601 was relatively lower in the Iceland and Sweden datasets than that in other examined populations (Thorleifsson et al., 2010). This might be due to the unique control population in Iceland. SNP rs4236601 is located in an intergenic region between the genes caveolin 1 and 2. *CAV1/CAV2* are expressed in the trabecular meshwork and retinal ganglion cells. These genes are involved in the formation of caveolae, ubiquitous plasma

membrane organelles that function as macromolecular vesicular transporters. How this variant is related to POAG susceptibility is unknown. However, it is of interest that OPTN and MYOC also appear to be involved in vesicle trafficking (Chi et al., 2010a; Park et al., 2006; Resch et al., 2010; Sahlender et al., 2005). Although the association of this locus with POAG was not replicated in a cohort from Iowa with 545 POAG cases and 297 controls (Kuehn et al., 2011), the lack of association may be due to either the sample size or population differences.

Cyclin-dependent kinase inhibitor 2B (*CDKN2B*)

CDKN2B, located on chromosome 9p21, forms a complex with CDK4/CDK6 and prevents the activation of the CDK kinases, which control cell cycle G1 progression. Its expression is induced by TGF-β. It was initially found to be associated with VCDR (vertical cup-disc ratio) in a GWAS study of optic disc parameters and was later identified to be associated with POAG risk through candidate gene studies (Fan et al., 2011; Ramdas et al., 2010; Ramdas et al., 2011). This association was recently replicated in another GWAS study by Burdon and co-workers (Burdon et al., 2011). It is interesting to note that CAV1 regulates mitogenic signaling and acts synergistically with *CDKN2A* gene, adjacent to *CDKN2B* gene (Williams et al., 2004). This locus is also associated with myocardial infarction, intracranial aneurysm, diabetes, breast cancer, endometriosis, and gliomas (Kathiresan et al., 2009; Shete et al., 2009; Turnbull et al., 2010; Uno et al., 2010; Wrensch et al., 2009; Zeggini et al., 2007). It remains unclear how this locus contributes to these different human diseases.

Transmembrane and coiled-coil domains 1 (*TMCO1*)

TMCO1 is located on chromosome 1q22-q25. It was recently identified to be associated with POAG in a GWAS study by Burdon and co-workers (Burdon et al., 2011). Homozygous mutations in *TMCO1* cause a syndrome with craniofacial dysmorphism, skeletal anomalies, and mental retardation (Xin et al., 2010). Protein encoded by *TMCO1* gene may localize to Golgi apparatus and endoplasmic reticulum or to the mitochondria depending on the type of the cells (Iwamuro et al., 1999; Zhang et al., 2010), which may play role in the apoptosis of retinal ganglion cells.

Chromosome 14q23 locus

Variants in chromosomal region 14q23 have been associated with vertical cup-disc ratio in a large GWAS study (Ramdas et al., 2010). Recently this locus was associated with risk of POAG in two separate candidate gene studies (Fan et al., 2011; Ramdas et al., 2011). These variants are located in the intergenic non-coding region between *SIX1* (Sine Oculis homeobox 1) and *SIX6* (Sine Oculis homeobox 6). *SIX1* is similar to the Drosophila gene ‘sine oculis’. Mutations in the ‘sine oculis’ gene cause mal-development of the visual system. *SIX1* mutations in humans cause deafness and branchio-oto-renal syndrome (OMIM 113650) (Ruf et al., 2004). *SIX6* mutations have been known to cause anophtalmia in mice and humans (Gallardo et al., 1999; Li et al., 2002). *SIX6* is expressed in the developing retina and optic nerve (Gallardo et al., 1999). Further studies need to be performed to determine whether and how SIX1 and/or SIX6 contribute to POAG risk.

Associations with Glaucoma-Associated Ocular Traits

An alternative approach to study POAG is to investigate the phenotypes that are associated with POAG risk, including central corneal thickness (CCT), VCDR, and optic disc area. Besides *CDKN2B* gene, a number of sequence variants have been associated with these ocular traits. Sequence variant in *ATOH7* are associated with VCDR, but not with glaucoma risk (Macgregor et al., 2010; Ramdas et al., 2010; Ramdas et al., 2011). Sequence variants near or in the genes of *ZNF469*, *COL5A1*, *AKAP13*, *COL8A2*, and *AVGR8* are associated with CCT (Lu et al., 2010; Vitart et al., 2010; Vithana et al., 2011). Variants in or near *ATOH7*, *TGFBR3*, *CARD10*, and *CDC7* are associated with optic disc area (Khor et al., 2011; Macgregor et al., 2010; Ramdas et al., 2010). It will be interesting to see how these variants relate to the POAG phenotype in different populations.

DNA Copy Number Variants

DNA copy number variants (CNVs) have been shown to play an important role in a number of human genetic diseases, such as autism and schizophrenia (Alkan et al., 2011). CNVs refer to changes in DNA copy number of a genomic region when compared to a reference genome. Although one study by Abu-Amero and colleagues found no evidence of CNVs associated with POAG, this study was limited by its relative small sample size of 27 POAG cases and 12 controls (Abu-Amero et al., 2009). A recent study by Davis and the colleagues indicates that rare copy number variation plays a role in the development of POAG (Davis et al., 2011). In this study 400 POAG cases and 500 individuals without glaucoma were examined using SNP-genotyping arrays. Duplications in the *TBK1* gene (TANK-binding kinase 1) have been implicated as a potential cause in familial normal tension glaucoma (Fingert et al., 2011). TBK1 interacts with OPTN, therefore it will be of great interest to see if this finding is replicated in cases of POAG as well as normal tension glaucoma. Another rare CNV change is a heterozygous deletion of the *GALC* gene (galactosylceramidase) (www.arvo.org 2011 ARVO abstract 3304/A552). In a preliminary report a deletion of *GALC* was found in 1.1% of POAG patients versus 0.3% controls. The heterozygous *GALC* deletion increased the risk of POAG by 4-fold. Interestingly, the homozygous deletion of *GALC* causes Krabbe disease in which patients develop optic neuropathy and vision loss (Wenger et al., 1997; Wenger et al., 2000). In summary, there is growing evidence that CNVs may play a role in the pathogenesis of POAG.

Exfoliation Glaucoma

Exfoliation glaucoma (XFG), also called pseudoexfoliation glaucoma, is the most common identifiable form of open angle glaucoma (Ritch and Schlotzer-Schrehardt, 2001). XFG occurs in direct association with exfoliation syndrome (XFS). XFS is a systemic disorder of extracellular matrix characterized by the accumulation of abnormal fibrillary material in multiple ocular tissues including the lens surface as well as tissues throughout the body (Ritch and Schlotzer-Schrehardt, 2001). XFG accounts for approximately 25% of all open-angle glaucoma cases globally (Ritch, 1994; Schlotzer-Schrehardt, 2009). XFG has a more aggressive clinical course and is associated with a greater risk of vision loss and blindness than POAG (Ritch, 2008). Researchers have long suspected that genetic factors play a role

in XFG and XFS. Familial studies have identified several genomic regions in strong linkage to XFS (Lemmela et al., 2007; Schlotzer-Schrehardt, 2009).

LOXL1

A GWAS study identified genetic variants in the *LOXL1* gene that are significantly associated with both XFS and XFG (Thorleifsson et al., 2007). Two of these associated variants, rs1048661 and rs3825942, are located in the exon 1 and code for amino acid changes R141L and G153D respectively. The association between these variants and XFS/XFG has been extensively replicated in many different populations (Chen et al., 2010a; Liu and Allingham, 2010). Lack of association between *LOXL1* variants and POAG confirms that XFG and POAG are genetically distinct (Liu et al., 2008). Among the replications, in several populations rs1048661 was not associated with XFG (Chen et al., 2010a). Furthermore, although the G allele of rs1048661 is associated with XFG in the Caucasians, the opposite (T) allele is associated with XFG in the Chinese and Japanese populations (Chen et al., 2010a). For SNP rs3825942, the G allele has been associated with XFG risk in all non-African populations while the A allele is associated with XFG risk in two black South African populations (Rautenbach et al., 2011; Williams et al., 2010). No additional coding variants in *LOXL1* have been found in association with XFG in the South African black population (Williams et al., 2010). These data indicate that coding changes in *LOXL1* are not functionally involved in XFG/S. Therefore, functional variants that regulate gene expression of *LOXL1* have been proposed as the central mechanism leading to XFS/G. A SNP located within the promoter region of *LOXL1*, rs16958477, was reported to affect promoter activity in vitro (Ferrell et al., 2009). However, this variant was not associated with XFG in the black South African or Caucasian populations (Williams et al., 2010).

LOXL1 mRNA and protein expression have been reported to be up-regulated in early stages of XFS and only to be down-regulated in later stages of exfoliation (Khan et al., 2010; Schlotzer-Schrehardt et al., 2008). LOXL1 is specifically involved in elastogenesis and is a major component of exfoliative material obtained from ocular tissues in patients with XFG/S (Schlotzer-Schrehardt, 2009). It is a critical enzyme in extracellular matrix formation, and catalyzes the covalent cross-linking of collagen and elastin in connective tissues. Distinct from other members of the lysyl oxidase family, LOXL1 intiates elastogenesis by binding to tropoelastin, a monomer of elastin, and fibulin-5 (Schlotzer-Schrehardt, 2009).

CNTNAP2

Variants of *CNTNAP2* (Contactin associated protein-like 2) have been found in association with XFS/XFG in two German populations (Krumbiegel et al., 2010). *CNTNAP2* is ubiquitously expressed in human ocular tissues, including retina. This gene has been associated with various neuropsychiatric disorders, including autism, mental retardation, schizophrenia, and epilepsy. However, the function of this gene still remains largely unknown. This association has yet to be replicated.

Primary Congenital Glaucoma

As the most common childhood glaucoma, PCG accounts for about 25% of all pediatric glaucoma cases (Vasiliou and Gonzalez, 2008). PCG is characterized by a developmental abnormality of the anterior chamber angle, which leads to obstruction of aqueous outflow and elevated IOP. Onset occurs within the first few years of life. Elevated IOP produces ocular enlargement, termed buphthalmos, increased corneal diameter, and corneal clouding. Patients frequently suffer from photophobia and epiphora (tearing). Three genetic loci (GLC3A, GLC3B, and GLC3C) have been linked to PCG (Akarsu et al., 1996; Sivadorai et al., 2008; Stoilov and Sarfarazi, 2002; Vasiliou and Gonzalez, 2008).

CYP1B1

CYP1B1, located on chromosome 2, was identified in the GLC3A locus by Stoilov and coworkers (Stoilov et al., 1997). Over 80 glaucoma-associated mutations in *CYP1B1* have been described to date (Vasiliou and Gonzalez, 2008). *CYP1B1* mutations have been found in patients with other forms of pediatric glaucoma including Peter's anomaly and Axenfeld-Rieger syndrome. Variants of *CYP1B1* may increase susceptibility in adult forms of POAG (Pasutto et al., 2010; Tanwar et al., 2010; Vasiliou and Gonzalez, 2008). *CYP1B1* has been described as a modifier gene for *MYOC*-associated POAG (Vasiliou and Gonzalez, 2008; Vincent et al., 2002). The additional presence of *CYP1B1* mutations correlates with an earlier onset of glaucoma in these individuals. In a knockout mouse model, *Cyp1b1*$^{-/-}$ mice develop ocular drainage structure abnormalities similar to the phenotypes in human PCG patients, including small or absent Schlemm's canal, hypoplastic trabecular meshwork, and focal angle abnormalities (Libby et al., 2003). The prevalence of *CYP1B1* mutations in PCG patients varies widely across populations, ranging from 20% in Caucasians and approaches 100% in Saudi Arabians and Slovakian Roms (Rao et al., 2011).

LTBP2

LTBP2, latent transforming growth factor beta binding protein 2 *(LTBP2)*, located in the GLC3C locus, was reported to be associated with PCG by two different studies and confirmed by Azmanov et al (Ali et al., 2009; Azmanov et al., 2010; Narooie-Nejad et al., 2009). Three *LTBP2* mutations were reported as either frameshift or nonsense mutations. *LTBP2* contains 36 exons and encodes a matrix protein with multi-domain structure. LTBP2 is a member of the TGF-β latent complex and binds to fibulin-5 and regulates elastic fiber assembly (Hirai et al., 2007). It was shown that the N-terminal region of LTBP2 has adhesive sites that interact with beta1 and alpha 3 integrins (Vehvilainen et al., 2003). LTBP2 is a member of TGF-β latent complex and a structural component of microfibrils, which is involved in cell adhesion.

Developmental Glaucoma

Developmental glaucoma includes so-called anterior chamber cleavage syndrome, Axenfeld anomaly, Rieger syndrome, and mesodermal dysgenesis of the cornea and iris (Liu and Allingham, 2010). They involve a variety of ocular and non-ocular abnormalities, primarily affecting tissues of the anterior segment of the eye, including the cornea, iris and anterior

chamber angle (Liu and Allingham, 2010). Approximately 50% of the patients with these developmental anomalies will develop glaucoma in their lifetime. Many genes contribute to developmental glaucomas. These include *PITX2*, *PITX3*, *FOXC1*, *FOXE3*, *PAX6*, *LMX1B*, and *MAF* (Gould and John, 2002; Gould et al., 2004) which collectively encode for transcription factors that bind to specific DNA segments and regulate gene expression. Mutations in these transcription factors interfere with cellular and extracellular matrix signaling during development. Two additional loci at chromosome 13q14 and 16q24 are linked with Axenfeld-Rieger syndrome, but the responsible genes have not been identified (Liu and Allingham, 2010).

Pigment Dispersion Syndrome (PDS) and Glaucoma (PG)

PDS was originally described in two cases in 1949 (Sugar and Barbour, 1949). PDS is characterized by the release of pigment granules into the aqueous humor that arise from the posterior pigmented iris epithelium (Niyadurupola and Broadway, 2008). The pigment particles deposit on or within various ocular structures, including the lens, anterior iris, posterior cornea, and trabecular meshwork (Allingham and Shields, 2011). Up to 50% of PDS patients may develop elevated IOP and glaucomatous optic neuropathy (Ritch, 1998). Autosomal dominant inheritance has been documented in some families with PDS. Linkage analysis was used to identify a region located in chromosome 7q35-q36 (Andersen et al., 1997). The gene for PDS within this locus has not been identified. A model of pigmentary glaucoma, the DBA/2J mouse, has mutations in two genes that encode for melanosomal proteins, TYRP1 (Tyrosine-related protein 1) and GPNMB (glycoprotein NMB). This mouse model shares some similarity to PDS (Anderson et al., 2006; Anderson et al., 2002; Mo et al., 2003). However, whether mutations or other variations in these two genes is associated with PDS in humans has not been determined (Lynch et al., 2002).

Angle Closure Glaucoma (ACG)

ACG is the second most common form of glaucoma and affects at least 16 million people globally. A recent study indicates that *Vav2/Vav3*-deficient mice show a disease that consists of iridocorneal angle closure with an associated elevation of intraocular pressure. These mice develop loss of retinal ganglion cells and optic nerve head cupping (Fujikawa et al., 2010). Two SNPs in human *Vav2* and *Vav3* genes have been associated with POAG in the Japanese population, but not in the Indian population with POAG or PACG (Rao et al., 2010). No mutations in *VAV2*/*VAV3* genes have been reported in ACG patients. Another report in a mouse model that contains mutations in the gene *PRSS56* (protease, serine, 56) has altered axial length and a phenotype that is similar to ACG (Nair et al., 2011). Mutated PRSS56 causes a significant reduction in the axial length of patients with posterior microphthalmia (Gal et al., 2011). The role of this gene in patients with ACG remains to be determined.

Angle-closure glaucoma is commonly found in persons with nanophthalmos, a condition that consists of markedly reduced axial length and thickening of the sclera. Nanophthalmos is inherited as an autosomal recessive or dominant trait. Mutations in 2 genes, *MFRP* (membrane-type frizzled-related protein) and *VMD2* (vitelliform macular dystrophy 2 or

bestrophin), have been found in patients with nanophthalmos (Sundin et al., 2005; Yardley et al., 2004). Two additional loci have been mapped to chr11p and chr2q11-q14, but without identification of the gene (Li et al., 2008; Othman et al., 1998).

Summary

Developments in the field of human genetics are accelerating rapidly. The contribution of new and known genes to our understanding of the genetic architecture of glaucoma has similarly advanced for both Mendelian as well as complex inherited forms of glaucoma. We are at an historic point in genetic investigation as multiple technologies converge to reveal the inherited mechanisms of health and disease. This is certainly true of the family of diseases we know as glaucoma. The advent of GWAS, exome and whole genome sequencing, and multiple approaches examining tissue expression and gene regulation will fundamentally alter our understanding of glaucoma. In order to fully utilize these investigations it is critically important to have access to glaucoma-affected ocular samples for future research to perform functional genomics, gene expression, pathway analysis, and epigenetics studies. Ultimately this knowledge will expand our understanding of the various molecular pathways leading to glaucoma. These glaucoma-related genes and pathways will guide the development of more effective diagnostic and treatment options for patients with this common, blinding disease.

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Highlights

1. A very comprehensive summary of the recent development in glaucoma genetics.
2. Genetics of POAG, ACG, XFG, PCG, developmental and pigment dispersion glaucoma.
3. Most recent development of GWAS studies in POAG and XFG.
4. Discussion of novel technology such as whole exome sequencing in ocular diseases.
5. New genes identified in primary congenital glaucoma and angle closure glaucoma.