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Glaucoma Genetics

Pratap Challa, MD

Glaucoma is one of the leading causes of blindness throughout the world[1,2] with a prevalence of over 2% in individuals over 40 years old.[3] It is a heterogeneous disorder characterized by a progressive degeneration of axons manifesting as optic nerve head cupping and field loss. Most glaucomas are asymptomatic until late in the disease course and therefore, many patients are diagnosed on routine examinations or only after advanced field loss has occurred. The molecular etiology of glaucoma is largely unknown, but there are numerous studies establishing a genetic etiology for this disorder. Mutations in specific genes are associated with the manifestations of open angle glaucoma (OAG), pseudoexfoliation glaucoma (XFG), congenital glaucoma, and the anterior segment dysgenesis syndromes. Understanding the molecular basis of glaucoma is important to several aspects of glaucoma diagnosis and management. Genetic testing could be used to identify individuals who are high risk for the development or progression of glaucoma. Identifying novel pathways could be used to design more specific and effective therapies. This article will review the genes associated with different forms of glaucoma AQ1(Table 1).

OAG

The most common form of glaucoma is primary open angle glaucoma (POAG), affecting over 33 million people worldwide.[1] This is a late-onset and complex disorder that is associated with elevated intraocular pressures (IOPs) leading to axonal degeneration and visual field loss. The IOP increase in this disorder seems to be owing to an “inefficiency” of the trabecular meshwork (TM) leading to decreased aqueous outflow facility. Its multifactorial etiology was first proposed in the year 1967[4] and it demonstrates a variable age of onset and severity. Most studies suggest an autosomal dominant inheritance with incomplete penetrance.[5] However, the inheritance pattern of this disorder seems to be multifactorial resulting from the interaction of one or more genes and/or environmental stimuli. To date, there have been over 20 genetic loci and 3 genes, MYOC (myocilin), OPTN (optineurin), and WDR36 that have been linked to POAG.

Like POAG, juvenile open angle glaucoma (JOAG) is also characterized by the presence of elevated IOPs, optic nerve cupping, and open angles. It has a variable age of onset, but typically presents with very high IOPs from ages 3 to 25 years. Like most glaucomas, it is not a single entity, but is rather a spectrum disorder in which some individuals present with developmental immaturities of the angle with an increased number of iris processes and a thicker, more compact tissue on the inner wall of Schlemm's canal.[6] However, other JOAG individuals present with anatomic and histologic findings indistinguishable from POAG. Moreover, JOAG patients tend to be less responsive to argon laser trabeculoplasty and are often more resistive to medical therapy than POAG. Therefore, different forms of JOAG seem to be distinct from POAG and they may actually be different disorders with similar phenotypes.

The first gene to be associated with the development of POAG and JOAG was myocilin (MYOC). Previously known as TM inducible glucocorticoid response protein or TIGR, this gene product was first identified while studying the effects of dexamethasone on TM cell cultures.[7] After prolonged dexamethasone exposure, this in vitro model for steroid-induced glaucoma resulted in the increased production of this protein. Initially localized to the GLC1A

locus in the year 1993[8] and subsequently linked to the MYOC gene in the year 1997,[9] there have been over 70 different point mutations in multiple ethnic groups identified worldwide. Mutations in the coding regions of MYOC are associated with 3% to 5% of POAG cases throughout the world[10–21] and account for a larger proportion of JOAG cases (from 6% to 36%).[22,23]

MYOC is expressed in multiple ocular and nonocular tissues and despite intense investigation, the function of this protein is largely unknown. It spans approximately 17λkb and contains 3 exons transcripting a 2.3-kb gene product. It contains 504 amino acids[24,25] and has a predicted molecular weight of approximately 57λkDa.[26] Most of the reported myocilin mutations occur in exon 3 at the C terminal of the protein.

The MYOC protein has 2 major domains with an N-terminal myosinlike domain and a C-terminal olfactomedinlike domain. The N-terminal is encoded by exon 1 and has approximately 25% to 30% amino acid homology with myosin heavy chain.[26,27] The C terminal is encoded by exon 3 and has approximately 46% to 50% amino acid homology to rodent and human olfactomedin.[26,28] The myosinlike domain seems to be more variable between species except for a highly conserved leucine-zipper element.[25,29–31] Such leucine zippers are found in many DNA-binding transcription factors and in proteins that form homodimers or heterodimers. The secreted form of myocilin seems to form multimers as has been shown in aqueous humor specimens.[32] The olfactomedin domain is also well preserved across species, but likewise its function is largely unknown.[29,31,33] Olfactomedins are proteins that were first identified in amphibian olfactory mucus and have now been widely identified in the mammalian brain.[34–36] They have a high sequence homology to a group of proteins called noelins that are involved in promoting neurogenesis during *Xenopus* development.[37] Furthermore, myocilin has been identified in the myelin sheath of the optic[38,39] and peripheral nerves.[40] Therefore, it has been hypothesized to play a role in neuronal support or structure. However, in vivo data from mice with null mutations of myocilin do not demonstrate glaucoma or any observable physical deficiencies.[41] Therefore, this mechanism may or may not play a role in the development of myocilin-associated glaucoma.

Myocilin is found in many tissues and organs of the body and throughout most ocular structures.[25,27,32,33,42] The highest concentrations are located in the iris, sclera, and TM.[27,28,43] TM cells from the juxtacanalicular, corneoscleral, and uveal layers all have nearly equal expression of myocilin.[44–47] Therefore, on the basis of an anatomic analysis of myocilin distribution, one would suspect that an increase in myocilin production would lead to TM “clogging” and increased IOPs.[33] This is supported by clinical observations in which patients with some myocilin mutations have higher IOPs[21,48,49] and reduced tonographic outflow facility.[50] However, the relationship between myocilin and outflow facility is unclear. Ocular perfusion studies in which recombinant myocilin was perfused into the anterior segments of cadaveric human eyes demonstrated decreased outflow facility.[51] However, adenoviral overexpression of myocilin by transfecting the TM of perfused anterior segments demonstrated an increase in outflow facility.[52] Furthermore, animal studies have not elucidated the mechanism behind myocilin glaucoma. In a rodent model, both null mice (that lack myocilin protein) and overexpression of mutant myocilin protein failed to induce glaucoma.[41,53] However, other investigators expressed the same myocilin point mutation in a transgenic mouse and were able to observe both a 2-mm Hg increase in IOP and retinal ganglion cell death.[54] The contradictory findings of these experiments underlie our relative lack of knowledge of this protein's function and some of the limitations of animal models in studying human disease.

Myocilin expression studies can also provide clues about its function. It is increased in response to elevated IOP, dexamethasone exposure, and other forms of trabecular “stress,” implying that it may have a protective or adaptive role in the outflow pathway. Therefore, it has been

compared with other molecular chaperones.[55] Furthermore, several studies have tried to elucidate the relationship between myocilin mutations, outflow facility, and glaucoma by studying the effects of mutated myocilin proteins. Some studies have shown that the mutated form of this protein is poorly secreted from cells and suppresses normal myocilin secretion. The myocilin products then accumulate within the endoplasmic reticulum.[56,57] Therefore, it has been hypothesized that mutant myocilin accumulation may overload the normal proteosome degradation pathway and lead to cellular dysfunction and death.[58] Future studies may help clarify this mechanism.

As mentioned previously, JOAG seems to be an autosomal dominant disorder, whereas POAG seems to be inherited as autosomal dominant with incomplete penetrance or a codominant disorder. Individuals heterozygous for myocilin mutations can exhibit a variable phenotypic expression of glaucoma.[10,12,59] Loss of function or haploinsufficiency does not seem to be the mechanism that leads to glaucoma development as there are reports of normal seeming individuals who lack a major portion[60] or an entire copy[61] of 1 myocilin gene. Furthermore, individuals homozygous for myocilin mutations lack glaucomatous findings and support the concept of a dominant-negative effect[62] and is probably the first identified example of "metabolic interference."[63] However, given the small number of patients with these findings, further studies are needed to determine the effect of myocilin mutations in glaucoma.

Myocilin mutations in general are more strongly associated with POAG and JOAG than other forms of glaucoma.[22,64,65] However, single individuals with myocilin mutations with documented pigmentary, pseudoexfoliative, and even angle closure glaucoma have been reported.[22,66] Additionally, a family with mixed-mechanism glaucoma in 4 individuals has been shown to harbor an MYOC mutation.[67] These may simply be coincidental findings or they may indicate that myocilin mutations act to increase an individual's susceptibility to glaucomatous damage. Moreover, other individuals in this mixed mechanism glaucoma family suggest a digenic or 2-gene interaction process leading to glaucoma development. The inheritance of a sole Gly399Val MYOC mutation leads to an adult form of OAG development with a mean age at onset of 51 years. When this MYOC mutation occurs in combination with a CYP1B1 mutation (Arg368His), these individuals had a younger mean age of onset—27 years. Hence, this family demonstrates that the interaction of different glaucoma genes can produce different phenotypes within a single family. Such digenic and polygenic interactions in which the severity of disease depends on the interaction of multiple genes had been demonstrated in other diseases such as Leber's hereditary optic neuropathy.[68]

Optineurin

Optineurin, or the OPTN gene, is also associated with OAG. It was initially localized to the GLC1E locus on chromosome 10p14 in the year 1998[69] and subsequently linked to the OPTN gene in the year 2002.[70] The investigators identified that polymorphisms occurred in 16.7% of their normal tension glaucoma families and the most prevalent polymorphism was the missense mutation Glu50Lys that occurred in 13.5% of these families. Furthermore, they identified a "risk-associated" variation (Met98Lys) in another 13.6% of affected families and 2.1% of controls. Subsequent studies have demonstrated that OPTN variations are associated with relatively rare familial forms of low tension glaucoma (LTG) andAQ2 infrequently associated with more common forms of OAG.[71–74] Overall, OPTN mutations likely account for &<1% of OAG.

Optineurin was previously known as *FIP-2* and its expression has been localized to several nonocular[75] and ocular tissues including the TM, retina, and nonpigmented ciliary epithelium.[70] OPTN contains 16 exons and alternative splicing yields at least 3 different isoforms coding for a 577 amino acid protein product. It has been detected in the aqueous humor of several

species, including humans, suggesting that it is a secreted protein.[70] Like myocilin, this protein's function and how its mutations lead to glaucoma is unknown. Perfusion studies using cadaveric human anterior segments demonstrate that optineurin expression increases after 2 to 7 days of elevated IOPs, 7 days of exposure to dexamethasone, and 3 days of exposure to tumor necrosis factor (TNF)-α.[76] This study suggests that optineurin may be a protein that is produced in response to trabecular stress and may have a protective role in glaucoma development. However, such a neuroprotective role is unclear as there is currently contradicting evidence. In a transgenic mouse model that overexpressed optineurin in the lens, this protein failed to protect against transforming growth factor-β1–induced apoptosis.[77] Whereas other investigators have shown that optineurin overexpression protects cells from hydrogen peroxide-induced cell death and that overexpression of the E50K mutation decreases this neuroprotective effect.[78] The role of optineurin in glaucoma pathogenesis requires further study.

Optineurin is also thought to have a putative role in the TNF-α signaling pathway and hence, may be involved in cellular apoptosis.[70] It has been shown to bind and interfere with an antiapoptosis adenoviral, E3-14.7K protein.[75] Moreover, optineurin's involvement with TNF-α signaling may have direct effects on the modulation of the extracellular matrix and outflow facility of the TM. TNF-α has been shown to modulate MMPs andAQ3 their inhibitors, TIMPs. This is a mechanism thought to be involved with both prostaglandin analogs[79] and laser trabeculoplasty.[80] Moreover, optineurin may be involved in the modulation of the cellular cytoskeleton of TM cells. FIP-2 or optineurin has been shown to bind to Rab8, a protein that is involved with changes in cell shape.[70] This is analogous to how drugs that disrupt the cytoskeleton of the TM can produce an increased outflow facility.[76] Further confirmation of this gene's role in the pathogenesis of glaucoma is underway and in particular, this gene's role in sporadic POAG and LTG needs to be further defined.

WDR36

Another gene associated with POAG is WDR36. Initially linked to the GLC1G locus at chromosome 5q22.1,[81] it was subsequently linked to the WDR36 gene in the year 2006.[82] It is a 23-exon gene that encodes a 100-kDa protein with mRNA transcripts that have been found within several intraocular structures and several organs including the heart, liver, and kidneys. The original glaucoma study described 4 disease-associated sequence variants occurring in a total of 5% of POAG families.[81] Subsequent studies have shown both low[83,84] and no association of WDR36 with OAG.[85,86] In another study, several sequence variants were identified, but none segregated consistently with the presence of glaucoma. However, these sequence variants did seem to be associated with increased severity of POAG suggesting that WDR36 may be a modifier gene for POAG.[87] Moreover, the original family that established linkage to the GLC1G locus did not demonstrate any of the WDR36 mutations and thus raises the possibility of another glaucoma gene at the GLC1G locus.[82]

WDR36 encodes a protein thought to be involved with T-cell activation and proliferation[88] and in ribosomal RNA processing. Diminished function of this gene activates the p53 stress response pathway and a zebrafish model demonstrates a smaller eye with lens abnormalities but no overt signs of glaucoma.[89] The exact role of WDR36 in the pathogenesis of both POAG and LTG needs to be further investigated.

Pseudoexfoliation Syndrome

Pseudoexfoliation (also termed exfoliation) syndrome (XFS) is the most common form of secondary OAG throughout the world. It is inherited as a complex and late-onset disorder with a higher prevalence among females and increasing age.[90] The incidence of XFS varies among ethnic groups[91] from virtually absent in Greenland Eskimos[92] to 20% to 25% in the

Scandinavian countries of Iceland and Finland.[93] XFS is associated with 20% to 60% of OAG in many regions of the world and can be a major cause of ocular morbidity.[91,94,95]

XFS is a systemic disorder in which an unidentified, fibrillar substance is produced by and accumulates within ocular tissues. This substance is associated with basement membranes and seems to obstruct the conventional outflow of aqueous humor. Electron microscopy studies demonstrate accumulation of the material in the TM and around Schlemm's canal with evidence of focal collapse of the canal.[96,97] This mechanical obstruction is the most likely reason for the decreased tonographic outflow facility and increased IOPs seen in XFG patients.

Recently, a genome-wide association study has identified a locus on 15q24 that is strongly associated with XFS. The gene has been identified as the lysyl oxidaselike 1 (LOXL1) gene and it has been strongly associated with both XFS and XFG. The investigators identified 2 single-nucleotide polymorphisms in the first exon of this gene and 1 single-nucleotide polymorphism in the first intron. The nonsynonymous variants, Gly153Asp and Arg141Leu, both cause missense changes in the LOXL1 protein and together account for nearly all of the observed cases (99%) of XFS and XFG in both Icelandic and Swedish cohorts.[98] The LOXL1 association has been replicated in several population cohorts around the world and Gly153Asp seems to be the major risk allele with a prevalence of 92% to 100% in XFS and XFG individuals.[99–104] Interestingly, the Arg141Leu variant has not been replicated to the same degree. This variant demonstrates association with pseudoexfoliation in Australia[103] and 2 United States cohorts,[99,101] but a third United States[100] and Indian[104] cohort do not demonstrate association. Furthermore, a Japanese study demonstrates that this variant has an inverse association with XFS.[102] Moreover, the non-XFS control groups in all of these studies demonstrate a high prevalence of the risk variants ranging from 46% to 88% of the patients. Therefore, although nearly all XFS and XFG patients have LOXL1 polymorphisms, the high prevalence of these polymorphisms in normal individuals implies that other factors must be playing a role in the pathogenesis of this syndrome and the development of glaucoma. This also makes LOXL1 a poor candidate for genetic testing.[99] Studies are currently underway to identify other genes or environmental factors that may contribute to this disorder.

The LOXL1 gene encodes an enzyme that is part of a family of lysyl oxidase genes (LOX) that are involved in the cross-linking of collagen and elastin polymers. LOXL1 oxidatively deaminates the lysine residues of tropoelastin to allow it to form covalently cross-linked elastin fibers.[105] This protein has been shown to be expressed in the cornea, iris, ciliary body, lens capsule, and optic nerve.[103] As XFS deposits are associated with extracellular basement membrane regions and given the function of LOXL1, it seems to be a legitimate functional candidate to be involved with XFS. Future studies will help elucidate the effect of LOXL1 mutations and other factors on the development of glaucoma in these patients.

Congenital Glaucoma

Primary congenital glaucoma (PCG) is a rare form of glaucoma that is commonly referred to as infantile or congenital glaucoma. It is the most common form of glaucoma in infants and more than 80% of cases manifest within the first year of life.[106] The clinical findings in these patients typically consist of epiphora, photophobia, corneal edema, and buphthalmos (enlargement of the globe). The elevated pressures can rapidly lead to axonal loss and permanent loss of vision in untreated individuals. About 60% to 80% of cases are bilateral and males (65%) are affected more frequently than females (35%).[106–108] Inheritance is primarily autosomal recessive with variable penetrance. Ninety percent of cases are sporadic and pseudodominant transmission has been demonstrated in some families.[109] This disorder is most likely owing to an abnormal development of the anterior chamber angle that impairs aqueous

outflow and decreases outflow facility.[110,111] Prevalence of PCG varies from a rate of 1:10,000 in the developed countries[112] to 1:2000 in the Middle East.[113]

To date, 3 genetic loci have been linked to PCG, GLC3A at chromosome locus 2p21,[114] GLC3B at chromosome locus 1p36,[115] and GLC3C at chromosome locus 14q24.3.[116] Several genes have been identified at these loci, but only the GLC3A locus has been linked to a specific gene. This gene is called CYP1B1 and it is the largest known enzyme of the human cytochrome p450 pathway. It is the first gene in this well-known gene family to result in a primary developmental defect.[117] Numerous mutations in this gene have been identified with nearly one-third presenting as insertions or deletions of the gene[117–126] indicating that this gene is relatively susceptible to recombination events. Mutations in this gene have been reported in 20% to 30% of ethnically mixed populations,[122,123,127,128] 50% to 80% of other more consanguineous groups,[118,120,124,126] and nearly 100% of highly consanguineous groups.[129] CYP1B1 contains 3 exons of which only exons 2 and 3 are translated resulting in a 543 amino acid protein.[130] It is expressed in nearly all studied tissues including the fetal brain[131] and TM.[117] It is a dioxin-inducible cytochrome that can both metabolize and activate carcinogenic chemicals and decrease estrogenic activity through the metabolism of 17β-estradiol.[132,133] In general, this enzyme superfamily is crucial for the metabolism of drugs and dietary compounds and the synthesis of steroid hormones and other lipid signaling molecules. It has been hypothesized that the cytochrome P450 enzymes are involved in regulating oxygenated molecules that can act on signal transduction pathway receptors. These receptors, in turn, regulate the differentiation and growth of tissues and therefore, CYP1B1 may be involved in early ocular differentiation.[117,134] Therefore, mutations of this gene may interfere with the normal physiology of CYP1B1 and disturb normal anterior chamber growth and development. Furthermore, cytochrome P450 enzymes may be involved in other physical findings of PCG patients. They have been shown to produce metabolites of arachidonic acid that can inhibit a corneal Na+/K+ ATPase that regulates corneal transparency. Therefore, they may make the cornea more susceptible to pressure-induced hydration and produce the feature of corneal clouding.[135]

In vivo studies to analyze the effects of CYP1B1 mutations were constructed by targeted gene disruption in rodents. These gene knockout mice revealed no unusual developmental defects on gross examination with normal seeming anterior segments and no evidence of glaucoma.[136] However, other investigators have shown focal histologic changes in the anterior segments of CYP1B1−/− knockout mice. Most of the angle structures in these mice were normal, but focal areas demonstrated some developmental abnormalities with structures that resembled those found in PCG. Prominent iris processes (to the TM), peripheral anterior synechiae, small or absent Schlemm's canal, and a basal lamina covering the TM were identified in the mouse knockouts. Interestingly, tyrosinase-deficient albino mice had more severe angle abnormalities than pigmented CYP1B1−/− mice indicating that tyrosinase may influence angle development through its regulation of L-Dopa levels. Therefore, when L-Dopa was administered to the knockout mice during development, they developed less angle dysgenesis than controls not supplemented with L-Dopa. These findings suggest that the L-Dopa pathway may also play a role in angle development. Furthermore, this work implies that other modifying factors such as external stimuli or genes (such as the tyrosine hydroxylase gene) may interact with CYP1B1 to produce PCG phenotypes.[137]

Another gene mutation that has been associated with PCG-like features is FOXC1 (formerly known as FKHL7). FOXC1 mutations are more commonly associated with anterior segment dysgenesis conditions (see following section) and 1 patient with a FOXC1 deletion has been reported to have PCG.[138] Haploinsufficient FOXC1+/− mice also exhibit anterior segment abnormalities (see following section).[139] Therefore, genetic defects of different genes may

produce common phenotypes. One day, we may find that PCG may arise from mutations in a number of critical genes involved in the development of the anterior segment.

Anterior Segment Dysgenesis Syndromes

The anterior segment dysgenesis syndromes are developmental abnormalities of the anterior segment resulting from abnormal migration and differentiation of neural crest derived endothelial cells. Embryonic neural crest cells migrate as a continuous endothelium that lines the anterior chamber in successive waves until the seventh or eighth gestational month. They form the connective tissues from the corneal endothelium to the lens and simultaneously differentiate with other structures of the drainage angle to form the outflow structures of the eye.[140,141] Alterations in the migration and/or differentiation of these cells can yield a "spectrum" of overlapping anterior segment abnormalities.[142] They are a heterogeneous group of disorders inherited as autosomal dominant conditions with variable penetrance. In general, they seem to be phenotypically and genotypically distinct from PCG although PCG individuals with defects of the FOXC1 gene have been identified.[138] The disorders have traditionally been given names on the basis of the degree of anterior segment dysgenesis. The mildest form is posterior embryotoxon in which a prominent and anteriorly displaced Schwalbe line is present. It can be found in approximately 15% of the population and as an isolated finding does not seem to confer an increased risk of glaucoma.[143] Iris hypoplasia and iridogoniodysgenesis (iris hypoplasia plus goniodysgenesis) are milder forms of anterior segment dysgenesis and seem to have a 50% to 75% risk of associated glaucoma.[144,145] The next group with anterior segment changes is Axenfeld-Rieger anomaly. This group can be considered as a single disorder with variable expression and has an approximately 50% risk of associated glaucoma.[111] Findings can vary from iris adhesions to Schwalbe line to iris stromal hypoplasia with correctopa and polycoria. If systemic findings, such as dental or skeleletal abnormalities, are present, then the term Axenfeld-Rieger syndrome (ARS) is used.

Several loci have been linked to the anterior segment dysgenesis syndromes. The primary causative genes that have been identified are 2 transcription factor genes. PITX2 (REIG1 locus) is at chromosomal location 4q25-26[146,147] and FOXC1 (formerly known as FKHL7) is at chromosomal location 6p25.[138,148] Other gene mutations have been reported in small numbers of patients involving the PAX6 gene at chromosome location 11p13,[149,150] FOXE3 gene at 1p32,[151] and the CYP1B1 gene.[152]

PITX2 was identified in the year 1996 as a causative gene associated with Rieger's syndrome.[146] It is a homeodomain containing transcription factor gene thought to be involved with embryonic development. Homeodomains are specific sequences within genes that allow their respective proteins to bind to DNA and regulate the expression of other genes.[153,154] Hence, this gene is a critical component in the development of the anterior segment. This is supported by animal studies in which the PITX2 null and hypomorphic alleles produce anterior segment changes similar to those seen in ARS.[155] ARS has been shown to result from a wide variety of PITX2 mutations and account for approximately 8% to 15% of cases.[147,156] Single base pair alterations, deletions producing a null allele, dominant-negative mutations, and duplications have all been associated with disease phenotypes.[146,156–158] Moreover, different mutations can produce a loss or gain in function (homeodomain encoded DNA binding) that can be measured by standard assays. Studies have shown that different mutant proteins can vary from a 99% reduction in activity to a 200% gain.[156] This finding implies that anterior segment development is tightly controlled and that the phenotypic variability of ARS may be owing to the spectrum of activity of the involved proteins. In addition to ARS, PITX2 mutations have also been associated with iris hypoplasia,[159] iridogoniodysgenesis,[160] and Peters anomaly.[161] As a homeodomain transcription factor gene, PITX2 seems to play a central role in the development of anterior segment structures.

FOXC1 is also a gene transcription factor that was initially linked with Axenfeld-Rieger anomaly and other anterior segment anomalies in the year 1998.[138,148] It is located at chromosome 6p25 and belongs to the forkhead family of transcription factors that have a highly conserved DNA binding domain (ie, forkhead domain). The protein products of these genes are thought to regulate embryonic development and organogenesis as they bind to other target DNA sequences.[162,163] Mutations in FOXC1 are associated with Axenfeld-Riegers,[138,148] iris hypoplasia,[138] posterior embryotoxon,[138] and Peters anomaly.[164] Gene changes are highly variable as is the phenotypic expression of this disorder. Point mutations, missense mutations, deletions, and duplications have been described in this gene. Like PITX2, disease manifestations can arise from either reductions in gene function (haploinsufficiency) or gain of function (duplications). Moreover, modifying genes or external stimuli may play a role in the resulting phenotypic expression of FOXC1. A single point mutation in this gene has been demonstrated to give rise to Axenfeld anomaly, Rieger syndrome, and Peters anomaly within a single family.[164] This reinforces the idea that common gene mutations can result in different phenotypes of anterior segment dysgenesis syndromes.

Animal models of heterozygous FOXC1+/− mutants have been constructed to analyze their effects on ocular development. These heterozygous mutant mice demonstrate anterior segment abnormalities similar to those found in ARS patients strengthening the assumption that this product plays a critical role in the development of the anterior segment.[139,165] Moreover, other modifier genes may play a role in the phenotypic development of this disorder. As discussed previously with homozygous CYP1B1−/− mice, the heterozygous FOXC1+/− rodents vary their phenotype on the basis of tyrosine gene mutations. In the presence of a mutant tyrosine gene, the heterozygous FOXC1+/− mice exhibited greater anterior chamber malformations. It is possible that the tyrosine hydoxlase/L-Dopa pathway may be a new pathway involved with the development of the anterior segment.[137]

Peters anomaly is another disorder that is grouped with the anterior segment dysgenesis syndromes. It is characterized by a congenital central corneal leukoma with defects in Descemet membrane and iridocorneal adhesions.[111] Its inheritance pattern is primarily sporadic although some pedigrees of autosomal recessive[166] and dominant[167] have been reported. Mutations associated with this disorder have been reported in the PAX6 gene for aniridia,[150] the PITX2 gene,[161] CYP1B1,[152] FOXC1,[164] and the MAF gene. The MAF gene is located at 16q23.2 and encodes a transcription factor that regulates crystallin expression during lens differentiation.[168] Mutations in the PAX6 gene have also been described in a single case of ARS.[149]

Discussion

Significant advances have been made in identifying glaucoma-associated genes and their associated pathways. Glaucoma is a heterogeneous group of disorders with both Mendelian and multifactorial traits. Even within individual families, there can be large variations in the phenotypic presentation of gene mutations. Therefore, other multifactorial etiologies must be involved in glaucoma development. This can include polygenic and environmental factors. Some genes may act as susceptibility factors that allow other genes or environmental influences to produce glaucoma. Furthermore, our knowledge will continue to expand aided by the use of novel animal models allowing genetic modifiers and the complex nature of glaucoma to be investigated. Thanks to the Human Genome Project, advances in bioinformatics, and advances in gene identification technologies, researchers now have powerful tools to decipher the cause of glaucoma and improve patient care with improved diagnostic tests, drug therapies, and gene therapy. Moreover, using modern gene array technologies, thousands of gene mutations can be screened on a single microarray chip using a very small amount of blood or tissue. By combining this information with advances in bioinformatics, scientists will be able to use

genotype/phenotype correlations to develop an overall risk profile for an individual. If such a profile determines that a given patient has a high likelihood of developing glaucoma, one may elect to start therapy before any signs or symptoms of glaucoma develop. Such risk assessment is being advocated by some authors for patients at high risk for breast cancer.[169]

Identifying glaucoma-associated genes will also help elucidate the biochemical pathways that produce glaucoma. Knowing such pathways will facilitate the development of novel drug therapies that can be tailored to individual forms of glaucoma. New therapies could include agents based on the protein, enzymes, or RNA transcripts associated with glaucoma. Scientists could create safer and more disease-specific therapies because the biochemical pathways involved in glaucoma could be specifically targeted. Moreover, the field of pharmacogenomics will continue to grow from genetic research. This field investigates the genetic characteristics of individuals who respond to specific medications. As a result, physicians could select appropriate medications at specific dosages for an individual on the basis of their genetic profile. This approach would lead to the more efficient treatment of patients compared with the current trial-and-error method of prescribing medications. Because glaucoma seems to be a polygenic condition, specific gene therapies aimed at individual mutations may be difficult to develop. Instead, future therapies could be aimed at common pathways that lead to glaucoma development.

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Table 1

Genes and Loci Associated With Glaucoma

Loci	Chromosome	Gene	Phenotype
λGLC1A	1q23-24	MYOC	JOAG, POAG
GLC1B	2cen-q13		POAG
GLC1C	3q21-24		POAG
GLC1D	8p23		POAG
GLC1E	10p14-15	OPTN	LTG, POAG
GLC1F	7q35-36		POAG
GLC1G	5q22.1	WDR36	POAG
GLC1H	2p16.3-p15		POAG
GLC1I	15q11-q13		POAG
GLC1J	9q22		JOAG
GLC1K	20p12		JOAG
GLC3A	2p21	CYP1B1	PCG, Peters
GLC3B	1p36		PCG
GLC3C	14q24.3		PCG
RIEG1 (IRID2)	4q25-27	PITX2	Axenfeld-Reiger, iridogoniodysgenesis
RIEG2	13q14		Axenfeld-Reiger
IRID1	6p25	FOXC1 (FKHL7)	Axenfeld-Reiger, PCG
PAX6	11p13	PAX6	Anirida, Peters, Axenfeld-Reiger
	15q24	LOXL1	Pseudoexfoliation glaucoma

JOAG indicates juvenile open angle glaucoma; LTG, low tension glaucoma; PCG, primary congenital glaucoma; POAG, primary open angle glaucoma.