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Primary Open-Angle Glaucoma Genetics in African Americans

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Abstract

Purpose of review—Individuals of African descent are at highest risk for developing primary open-angle glaucoma (POAG), a devastating disease and major contributor of blindness worldwide. Currently, there is a large dearth of knowledge in this area despite a critical need for better understanding the underlying genetic and environmental factors afflicting this population. Here we highlight the current literature exploring the genetics of POAG in African Americans.

Recent findings—Current studies have yet to replicate European POAG index variants (i.e. *CDKN2B-AS1* and *SIX1/SIX6*) in African Americans or to definitely exclude that these loci contribute to risk in African descent populations. Recent studies have evaluated clinical features that may account for some differences in POAG risk between African Americans and European Americans.

Summary—In summary, little headway has been made in elucidating the genetics of primary open-angle glaucoma in African Americans and other individuals of African descent.

Keywords

African American primary open angle glaucoma; glaucoma genetics

Introduction

Glaucoma is a heterogeneous group of eye diseases characterized by chronic, progressive degeneration of the optic nerve leading to peripheral vision loss and, in severe cases, blindness. Glaucoma is distinguishable from other optic neuropathies by differences in the appearance of the optic-nerve tissue (i.e. pink versus loss of color) and by the presence of cupping, a process that does not occur in most other optic neuropathies (1). In glaucoma, cupping of the optic nerve results as a consequence of the loss of retinal ganglion cell (RGC) axons and degeneration of the underlying support vasculature. Left untreated, individuals with glaucoma suffer from gradual loss of peripheral vision that can progress to blindness over time. Primary open angle glaucoma (POAG) accounts for ~75% of glaucoma cases in the U.S. (2). POAG results from abnormal drainage of the aqueous humor from the anterior chamber through the trabecular meshwork, despite a normal ocular angle. In most POAG

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cases, increased fluid raises the intraocular pressure (IOP) and, if not controlled, this can irreversibly damage the optic nerve. Despite other mechanisms modulating the glaucomatous process, treatment is directed at lowering IOP and can include medication and/or surgery. Unfortunately, vision continues to decline in approximately 30% of patients who, despite aggressive treatment (reviewed in (3)), experience progressive optic nerve damage without increased IOP ([normal tension glaucoma]; reviewed in (4)). These patients and others are thought to suffer from vision loss due to different underlying pathophysiology.

Competing theories of molecular underpinnings of glaucoma

In trying to understand how clinical and epidemiological risk factors biologically impact disease, it helps to note that POAG can be triggered by various mechanical, environmental, molecular, or infectious agents. IOP in particular is such a strong modifier of POAG risk that some clinicians use it as a glaucoma diagnostic criterion. The mechanical theory of glaucoma revolves around the destruction of the optic nerve through the biomechanical forces of IOP being applied to the lamina cribrosa. The lamina cribrosa is a mesh-like network of collagen fibers located at the optic nerve head and forms a barrier between the vitreous humor and the retrobulbar space behind the eye(5). Unmyelinated retinal ganglion cell axons pass through the lamina cribrosa, and then are myelinated in the retrobulbar space forming the optic nerve bundle. At a sufficiently high level, IOP forces can displace the lamina cribrosa pushing it to the posterior of the globe of the eye and thereby reduce the velocity and quantity of retinal blood and increasing the expression of cytokines(6).

Additionally, epidemiology studies that have found significant correlations between the risk of POAG and myopia may only be measuring the association of mechanical properties of myopia, such as increased axial length. It has already been postulated that an increase in the axis of the eye results in a subsequent increase in stressor forces on the sclera. In the prospective Los Angeles Latino Eye study (LALES), individuals with axial myopia had higher baseline levels of IOP and greater rates of POAG with a sharp increase in incidence in eyes longer than 25mm(7;8).

The mechanical theory and its targeted IOP lowering treatment regimens protect many, but not all, patients from additional vision loss. The etiology of glaucoma remains confounded by both patients who have normal IOP levels (IOP ≤ 20 mmHG) and still develop glaucomatous vision loss(9;10) as well as by those with ocular hypertension (IOP ≥ 22mmHG) who never go on to develop glaucoma. Traditionally, glaucoma associated vision loss has been attributed to degeneration of RGCs as a result of IOP-dependent or IOP-independent stressors on a background of age-related factors. Another theory of glaucoma etiology posits that some patients may develop vision loss not as a consequence of the accumulation of mechanical or vascular stressors, but as a result of axonopathy (disruption of normal axon function) in RGC(11). Animal models of glaucoma provide evidence that glaucomatous optic neuropathy results, in part, from deficits in axonal transport of mitochondria to and away from areas of the axon requiring greater availability of ATP for hydrolyzation(12). Mitochondria accumulate in key points of the axon, leading to a buildup of reactive oxygen species that damage the axonal milieu and subsequently trigger a

Wallerian-like degeneration at distal points (11;13). While not studied in a human-based system, a similar effect is believed to occur in individuals with normal tension glaucoma as a result of IOP "sensitivity"(14-16).

POAG epidemiological risk factors

POAG risk is complex; various factors have been reported to influence POAG risk, yet the interaction and measurable impact of these is not fully understood (e.g. (17-19)). The most significant risk factor for POAG is age, as POAG generally presents after the age of 40. Various intricately related quantitative traits also influence POAG susceptibility. One such trait is intraocular pressure (IOP) which is itself influenced by multiple factors including production and drainage of aqueous humor, and which is also affected by ocular anatomy (reviewed in (3;17)). IOP is modified by various lifestyle activities (17) but, further complicating the association of IOP with POAG, IOP has not been show to increase with age (reviewed in (3)). Interestingly, African Americans are more likely to experience visual field damage at higher IOP levels (20) suggesting a greater IOP "sensitivity".

Other physical modifiers of POAG risk include myopia, central corneal thickness (CCT), and cup-to-disc ratio (CDR; reviewed in (3)) all of which are more severe in African Americans. Non-genetic factors that influence POAG include exercise, caffeine intake, cigarette smoking/exposure, alcohol use, postmenopausal hormone use, diet, and BMI (reviewed in (17)). It is generally believed that these risk factors may influence POAG by altering IOP, blood flow to the optic nerve, and/or by varying the rate of RGC apoptosis (17). Further complicating the influence of many of these factors on POAG risk is that they have not been meaningfully evaluated across ethnic groups to determine what commonalities and differences exist among and between POAG patients. This deficit of knowledge offers a valuable opportunity to address health disparities by determining what non-genetic factors correlate with POAG risk in African Americans.

Genetic epidemiology of POAG

The global prevalence of glaucoma for individuals between 40 and 80 years of age is ~3.5% (~64.3 million people) (21). The rates of glaucoma have been found to be similar between European, Japanese, and Indian populations with rates approaching those observed in African descent populations in China only within the oldest age categories (22). Globally, POAG prevalence is highest in Africa (21). With improvements in medical care, the average life expectancy has risen and therefore the aging population is growing; without better detection methods and intervention therapies, the number of glaucoma patients will also rise. In 2020, it is expected that 76 million people will have glaucoma and this number is predicted to exceed 111 million by 2040 (21).

In the U.S., the prevalence of glaucoma is 3.4% in African Americans, 1.7% in Caucasians, and 1.5% in Hispanics (23). Disturbingly, POAG is more likely to result in vision loss and blindness in African Americans compared to other populations in the U.S.; African Americans typically suffer from higher mean IOP levels and not unsurprisingly, African American race has been found to predict visual field damage (20). Further, ocular anatomy

may differ across ethnic groups - height of trabecular meshwork in African Americans is shorter, on average, when compared with Asians and Caucasians (24). While African Americans are the group at highest risk of developing glaucoma-related vision problems, likely attributable to genetic and environmental factors that trigger pathogenesis at an earlier age, many cases remain undiagnosed until later stages of disease due to limited access to medical intervention. The combination of higher lifetime risks and lower medical support place a double burden on this group. Previous studies have suggested that nationwide implementation of screening middle aged African Americans could decrease the rate of undiagnosed glaucoma from 50% to 27%(25). Earlier screening and diagnosis enables patients to more effectively leverage current treatment options to reduce the risk of bilateral blindness later in life(25).

Interestingly, treatment efficacy and efficiency appear to differ between racial/ethnic groups even within controlled clinical trials. In a long term treatment study of African American and Caucasian patients with pharmacologically uncontrolled glaucoma, African Americans experienced better visual outcomes when argon laser trabeculoplasty (ALT) was performed prior to a two-step trabeculectomy procedure. This is in contrast to Caucasians who experienced better control of IOP when ALT was performed “between” the two rounds of trabeculectomy (26). This potentially supports biological differences between the groups. In a separate clinical trial, postoperative treatment outcomes for the Ex-PRESS glaucoma filtration device were comparable between African American and Caucasian patients (27). Additionally, glaucoma patients of African descent in St. Lucia experienced greater effectiveness of selective laser trabeculoplasty in reducing IOP by an average of 7.6-8.2 mmHg over the course of a year (28).

In addition to IOP, the most significant known risk factors for POAG include age, ethnicity, and genetics. In fact, more than a dozen loci have been identified that associate with POAG and endophenotypes of POAG including IOP, anatomical optic measures, and optic nerve parameters (reviewed in (4); see Table 1 for list of adult-onset POAG-associated variants). While it is known that ocular anatomical features in African Americans likely put them at higher risk for developing POAG (24), the genetic basis for this risk has yet to be elucidated. There is only one published genome-wide association study evaluating glaucoma in African Americans, and it showed that several known glaucoma variants, generally identified in populations of primarily European ancestry, are not reflective of genetic risk in African Americans (29).

Early gene-based studies in 1997 first identified Myocilin (*MYOC*), originally named the Trabecular Meshwork-Inducible Glucocorticoid Response Protein (*TIGR*) gene(30). The protein encoded by *MYOC* is expressed in the sclera, choroid, cornea, and trabecular meshwork (31-33); it is thought that mutated versions of MYOC are unable to be appropriately secreted into the aqueous humor (34). Buildup of MYOC proteins can block the flow of the aqueous humor through the trabecular meshwork, resulting in increased IOP and subsequent optic nerve damage. *MYOC* mutations have been shown to follow a Mendelian mode of inheritance in families of varied ethnic backgrounds with juvenile glaucoma (35-38); these findings suggest that variants in MYOC significantly influence the protein structure stability. Mutations of a less deleterious nature likely account for some of

the population-based studies that have found that *MYOC* mutations contribute to risk of POAG in a small subset of patients (3-4%) whose conditions are not solely explained by *MYOC* variants (39;40).

To investigate the role of *MYOC* mutations in African Americans, Liu and colleagues sequenced the coding region of *MYOC* in 529 African Americans with POAG and 270 African American controls (41). This group identified 29 MYOC variants including six potential MYOC mutations, and two novel mutations that were detected solely in cases. Four previously reported MYOC mutations were present in only cases in this study. Overall, MYOC mutations were rare in this African American population sample.

Other early candidate gene-based studies found evidence for association of coding variants in the optineurin gene (*OPTN, GLC1E*). These studies led Liu *et al.* to investigate the role of OPTN sequence variants in a Ghanaian population of POAG patients (West Africa) using a case-control approach (140 POAG cases and 130 non-POAG controls)(42). Sequencing the *OPTN* coding exons identified novel coding variants, but no significant differences in allele frequencies between cases and controls. For two novel variants in which one copy was present in a POAG case and zero copies were detected in controls, age of onset of POAG was relatively young, 40, and 59 years old) and the patients' IOP were relatively high (>30mmHg).

Jiao and colleagues performed family-based, genetic linkage analyses in 146 multiplex families from the Afro-Caribbean population of Barbados in the West Indies, with the goal of identifying genetic loci accounting for increased POAG risk compared to European descent populations (43). A strong linkage signal was detected on chromosome 2p (logarithm of odds score= 6.64); subsequent analyses of SNPs from this region were performed in two independent groups of unrelated cases and controls wherein an association was detected for three SNPs: rs12994401, rs10202118, and rs1533428 (43). Liu *et al.* genotyped these three SNPs in African-American and Ghanaian (West African) samples and also detected an association at rs12994401 in the African-American population(44). Interestingly the risk alleles reported between these two studies were for opposite alleles with the 'T' allele associated with risk in Jiao *et al.* and the 'C' allele similarly associated with risk in Liu *et al.* This reverse correlation may be due to the effects of differing levels of European ancestry admixture between African Americans (~21%) and Barbadians (~10%) or a result of a genotyping call error (44).

With regard to adult-onset POAG, recent studies have focused on *CDKN2B-AS1*; a gene originally found to contribute to cardiovascular disease(45-48). It has also shown strong pleiotropy with other diseases such as cancer(49;50), T2D (51;52), endometriosis(53), and notably glaucoma (54-57). In several studies of European and Asian descent populations, variants within *CDKN2B-AS1* have been found to be associated with POAG, normal tension glaucoma, and quantitative glaucoma traits, such as CDR (54;56-58). Liu and colleagues evaluated this gene region and others in an effort to evaluate known adult-onset POAG loci in 2013, focusing on five loci - *CDKN2B-AS1, TMCO1, CAV1/CAV2*, chromosome 8q22 intergenic region, and *SIX1/SIX6*- in populations of African ancestry including African American (1150 cases and 999 controls) and Ghanaians (West Africa; 483 cases and 593

controls) (55). They genotyped 57 single nucleotide polymorphisms and evaluated POAG as well as normal tension (maximum IOP 21 mm Hg) and high tension glaucoma (IOP >21 mmHg). Their results revealed association of *CDKN2B-AS1* SNP rs10120688 with POAG; *CDKN2B-AS1* SNP rs10965245 was associated with high tension glaucoma and *SIX1/SIX6* SNP rs11849906 was associated with high tension glaucoma. No significant signals were detected in the Ghanaian samples. In another study of African Americans with POAG, Restrepo and colleagues did not find that SNPs in this gene contributed to POAG risk even after performing a fine-mapping analysis that included 286 SNPS within *CDKN2B-AS1* (59).

In a recently reported study, Bonnemaijer and colleagues evaluated genetic African ancestry in 268 POAG patients and 137 controls from two South African population samples, the South African Colored (SAC) and a South African Black (SAB) populations (60). Genetic African Ancestry was significantly associated with both thinner CCT and higher IOP in POAG patients; however, when stratified by genetic African ancestry (applying a cutoff of 60%), CCT was not associated with POAG, suggesting that thinner CCT is not associated with POAG in this African population sample. The use of African genetic ancestry as a defining variable has also shown some promise for elucidating complex genetic associations in other studies, such as in Restrepo *et al.*, where percentage of African Ancestry in an African American cohort was associated with POAG at the *CDKN2B-AS1* locus, even though single SNP analysis failed to identify such a correlation (59).

Current larger scale efforts to ascertain and study POAG in African Americans

The recently reported Primary Open-Angle African American Glaucoma Genetics (POAAGG) study is currently the largest single-site collection of African American POAG patients (at the University of Pennsylvania [UPenn], Department of Ophthalmology, Scheie Eye Institute) to date(61). This greater Philadelphia, Pennsylvania-based study is a population-based, cross-sectional, case-control study that currently includes at least 2520 African Americans 35 years or older from neighborhoods with low income and high unemployment. Participants underwent extensive eye examinations and detailed interviews to collect behavioral, medical, and demographic information; cases were more likely to have a history of blindness and lower BMI compared to controls. Only limited genetic studies pertaining to this cohort have been published.

A subset of POAAGG patients were screened for legal blindness due to POAG (62). A total of 118 eyes were examined with half legally blind due to POAG and half afflicted with POAG but retaining vision (age- and sex-matched). In an evaluation of risk factors based on chart review, they determined access to care, initial visual acuity worse than 20/40, and poor IOP control to be major risk factors associated with POAG related blindness.

Collins *et al.* studied whether mitochondrial genetics and haplogroups, were potential markers of POAG risk in a subset of the POAAGG study (30;63). While the common African haplotypes were broadly similar to prior reports, L1c2, L1c2b, and L2 haplogroups were enriched in cases. These haplogroups include several missense mutations in the

cytochrome c oxidase subunit 1 (MT-CO1) gene and by a variant in MT-RNR2 that encodes the gene for the mitochondrial ribosomal 16s RNA (30;63). Because an estimated one out of four African Americans carries these haplotypes, Collins *et al.* hypothesized that individuals with these mitochondrial ancestries could be contributing to the elevated risk of glaucoma in this population (30;63). Additionally, variants in *MT-RNR2* have been associated with increased risk of other ocular diseases (age-related macular degeneration) in Mexican Americans (64) who also share a complex genetic admixture of European and African ancestries.

Prior studies suggest that there is a distinct genetic architecture for glaucoma in African Americans (29); given the differences in POAG risk allele frequencies when comparing individuals of European and African ancestral backgrounds (Table 1), this is not surprising. Teasing apart the genetics of POAG in African Americans using various genetic approaches including large-scale genome-wide association studies, family-based studies, and admixture mapping is key to understanding this devastating disease in a population that is at much greater risk compared to populations of other ancestral backgrounds that have been studied at greater frequency. And while evaluating disease in one population will not fully inform on all global populations, it is worthwhile to consider that by broadening the focus beyond where it has been previously concentrated, there is major potential to understand the biology in an impactful way for a much larger number of people.

Conclusion

Glaucoma is a disease of the eye characterized by progressive degeneration of retinal ganglion cells and subsequently damage to the optic nerve; this pathology is a leading cause of irreversible blindness worldwide. Primary open-angle glaucoma (POAG), the most common form of glaucoma, typically manifests after the age of 40 and, while treatable if detected early, there is no treatment for restoring lost vision. Known risk factors for POAG include age, intraocular pressure (, ethnicity, genetics, central corneal thickness and myopia. Various reports have presented conflicting evidence for additional risk factors including smoking status, diabetes, hypertension, eye injury, hormone replacement therapy, and corticosteroid use. Despite numerous studies, molecular and environmental factors that contribute to POAG remain elusive. Interestingly, POAG risk is more than two-fold higher in African Americans compared to other U.S. racial/ethnic groups (21). POAG also manifests at a younger age and results in more cases of blindness in African Americans. Further, there is a scarcity of research addressing the increased risk in African Americans, exposing a critical health disparities issue in this underserved population. Remarkable advances in scientific research have resulted in the discovery of vast amounts of coding and noncoding DNA sequence over the past century and a half. In the more recent past, scientists have determined that mutations throughout the genomes of individuals can contribute to and in some cases are directly responsible for or indicative of disease incidence or progression. There are also differences in the DNA sequence of individuals from distinct ancestral backgrounds that influence disease susceptibility, progression, and response to treatment (reviewed in (65)). These differences are crucial to consider in genetic analyses that aim to elucidate genetic variants contributing to diseases in order that all individuals, regardless of

ethnicity, are able to benefit (66-68). For POAG in particular, assessing differences across ethnic groups could illuminate novel genetic and environmental mediators of the disease.

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Table 1

Known POAG Risk Loci.

Candidate Gene	Index SNP	Location (chr:bp*)	Reported Risk Allele	1000 Genomes Frequency		Reference
				African	European	
FOXC1	rs2745572	6:1548369	A	0.850	0.636	(69)
TGFBR3	rs1192415	1:92077097	G	0.205	0.173	(70)
TMCO1	rs4656461	1:165687205	G	0.256	0.141	(54)
FNDC3B	rs6445055	3:171992387	G	0.638	0.826	(71)
AFAP1	rs4619890	4:7853160	G	0.859	0.466	(72)
GMDS	rs11969985	6:1922907	G	0.741	0.851	(72)
CAV1	rs4236601	7:116162729	A	0.399	0.259	(73)
CDKN2B-AS1	rs4977756	9:22068652	A	0.680	0.600	(54)
ABCA1	rs2472493	9:107695848	G	0.311	0.418	(72)
ATXN2	rs7137828	12:111932800	T	0.981	0.536	(69)
SIX1/SIX6	rs10483727	14:61072875	A	0.966	0.404	(57)
PMM2	rs3785176	16:8896931	G	0.251	0.096	(74)
GAS7	rs9897123	17:10020501	C	0.533	0.504	(69)
TXNRD2	rs35934224	22:19872645	C	0.691	0.846	(69)

*Location based on ENSEMBL build 37: chr=chromosome, bp=base pair position; 1000 Genomes allele frequencies as reported by ENSEMBL.