AMERICAN ACADEMY OF OPHTHALMOLOGY®

A Whole-Genome Sequence Genome-Wide Association Study in *All of Us* Identifies a Novel Glaucoma Risk Locus in African Individuals

Inas F. Aboobakar, MD,[1,2,3,*] *Lauren A. Cruz, MPH,*[4,5,*] *Tyler G. Kinzy, MS,*[6,7] *Yuyang Luo, PhD,*[1,2,3] *Sanjana Nallapaneni, MPH,*[4,5,8] *Ron Do, PhD,*[9] *Thi Ha Vy, PhD,*[9] *Hetince Zhao, MD,*[9] *Jessica H. Tran, MD, MSCR,*[9] *Pirro G. Hysi, MD, PhD,*[10] *Anthony P. Khawaja, PhD, FRCOphth,*[10] *Puya Gharahkhani, PhD,*[11] *Louis R. Pasquale, MD,*[9] *Michael A. Hauser, PhD,*[12] *Ayellet V. Segrè, PhD,*[1,2,3] *Dana C. Crawford, PhD,*[4,5] *Janey L. Wiggs, MD, PhD,*[1,2,3,†] *Jessica N. Cooke Bailey, PhD, MA,*[6,7,†] *International Glaucoma Genetics Consortium*

Objective: To assess how whole genome sequencing (WGS) and varying phenotype definitions influence genetic discovery for primary open-angle glaucoma (POAG) in a diverse population.

Design: Ancestry-stratified genome-wide association studies (GWASs) and cross-ancestry meta-analyses of POAG cases and controls using 2 phenotype definitions.

Participants: Cases (age ≥40 years) and controls (age ≥65 years) were identified in the National Institutes of Health *All of Us* Research Program v8 data release and subdivided into genetically inferred ancestral groups. Using the relaxed phenotype (International Classification of Diseases [ICD] codes only), case/control counts were European (EUR; 1846/84 654), African (AFR; 1042/15 966), and Latino/Admixed American (AMR; 305/10 167). Using the stringent phenotype (ICD codes and evidence of glaucoma treatment in the electronic health record), case/control counts were EUR (1528/79 276), AFR (862/14 076), and AMR (250/9668). Cross-ancestry meta-analyses included 3193 cases/110 787 controls for the relaxed phenotype and 2640 cases/103 020 controls for the stringent phenotype.

Methods: Genome-wide association studies were conducted within EUR, AFR, and AMR ancestry groups individually using firth logistic regression with age, sex, and the top 10 genotype principal components included as covariates. The ancestry-stratified GWASs were then meta-analyzed using a fixed-effects, inverse variance-weighted approach.

Main Outcome Measures: Identification of genome-wide significant loci ($P < 5 \times 10^{-8}$) for POAG using different phenotype definitions and ancestry groups.

Results: Known POAG risk loci (e.g., *TMCO1*, *CDKN2B-AS1*, and *GMDS*) reached genome-wide significance in both the EUR GWASs and cross-ancestry meta-analyses (odds ratio range: 1.19–1.38). A novel risk locus near *CYP2A7* (rs76935404[T], odds ratio = 1.35) was identified in the AFR ancestry GWAS using the stringent phenotype definition. Effect sizes for known POAG risk loci from prior large-scale meta-analyses strongly correlated with effect sizes in this study (Pearson r = 0.75–0.84, $P < 1 \times 10^{-5}$ for all). The strength and consistency of these correlations support the robustness of the findings.

Conclusions: This study demonstrates the value of WGS, diverse ancestry inclusion, and phenotypic refinement in uncovering novel POAG genetic risk loci. The findings underscore the need to prioritize both genetic diversity and refined case/control definitions to advance understanding of this complex ocular disease.

Financial Disclosure(s): Proprietary or commercial disclosure may be found in the Footnotes and Disclosures at the end of this article. *Ophthalmology Science 2026;6:101298*

Supplemental material available at www.ophthalmologyscience.org.

While primary open-angle glaucoma (POAG) is prevalent in all populations, population-based studies suggest it disproportionately affects African and Latino individuals, who have a younger age at onset, present at more advanced disease stages, and have greater risk of blindness compared to non-Hispanic Whites.[1–5] More than 300 risk loci have been identified in prior analyses of this highly heritable complex disease,[6–8] which have mainly been conducted in

http://doi.org/10.1016/j.xops.2026.101298
ISSN 2666-9145/26

individuals of European (EUR) ancestry. However, few are conclusively associated with risk of glaucoma in individuals of African (AFR) continental genetic ancestry,[9–14] and even fewer in those with Latino/Admixed American (AMR) ancestry.[10,14]

In addition to the limited ancestral diversity in prior POAG studies, most known loci have been identified in genome-wide association studies (GWASs) conducted on genotyping arrays, where only a subset of variants (~2%) across the genome are directly assayed.[15] The remaining variants examined in these GWASs are typically imputed, requiring large reference panels of sequenced individuals of similar ancestry to the population being studied.[16] Imputation accuracy is highly variable and especially dependent on the ancestry of the reference and genotyped population samples.[17] In contrast, whole genome sequencing (WGS) can provide more comprehensive ascertainment of both common and rare putative causal variants in genetic risk loci.[18]

Phenotype definitions also vary widely across genetic studies, ranging from self-reported diagnosis or International Classification of Diseases (ICD) 9/10 codes alone to comprehensive clinical examinations by ophthalmologists. Studies using large-scale biobanks as a sample source often rely on ICD diagnosis codes for disease ascertainment, as ocular examination and imaging data are often limited.[19] However, ICD codes as phenotype definitions may have reduced specificity and potentially greater heterogeneity, diminishing statistical power to detect genetic differences between individuals with and without a disease of interest.

The National Institutes of Health *All of Us* (*AoU*) Research Program data set enables examination of the impact of phenotype variability and WGS on genomic discovery for complex-inherited diseases such as POAG. *All of Us* aims to enroll >1 million individuals of diverse backgrounds to improve disease diagnosis, treatment, and prevention.[20] Data from surveys, WGS, electronic health records (EHRs), physical measurements, and wearable devices are available in the *AoU* Researcher Workbench.[20,21] To date, WGS data have been released for >414 000 participants (v8), nearly half of whom are from groups historically under-represented in biomedical research.[21] In this study, we apply 2 phenotype definitions (relaxed and stringent) for POAG cases and controls in *AoU*. We then perform ancestry-stratified GWASs and cross-ancestry meta-analyses of EUR, AFR, and AMR individuals using WGS data. Using this approach, we have replicated known POAG risk loci and identified a novel risk locus in AFR individuals.

Methods

An overview of the study design is shown in Figure 1. Informed consent was obtained for all participants enrolled in *AoU*. The *AoU* Institutional Review Board follows the regulations and guidance of the National Institutes of Health Office for Human Research Protections for all studies, ensuring that the rights and welfare of research participants are overseen and protected uniformly.[20,21] The described research adhered to the tenets of the Declaration of Helsinki.

Case/Control Definitions

Our baseline inclusion criteria were as follows: *AoU* participants with WGS data and current age ≥40 years at the time of analysis (February 2025), which were identified using the cloud-based *AoU* Researcher Workbench. For Phenotype 1 (relaxed), POAG cases were defined as individuals aged ≥40 years with an ICD-9/ICD-10 diagnosis code for POAG, but no code for other secondary forms of open-angle glaucoma or primary/secondary angle closure glaucoma (Supplementary Table 1, available at www.ophthalmologyscience.org). Controls were aged ≥65 years and did not have any ICD-9/ICD-10 diagnosis codes for POAG, any other form of glaucoma, glaucoma suspect, ocular hypertension, or family history of glaucoma; an older cohort was used for controls to minimize the likelihood of undiagnosed cases in the control data set. For Phenotype 2 (stringent), POAG cases met criteria for Phenotype 1 and also had evidence of glaucoma treatment (topical intraocular pressure lowering drops, laser trabeculoplasty, minimally invasive glaucoma surgery, or incisional glaucoma surgery) via RxNorm and Current Procedural Terminology codes in the EHR; controls met the criteria for Phenotype 1 and also did not have any evidence of glaucoma treatment in their EHR (Supplementary Table 1).

WGS Data and Quality Control

The *AoU* WGS protocol has been extensively described previously.[21] Briefly, WGS was performed on the Illumina NovaSeq 6000 instrument, and analyses were performed on the Illumina Dynamic Read Analysis for GENomics platform. Quality control metrics included the following: mean coverage (threshold of ≥30x), genome coverage (threshold of ≥90% at 20x), coverage of hereditary disease risk genes (threshold of ≥95% at 20x), aligned Q30 bases (threshold of $\geq 8 \times 10^{10}$), contamination (threshold of ≤1%), and concordance to independently processed array data.[21] Additional sample quality control metrics were also applied by *AoU*, including fingerprint concordance, sex concordance, and cross-individual contamination rate. Whole genome sequencing from 414 830 participants passed all quality control metrics and are available in the *AoU* v8 data release.

Genetically inferred ancestry was derived by *AoU* for all participants with WGS data in the v8 data release; the ancestry labels are consistent with those in Genome Aggregation Database, the Human Genome Diversity Project, and 1000 Genomes.[21] Individuals with kinship scores >0.1 suggesting relatedness (n = 30 584), ancestral outliers on principal components analysis (n = 987), or sex ploidy mismatch (n = 1476) were excluded from the POAG GWASs.

Ancestry-Stratified GWASs and Cross-Ancestry Meta-Analyses

Variants with >2% missing genotypes, minor allele frequency <0.01, and evidence of significant deviations from Hardy-Weinberg Equilibrium ($P < 1 \times 10^{-8}$) were excluded; these filters were applied separately for each ancestral group and each phenotype definition. Firth logistic regression analyses were then performed for each ancestral group individually for each phenotype definition, with age, sex, and the top 10 genotype principal components included as covariates.

Genetic heterogeneity across the individual GWASs was assessed using the I^2 test in Meta-Analysis of Genome-Wide Association Scans; there was no evidence of significant heterogeneity in the EUR, AFR, and AMR GWASs.[22] The summary statistics for each phenotype definition were meta-analyzed using a fixed-effects, inverse variance-weighted approach in Meta-

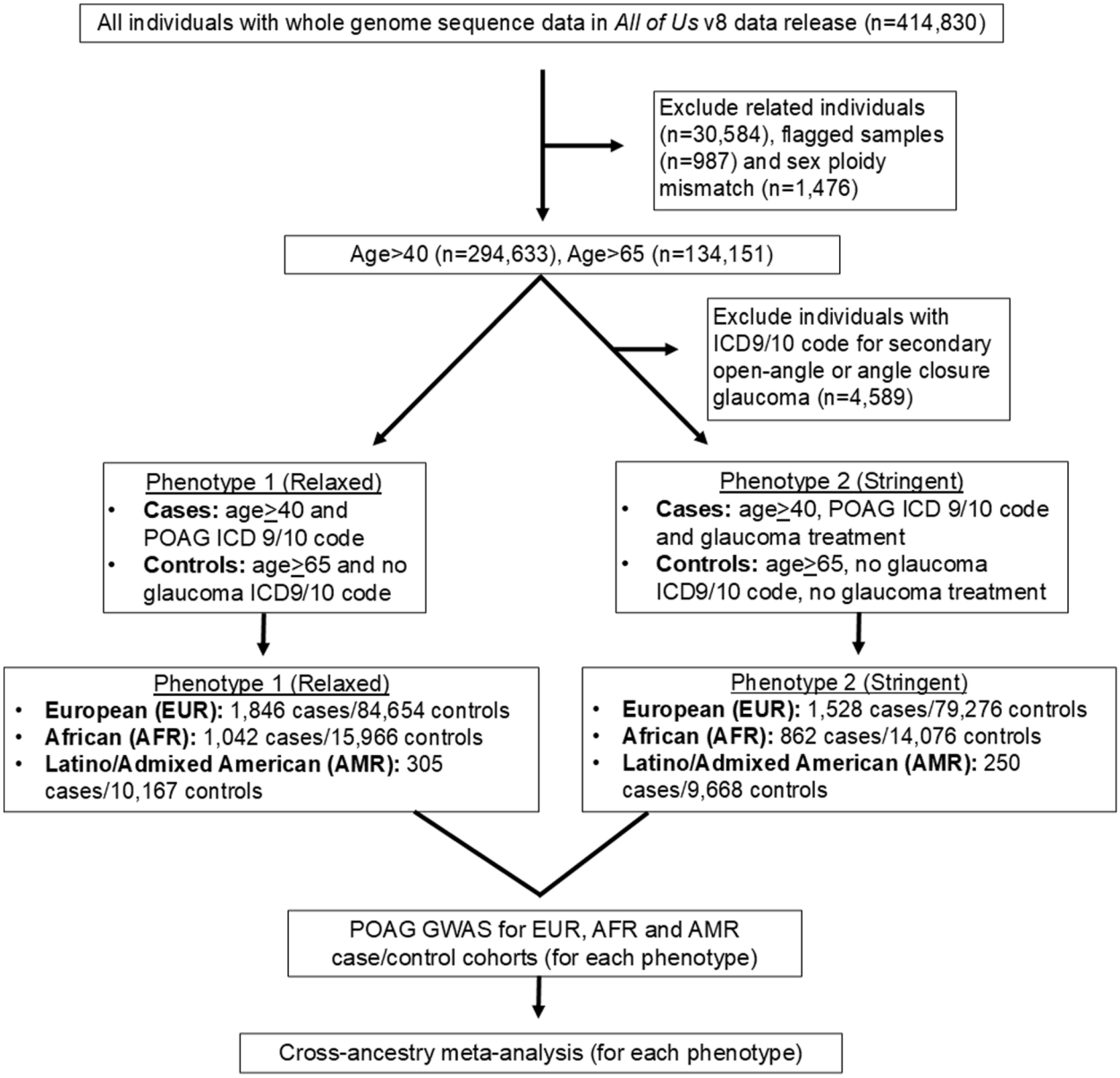

Figure 1. Study design. GWAS = genome-wide association study; ICD = International Classification of Diseases; POAG = primary open-angle glaucoma.

Analysis of Genome-Wide Association Scans (release date March 25, 2011) (3193 cases and 110 787 controls for Phenotype 1; 2640 cases and 103 020 controls for Phenotype 2).[22] To ensure that a random-effects model would yield a consistent result, the GWAS summary statistics were also meta-analyzed using Meta-Regression of Multi-Ethnic Genetic Association.[23] Manhattan plots, quantile-quantile plots, and LocusZoom plots were created in LocusZoom.js (v0.12).[24]

Correlation of Effect Sizes for Known POAG Variants

The effect sizes (beta coefficients) of POAG-associated variants identified in previously reported cross-ancestry meta-analyses, including the International Glaucoma Genetics Consortium (IGGC) meta-analysis (127 variants)[7] and the multitrait analysis of GWAS (MTAG) meta-analysis (312 variants)[8] were compared to the *AoU* POAG cross-ancestry meta-analyses for both the relaxed and stringent phenotype definitions. Additionally, the effect sizes for POAG variants identified in the IGGC EUR GWAS meta-analysis (68 variants)[7] were compared to their effect sizes in the *AoU* EUR GWASs. The correlation between effect sizes was assessed using Pearson correlation coefficient (r).

Cross-Reference of the Novel Genome-Wide Significant Locus in an External Data Set

To evaluate the robustness of the novel genome-wide significant variant (rs76935404[T] near *CYP2A7*), it was queried in an independent data set from the Genetics of Glaucoma in People of

African Descent (GGLAD) Consortium recruited at Duke University (GGLAD-Duke). The GGLAD-Duke data set consists of genotype array data from 701 cases and 606 controls, as previously described.[11] The association statistics for rs76935404 were derived using the same phenotype definition of POAG and standard GWAS quality control procedures applied in the original study. After nominal replication was noted, the GGLAD-Duke summary statistics were meta-analyzed with the AFR GWAS summary statistics for each phenotype definition using a fixed-effects, inverse variance-weighted approach in Meta-Analysis of Genome-Wide Association Scans.[22]

In-Silico Annotation

To assess whether any novel genome-wide significant variants were expression quantitative trait loci (eQTLs) that could regulate the expression of neighboring or distant genes, these variants were queried in the Gene-Tissue Expression database[25] and the University of Michigan's FIVEx[26] browser. Because ocular tissue expression data are not currently available in existing databases, we used other neuronal tissues as a surrogate given that POAG is also a neurodegenerative disease. The Broad Institute Single Cell Portal[27] was queried to identify ocular cell types in which genes located within novel risk loci are expressed.

Results

POAG GWASs in the *AoU* EUR, AFR, and AMR Cohorts

Results from the EUR (1846 vs. 1528 cases/84,654 vs. 79 276 controls), AFR (1042 vs. 862 cases/15 966 vs. 14 076 controls), and AMR (305 vs. 250 cases/10 167 vs. 9668 controls) GWASs for each phenotype definition are shown in Figure 2 and Table 1. There was no evidence of significant genomic inflation or deflation in any of these GWASs (lambda = 1.0−1.02) (Supplementary Figure 1A−C, available at www.ophthalmologyscience.org). For Phenotype 1 (relaxed), 2 loci reached genome-wide significance ($P < 5 \times 10^{-8}$) in the EUR GWAS, both of which are known POAG risk loci: *TMCO1* (rs6426939[C], odds ratio [OR] = 1.32, $P = 1.7 \times 10^{-8}$) and *CDKN2B-AS1* (rs3217977[C], OR = 1.21, $P = 3.8 \times 10^{-08}$). No significant loci were detected in the AFR or AMR GWASs. For Phenotype 2 (stringent), 1 locus reached genome-wide significance in the EUR GWAS, which is also a known locus: *GMDS* (rs1570537[C], OR = 1.38, $P = 1.0 \times 10^{-08}$). Although the stringent phenotype definition was designed to improve case specificity, it also reduced the number of cases and controls available for analysis, likely explaining why the established POAG risk loci *TMCO1* and *CDKN2B-AS1* that were detected at genome-wide significance with the relaxed definition became subthreshold with the stringent definition. In contrast, *GMDS* reached genome-wide significance under the stringent EUR GWAS, illustrating that loci may differ in their sensitivity to phenotype refinement.

No significant loci were identified in the stringent phenotype AMR GWAS. Interestingly, a novel risk variant near *CYP2A7* was identified in the AFR GWAS (rs76935404[T], OR = 1.35, $P = 1.2 \times 10^{-8}$). LocusZoom plots for genome-wide significant loci are shown in Supplementary Figure 2, available at www.ophthalmologyscience.org.

The novel variant rs76935404 is found in a noncoding region of the genome upstream of the promoter for the *CYP2A7* gene. As noncoding variants can regulate the expression of both neighboring and distant genes,[28] we queried whether this variant is an eQTL and thereby influences gene expression. Because existing databases do not contain ocular tissue expression data, neuronal tissues were used as a surrogate given POAG is also a neurodegenerative disease. rs76935404 was found to be a significant eQTL for: (1) *CYP2A7* in the brain hypothalamus, basal ganglia, and hippocampus; (2) *EGLN2* in sensory neuronal tissue; and (3) the uncharacterized long noncoding RNA AC092071.1 in the dorsal prefrontal cortex ($P < 0.05$ for all). Intriguingly, the coding genes have POAG-relevant biological functions: *CYP2A7*[29,30] is a member of the Cytochrome P450 superfamily of enzymes that function in drug metabolism and steroid/lipid biosynthesis, while *EGLN2*[31−33] plays roles in oxygen sensing, apoptosis, and mitochondrial homeostasis. Single-cell data also show detectable expression of both genes in disease-relevant ocular tissues from healthy donor eyes.[27,34] *CYP2A7* is expressed in optic nerve astrocytes, lens, Müller glia, and retinal ganglion cells, while *EGLN2* is expressed in optic nerve astrocytes, lens, and optic nerve head fibroblasts.

To further validate the novel variant rs76935404 identified in the Phenotype 2 (stringent) AFR GWAS, we queried this variant in a subset of the GGLAD-Duke after a comprehensive ocular examination by an ophthalmologist (701 cases/606 controls).[11] rs76935404 replicated with same direction of effect and nominal significance in the GGLAD-Duke data set (OR = 1.34, $P = 5.8 \times 10^{-3}$) (Table 2). Given there was evidence of replication, we meta-analyzed the GGLAD-Duke summary statistics with the *AoU* AFR GWASs for each phenotype definition using a fixed-effects, inverse-variance weighted approach. Meta-analyses showed that rs76935404 reached genome-wide significance using the relaxed phenotype definition (OR = 1.29, $P = 9.6 \times 10^{-9}$) and maintained significance using the stringent definition (OR = 1.35, $P = 2.3 \times 10^{-10}$) (Supplementary Figure 3, available at www.ophthalmologyscience.org). These meta-analyses did not show any evidence of significant genomic inflation (lambda = 1.02−1.03) (Supplementary Figure 4, available at www.ophthalmologyscience.org).

Cross-Ancestry POAG GWAS Meta-Analyses of the *AoU* EUR, AFR, and AMR Cohorts

The known POAG risk loci *TMCO1* (rs35862498[A], OR = 1.23, $P = 1.1 \times 10^{-9}$) and *CDKN2B-AS1* (rs3217977[C], OR = 1.19, $P = 5.9 \times 10^{-9}$) were genome-wide significant in a fixed-effects, inverse variance-weighted cross-ancestry meta-analysis using Phenotype 1 (relaxed) (3193 cases/110 787 controls), while only *TMCO1* (Chr1:165730355[CA], OR = 1.26, $P = 3.5 \times 10^{-9}$) was significant using Phenotype 2 (stringent) with a reduced cohort size of 2640 cases and 103 020 controls (Fig 3, Table 3, Supplementary Figure 5,

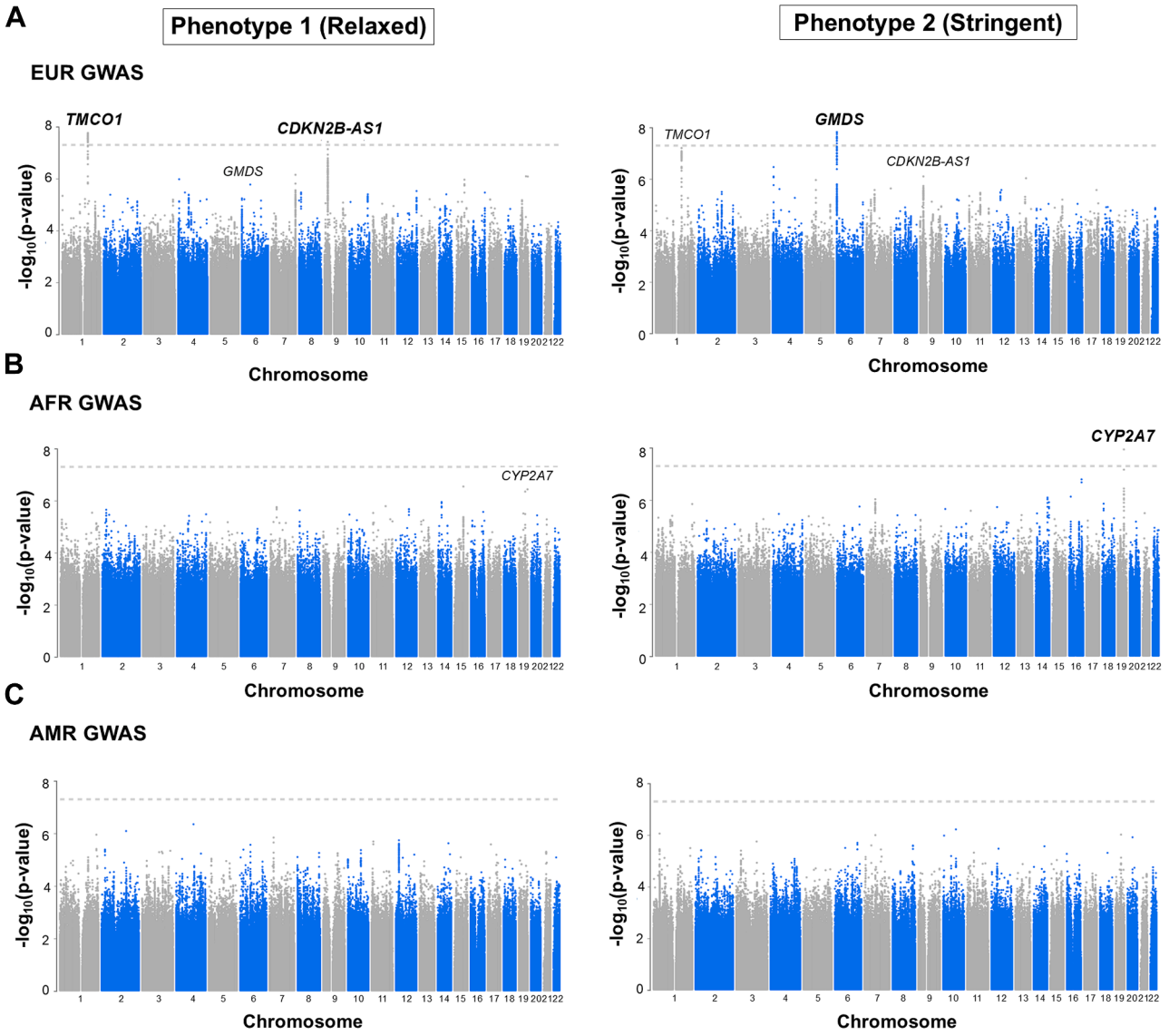

Figure 2. Manhattan plots for primary open-angle glaucoma (POAG) ancestry-stratified genome-wide association studies (GWASs) in the *All of Us* Research Program (**A**) European (EUR), (**B**) African (AFR), and (**C**) Latino/Admixed American (AMR) cohorts using each phenotype definition (relaxed and stringent). Each dot represents a specific variant. The x-axis displays the chromosome where each variant is located and the y-axis displays the -$\log_{10}$ *P* value for association of the variant with POAG. The gray dashed line represents the genome-wide significance threshold ($P = 5 \times 10^{-8}$, -$\log_{10}$ $P = 7.30$). For variants reaching genome-wide significance, the nearest gene to the lead variant in the locus is labeled and bolded. The nearest gene(s) to genome-wide significant loci using one phenotype definition are also labeled on the respective Manhattan plots for the second phenotype definition.

available at www.ophthalmologyscience.org). Neither GWAS meta-analysis demonstrated evidence of genomic inflation (lambda = 1.0−1.01) (Supplementary Figure 1D). To ensure the results would be consistent with a random-effects model, the meta-analyses were repeated with this approach, which yielded the same genome-wide significant loci (Supplementary Figure 6, available at www.ophthalmologyscience.org). Notably, at the *CDKN2B-AS1* locus, rs3217977[C] differed in allele frequency across ancestry groups, with lower minor allele frequency in AFR than EUR (Table 3). Although genome-wide significance was observed in EUR, the direction of effect was similar across ancestry groups in the cross-ancestry meta-analysis and there was no evidence of heterogeneity. These findings illustrate how ancestry-related differences in allele frequency, linkage disequilibrium structure, and sample size can influence locus-level discovery even at established POAG loci.

The novel risk locus identified in the AFR Phenotype 2 GWAS (rs76935404 near *CYP2A7*) was polymorphic in and exhibited a similar direction of effect across all ancestries, although the strength of effect was strongest in the AFR cohort; consequently, this locus did not remain significant in the cross-ancestry meta-analyses (OR = 1.09−1.11, *P* <

Table 1. Genome-Wide Significant Variants in the *All of Us* Ancestry-Specific POAG GWASs Using Each Phenotype Definition. Phenotype 1 (Relaxed)

GWAS	Cases/Controls	Chr	Position (GRCh38)	Lead Variant	Nearest Gene	Effect Allele	Other Allele	OR	95% CI	P Value	MAF	Known or Novel Locus
EUR	1846/84 654	1	165 746 063	rs6426939	*TMCO1*	C	T	1.32	1.20-1.45	1.7E-08	0.12	Known
		9	22 007 358	rs3217977	*CDKN2B-AS1*	C	CA	1.21	1.13-1.29	3.8E-08	0.45	Known

GWAS	Cases/Controls	Chr	Position (GRCh38)	Lead Variant	Nearest Gene	Effect Allele	Other Allele	OR	95% CI	P-value	MAF	Known or Novel Locus
EUR	1528/79 276	6	1 962 530	rs1570537	*GMDS*	C	T	1.38	1.24-1.55	1.0E-08	0.14	Known
AFR	862/14 076	19	40 913 389	rs76935404	*CYP2A7*	T	C	1.35	1.22-1.50	1.2E-08	0.29	Novel

AFR = African; Chr = chromosome; CI = confidence interval; EUR = European; GRCh38 = Genome Reference Consortium Human Build 38; GWAS = genome-wide association study; MAF = minor allele frequency; OR = odds ratio; POAG = primary open-angle glaucoma.
Minor allele frequency (in specific population in which GWAS was performed).

5E-03 for all) (Supplementary Table 2, available at www.ophthalmologyscience.org).

Correlation of Published Effect Sizes at Known POAG Risk Loci with Effect Sizes in the *AoU* Meta-Analysis

As measures of data quality, validity, and to evaluate the utility for additional genetic studies of POAG, we compared the effect sizes (beta regression coefficients) for known POAG risk loci with their effect sizes in the *AoU* GWASs. Figure 4A shows the effect size comparisons of 127 variants identified in the IGGC POAG cross-ancestry meta-analysis (34 179 cases/349 321 controls).[7] Figure 4B shows the effect size comparisons of 312 variants identified in the MTAG POAG cross-ancestry meta-analysis (39 457 cases/392 560 controls).[8] For the 127 IGGC variants as well as the 312 MTAG variants, there was strong correlation between effect sizes from the prior analyses and the *AoU* meta-analyses using both phenotype definitions ($r = 0.83-0.84$ for IGGC variants, $P < 1 \times 10^{-5}$; $r = 0.75-0.79$ for MTAG variants, $P < 1 \times 10^{-5}$, respectively). For the 68 variants previously identified in the IGGC EUR POAG meta-analysis (16 677 cases/199 580 controls),[7] the correlation between IGGC EUR effect sizes and the *AoU* EUR effect sizes using both phenotype definitions was also strong ($r = 0.86-0.89$, $P < 1 \times 10^{-5}$; Supplementary Figure 7, available at www.ophthalmologyscience.org). For internal validation, the effect sizes of top variants ($P < 1 \times 10^{-5}$) from ancestry-stratified and cross-ancestry meta-analyses applying Phenotype 1 and Phenotype 2 were also compared; correlation was again strong ($r = 0.96-0.99$, $P < 1 \times 10^{-5}$, Supplementary Figure 8, available at www.ophthalmologyscience.org).

Discussion

While POAG disproportionately impacts individuals of AFR and AMR ancestry, studies aiming to identify genetic risk factors have predominantly enrolled individuals of EUR ancestry,[6] consistent with the approach for other common diseases.[35] Additionally, these studies have used genotype arrays, which directly assay ~2% of variants throughout the genome and have historically not been robust to differences in continental genetic ancestry.[36] Successfully imputing missing genotypes is highly dependent on the size of reference panels, linkage disequilibrium variation between populations, variant minor allele frequency, array marker density, and sequence quality, among other factors.[17] For samples from populations with more AFR and/or AMR continental genetic ancestry, for which reference panels are smaller than EUR reference panels, accuracy varies widely.[17] To overcome these shortcomings, this work is the first cross-ancestry GWAS meta-analysis for POAG using WGS data in the ancestrally diverse *AoU* Research Program. In addition, we aimed to overcome the limitations of using ICD codes alone for disease ascertainment

Table 2. Association of the Novel Genome-Wide Significant Variant From the *All of Us* AFR Phenotype 2 (Stringent) POAG GWAS (rs76935404[T]) in an Independent Cohort

Cohort	Cases/Controls	OR	95% CI	*P* Value
All of Us AFR phenotype 2 (stringent)	862/14 076	1.35	1.22-1.50	1.2E-08
All of Us AFR phenotype 1 (relaxed)	1042/15 966	1.28	1.16-1.41	4.5E-07
GGLAD-Duke	701/606	1.34	1.09-1.65	5.8E-03

AFR = African; CI = confidence interval; GGLAD-Duke = Genetics of Glaucoma in People of African Descent Consortium recruited at Duke University; GWAS = genome-wide association study; OR = odds ratio; POAG = primary open-angle glaucoma.

by applying different levels of phenotype definition stringency. The combination of these strengths replicated known POAG risk loci and also allowed us to identify a novel AFR risk locus. Moreover, the strong correlation of effect sizes for previously identified variants in the IGGC (r = 0.83−84) and MTAG (r = 0.75−79) POAG

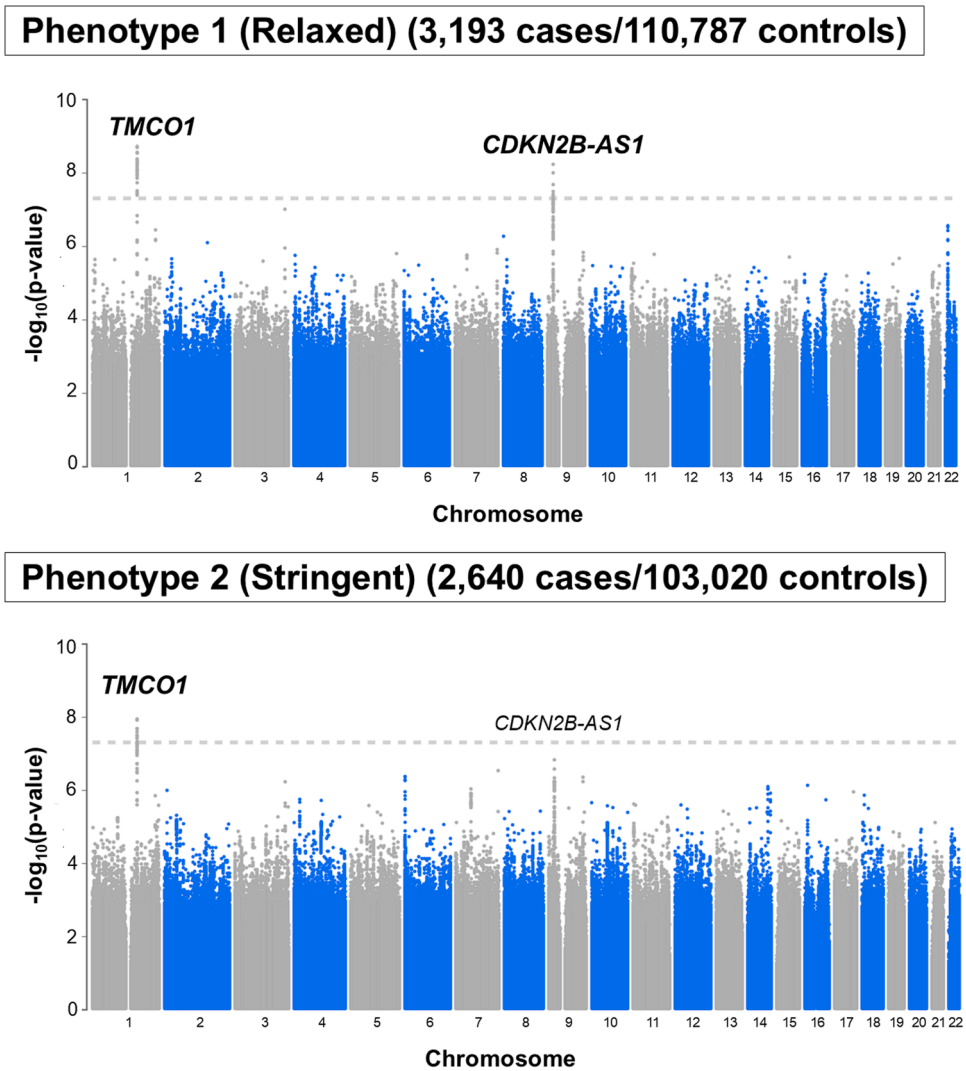

Figure 3. Manhattan plots for the *All of Us* Research Program cross-ancestry primary open-angle glaucoma (POAG) genome-wide association study meta-analyses using each phenotype definition (relaxed and stringent). Genome-wide association studies were performed for the European, African, and Latino/Admixed American cohorts using a relaxed and stringent phenotype (Figure 2) and the results were then meta-analyzed for each phenotype definition. Each dot represents a specific variant. The x-axis displays the chromosome where each variant is located and the y-axis displays the -$\log_{10}$ *P* value for association of the variant with POAG in the respective cross-ancestry meta-analysis. The gray dashed line represents the genome-wide significance threshold ($P = 5 \times 10^{-8}$, -$\log_{10} P = 7.30$). For variants reaching genome-wide significance, the nearest gene to the lead variant in the locus is labeled and bolded. The nearest gene(s) to genome-wide significant loci in one phenotype definition are also labeled on the Manhattan plot for the second phenotype definition.

Table 3. Genome-Wide Significant Variants in the *All of Us* Cross-Ancestry POAG GWAS Meta-Analyses Using Each Phenotype Definition. Phenotype 1 (Relaxed) (3193 Cases/110 787 Controls)

Chr	Position (GRCh38)	Lead Variant	Nearest Gene	Effect Allele	Other Allele	OR Meta	95% CI Meta	P Value Meta	OR EUR	95% CI EUR	P Value EUR	MAF EUR	OR AFR	95% CI AFR	P Value AFR	MAF AFR	OR AMR	95% CI AMR	P Value AMR	MAF AMR	I^2 Heterogeneity	P Value Heterogeneity (q)	Known or Novel Locus
1	165 730 361	rs35862498	*TMCO1*	A	C	1.23	1.15-1.31	1.1E-09	1.28	1.16-1.40	2.8E-07	0.13	1.25	1.13-1.39	2.9E-05	0.22	0.94	0.77-1.16	0.57	0.20	71.8	0.03	Known
9	22 007 358	rs3217977	*CDKN2B-AS1*	C	CA	1.19	1.13-1.27	5.9E-09	1.21	1.13-1.29	3.8E-08	0.45	1.14	0.95-1.37	0.15	0.07	1.16	0.95-1.42	0.16	0.24	0	0.85	Known

Chr	Position (GRCh38)	Lead Variant	Nearest Gene	Effect Allele	Other Allele	OR Meta	95% CI Meta	P Value Meta	OR EUR	95% CI EUR	P Value EUR	MAF EUR	OR AFR	95% CI AFR	P Value AFR	MAF AFR	OR AMR	95% CI AMR	P Value AMR	MAF AMR	I^2 Heterogeneity	P Value Heterogeneity (q)	Known or Novel Locus
1	165 730 355	-	*TMCO1*	CA	C	1.26	1.17-1.36	3.5E-09	1.29	1.16-1.43	2.0E-06	0.12	1.31	1.15-1.49	5.5E-05	0.15	0.98	0.76-1.30	0.90	0.14	50.1	0.13	Known

AFR = African; AMR = Latino/Admixed American; Chr = chromosome; CI = confidence interval; EUR = European; GRCh38 = Genome Reference Consortium Human Build 38; GWAS = genome-wide association study; MAF = minor allele frequency; OR = odds ratio; POAG = primary-open angle glaucoma.

cross-ancestry meta-analyses provides support for data quality and utility of this data set for future POAG genetic studies.

Prior GWASs in AFR ancestry populations have identified relatively few POAG risk loci compared with studies conducted in EUR ancestry populations. For example, variants near *APBB2* were previously reported as genome-wide significant in AFR ancestry individuals in the GGLAD Consortium.[11] In the present study, while previously reported POAG loci were well represented among sub−genome-wide significant signals, no variants at the *APBB2* locus reached genome-wide significance in the *AoU* AFR GWAS. Differences in sample size, phenotype definition, study design, and underlying genetic architecture may contribute to variability in locus discovery across studies. These findings underscore the complementary nature of diverse data sets and reinforce the importance of continued large-scale genetic studies in ancestrally diverse populations.

The significant signal observed for rs76935404[T] in the stringently phenotyped AFR GWAS replicated in the GGLAD-Duke data set, and the effect size was also consistent with the observation in *AoU* (OR = 1.34). Notably, stronger effect sizes were detected in data sets with more carefully phenotyped POAG cases. Phenotype 2 in our study considers not only POAG-related ICD 9/10 codes but also Current Procedural Terminology and RxNorm codes for glaucoma treatment to more precisely define POAG cases compared to Phenotype 1. Genetics of Glaucoma in People of African Descent Consortium recruited at Duke University POAG cases and controls were clinically examined for diagnosis.[11]

The novel locus is ∼30 kilobases upstream of the *CYP2A7* gene promoter. *CYP2A7* encodes an orphan cytochrome P450 protein that localizes to the endoplasmic reticulum.[37] While *CYP2A7* has not been reported in the GWAS Catalog as associated with any ocular phenotypes,[38] another cytochrome P450 gene, *CYP1B1*, has been implicated in primary congenital glaucoma.[39] Both *CYP2A7* and *CYP1B1* belong to a large cluster of cytochrome P450 genes on chromosome 19q. More targeted high-resolution sequencing interrogation across this region would be needed to confirm a causal variant(s)/gene(s).

While the novel index variant is canonically closest to *CYP2A7*, evidence from the Gene-Tissue Expression and FIVEx databases suggest that rs76935404 may also be an eQTL for *EGLN2*, which encodes an enzyme with a crucial role in oxygen sensing. This enzyme catalyzes hydroxylation of specific proline residues in hypoxia-inducible factor alpha (HIF-1α) subunits when oxygen is abundant.[32] This hydroxylation marks HIF-1α for degradation, effectively regulating cell response to changing oxygen levels. Hypoxia-induced retinal ganglion cell death is implicated in glaucoma pathophysiology.[40] Interestingly, a recent analysis of rare variants identified using whole exome sequence data reported significant association between variants in *EGLN2* and intraocular pressure.[41] This study also reported that *EGLN2* is a drug target for 3 hypoxia-inducible factor

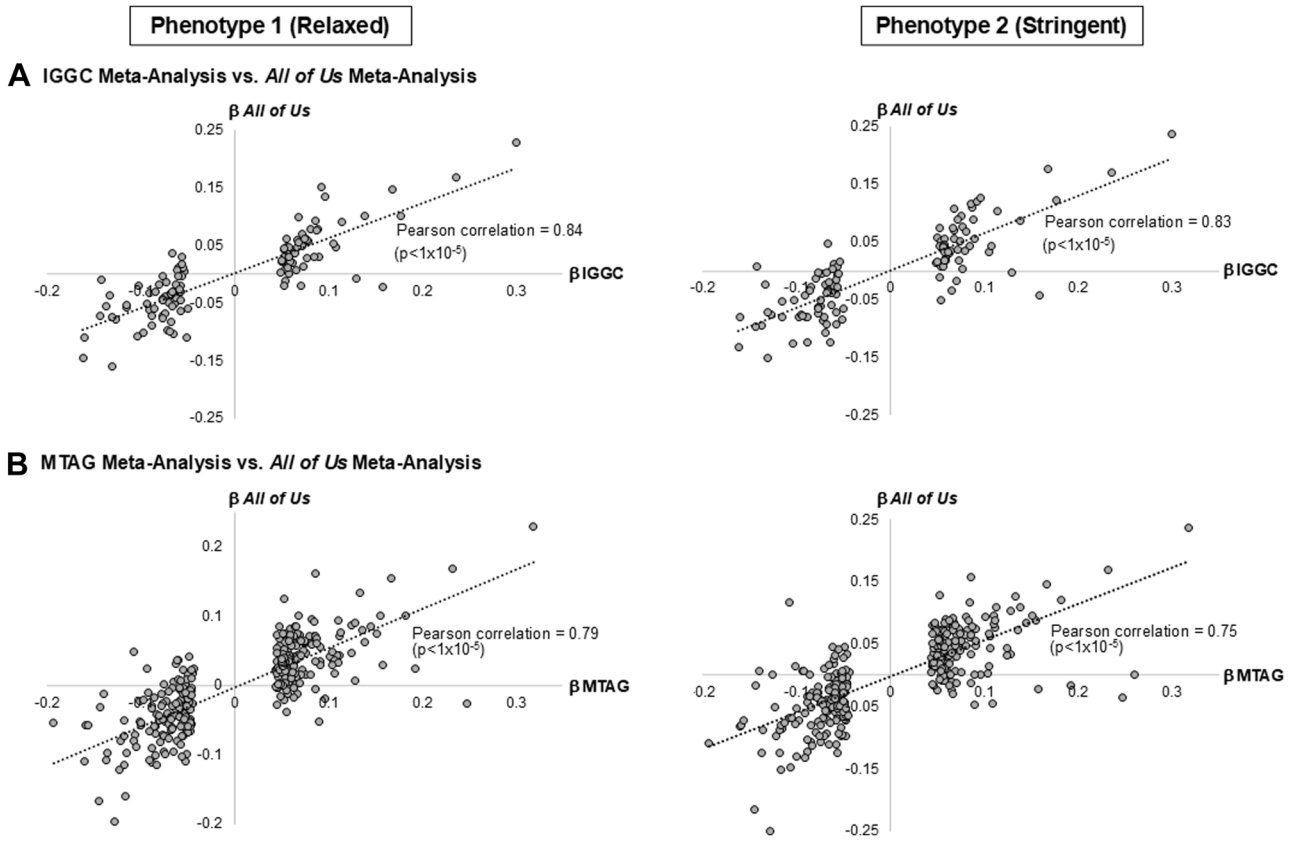

Figure 4. Correlation of effect sizes for known primary open-angle glaucoma (POAG)-associated variants with their effect sizes in the *All of Us* Research Program cross-ancestry meta-analyses using each phenotype definition (relaxed and stringent). Correlation analyses were performed for all POAG-associated variants identified in the (A) International Glaucoma Genetics Consortium (IGGC) POAG cross-ancestry meta-analysis (34 179 cases/349 321 controls; 127 variants)[7] and the (B) multitrait analysis of genome-wide association study (MTAG) POAG cross-ancestry meta-analysis (39 457 cases/392 560 controls; 312 variants).[8] Each dot represents a specific variant. The beta regression coefficients (ß) from the IGGC/MTAG cross-ancestry meta-analyses are plotted on the x-axis, while the ß from the *All of Us* Research Program cross-ancestry meta-analyses are plotted on the y-axis.

prolyl hydroxylase inhibitors (roxadustat, daprodustat, and vadadustat).

The hypoxia response pathway has been implicated in various adaptive responses to environmental pressures,[42] and variants in oxygen-sensing genes have shown population-specific distributions that may reflect past selective pressures. For example, HIF-1α is induced in host tissues during malaria infection, a disease that has influenced selection pressure of other disease-causing genes (e.g., sickle cell in AFR populations).[43] Activation of the host HIF-1α pathway improves survival of liver-stage malaria parasites in hepatocytes.[44] In context, continental AFR populations faced unique selective pressures from endemic diseases such as malaria, sleeping sickness, and various parasitic infections, potentially favoring variants that enhance detoxification capacity or immune responses. The evolutionary maintenance of these variants in AFR populations suggests they may represent "population-private" risk alleles that contribute to health disparities in complex diseases. This pattern has been observed for other conditions, such as *APOL1* variants that protect against trypanosomiasis but increase kidney disease risk in African Americans.[45] Interestingly, in our ancestry-stratified GWASs, the direction of effect for rs76935404[T] was consistent across ancestries, although the effect size was much larger in the AFR GWAS, supporting this theory. Importantly, *CYP2A7* and *EGLN2* expression is detected in disease-relevant ocular tissues from healthy donor eyes (*CYP2A7* is expressed in optic nerve astrocytes, lens, Müller glia, and retinal ganglion cells, while *EGLN2* is expressed in optic nerve astrocytes, lens, and optic nerve head fibroblasts), supporting a potential functional role in POAG pathogenesis. Further functional work is needed to prioritize the causal gene(s) in this locus and is an important future research direction.

A major strength of the present study is the ancestrally diverse population of research participants. This increases statistical power to detect novel POAG susceptibility loci that were previously undiscovered due to lack of representation of non-EUR individuals in most GWASs to date. Another strength of this study is the use of WGS data; imputed array data are currently more commonly used in GWASs than WGS data, although as WGS becomes cheaper and more widely available, more GWASs will likely shift toward WGS data to eliminate the need for imputation and better facilitate harmonization of genomic

data collected across different studies/sequencing platforms. Greater use of WGS will also enable discovery of disease-causing rare variants. Finally, our thorough phenotyping strategy allowed us to compare a relaxed versus stringent case/control definition using ICD9/10, RxNorm, and Current Procedural Terminology codes. As with many studies that rely on EHR data, the present study encountered limitations with regard to available phenotypic data. For example, no ophthalmology clinic notes, intraocular pressure measurements, or ocular imaging data are currently available for *AoU* participants.

In summary, our multiancestry GWASs and meta-analyses of WGS in the ancestrally diverse *AoU* Research Program replicated known POAG loci and identified a novel locus in AFR individuals that replicates in an independent data set and contains genes with disease-relevant biological functions. While additional fine-mapping and functional studies will be required to identify the causal variant(s) and gene(s) at this locus, the replication of rs76935404[T] in an independent clinically phenotyped AFR ancestry cohort supports the robustness of this association. Ongoing efforts to increase the size and diversity of multiple data sets with WGS will further improve our understanding of the genetic architecture of this common, blinding disease. Ultimately, this can lead to improved approaches to disease diagnosis, treatment, and prevention that will benefit all individuals.

Acknowledgments

The authors gratefully acknowledge *All of Us* Research Program participants for their contributions, without whom this research would not have been possible. The authors also thank the National Institutes of Health's *All of Us* Research Program for making available the participant data and whole genome sequences examined in this study.

Footnotes and Disclosures

Originally received: March 5, 2026.
Final revision: June 9, 2026.
Accepted: June 15, 2026.
Available online: June 23, 2026. Manuscript no. XOPS-D-26-00144.

[1] Department of Ophthalmology, Harvard Medical School, Boston, Massachusetts.

[2] Department of Ophthalmology, Ocular Genomics Institute, Massachusetts Eye and Ear, Boston, Massachusetts.

[3] Broad Institute of Harvard and MIT, Cambridge, Massachusetts.

[4] Department of Population & Quantitative Health Sciences, Case Western Reserve University School of Medicine, Cleveland, Ohio.

[5] Cleveland Institute for Computational Biology, Case Western Reserve University School of Medicine, Cleveland, Ohio.

[6] Department of Pharmacology & Toxicology, Brody School of Medicine, East Carolina University, Greenville, North Carolina.

[7] Center for Health Disparities, East Carolina University, Greenville, North Carolina.

[8] College of Medicine, Northeast Ohio Medical Center, Rootstown, Ohio.

[9] Department of Ophthalmology, Icahn School of Medicine at Mount Sinai, New York, New York.

[10] NIHR Biomedical Research Centre, Moorfields Eye Hospital NHS Foundation Trust and UCL Institute of Ophthalmology, London, UK.

[11] QIMR Berghofer Medical Research Institute, Brisbane, QLD, Australia.

[12] Departments of Ophthalmology and Medicine, Duke University, Durham, North Carolina.

*These authors contributed equally.

[†]These authors jointly supervised the work and are co-senior/supervising authors.

Disclosure(s):

All authors have completed and submitted the ICMJE disclosures form.

The authors made the following disclosures:

D.C.C.: All support for the present manuscript - R01EY033829; Grants or contracts from any entity - UM1TR004528, R01LM014520, U01AG084545, P30AG072959, R03OD039848, Healthy Americas Research Consortium Grant, Research & Professional Development Grant, Northeast Ohio Renal Research Innovation Award, R21HG103814, R01AG058066-04S1, CTSC Annual Pilot Study, R25GM075207, R25GM075207-17S1, I01BX004557, U01DK114908, R13HG011436, UL1TR002548; Consulting fees - University of Michigan; Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events - American Society for Microbiology, National Institutes of Health.

P.G.: Grants or contracts from any entity - NHMRC Ideas Grants #2036819; Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid - Chair of the QIMRB Population Health Research Committee, Member of the Human Scientific Sub-Committee (HSSC) of the QIMRB HERC; No payment was received from the Population Health Research Committee; A small honorarium was received for serving as a member of the Human Scientific Sub-Committee of the QIMRB HREC.

M.A.H.: All support for the present manuscript - NIH/NEI grant EY033829; Support for attending meetings and/or travel - NIH/NEI grant EY033829.

L.R.P.: All support for the present manuscript - NEI, The Glaucoma Foundation (NYC), The Barry Center for Artificial Intelligence.

J.L.W.: All support for the present manuscript - NIH/NEI; Consulting fees - Genetech/Roche.

A.V.S.: All support for the present manuscript - NIH/NEI R01 EY031424, NIH/NEI P30 EY014104.

A.K.: All support for the present manuscript - UK Research and Innovation Future Leaders Fellowship, Alcon Research Institute Young Investigator Award, Lister Institute Fellowship; Consulting fees - AbbVie, Aerie, Google Health, Novartis, Qlaris Bio, Regeneron, Reichert, Santen, Thea, Topcon; Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events - Heidelberg Engineering; Stock or stock options - Seonix Bio, Tavo Biotherapeutics.

J.N.C.B.: All support for the present manuscript - Million Veteran Program (MVP), US Department of Veterans Affairs: This work used data from the Million Veteran Program (MVP), US Department of Veterans Affairs, Office of Research and Development: I01 BX004557, IK6 BX005233 (support for investigator effort), National Institutes of Health (NIH), National Eye Institute: R01 EY033289 (JNCB), supporting glaucoma genetics research; Consulting fees - Case Western Reserve University — NEIGHBORHOOD Consortium: Paid consulting for statistical genetics analyses related to primary open-angle glaucoma (NIH R01EY022305), Case Western Reserve University: Paid consulting for genomic data analysis using the *All of Us* Research Program (PI: Dana Crawford, PhD).

L.C.: Grants or contracts from any entity - National Institutes of Health (NIH), National Eye Institute: T32 EY007157-22, supporting PhD student doing glaucoma genetics research, Prevent Blindness Ohio: Award for female scholars in vision research, National Institutes of Health (NIH), National Heart, Lung, and Blood Institute: T32 HL007567-36, supporting PhD student doing vascular genetics research; Support for attending meetings and/or travel - Knights Templar Eye Foundation: ARVO conference travel grant.

T.G.K.: All support for the present manuscript - Million Veteran Program (MVP), US Department of Veterans Affairs: This work used data from the Million Veteran Program (MVP), National Institutes of Health (NIH), National Eye Institute: R01 EY033289 (PI: Jessica Cooke Bailey), supporting glaucoma genetics research, US Department of Veterans Affairs, Office of Research and Development: I01 BX004557, IK6 BX005233 (support for investigator effort); Consulting fees - Case Western Reserve University — NEIGHBORHOOD Consortium: Paid consulting for statistical genetics analyses related to primary open-angle glaucoma (NIH R01EY022305).

R.D.: Grants or contracts from any entity - NIH NIGMS: 5R35GM124836; Consulting fees - Cytokinetics, Variant Bio, Character Bio; Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events - Cytokinetics; Stock or stock options - Pensieve Health (pending).

The study presented in this manuscript was funded by the National Institutes of Health (K23EY035734 to I.F.A., 5T32EY007157 and 5T32HL007567 to L.A.C., R01EY022305 to J.L.W., R01EY033829 to J.N.C.B., R01EY031424 to A.V.S., R01EY032559 to L.R.P. and J.L.W., R01EY036460 to L.R.P., and P30EY014104 to Massachusetts Eye and Ear), Research to Prevent Blindness (Tom Wertheimer Career Development Award in Data Science to I.F.A.), American Glaucoma Society (MAPS Award and Young Clinician-Scientist Grant to I.F.A.), Prevent Blindness Ohio (Young Investigator Student Fellowship Award for Female Scholar in Vision Research to L.A.C.), The Glaucoma Foundation (L.R.P.), UK Research and Innovation Future Leaders Fellowship (MR/Y033930/1 to A.P.K.), Alcon Research Institute (Young Investigator Award to A.P.K.), Lister Institute for Preventive Medicine Award (A.P.K.), NIHR Biomedical Research Centre at Moorfields Eye Hospital (A.P.K.), UCL Institute of Ophthalmology (A.P.K.), and the Barry Center for Ophthalmic Artificial Intelligence (L.R.P.). The sponsor or funding organizations had no role in the design or conduct of this research.

This study was presented at the American Glaucoma Society 2025 Meeting (Top 5 Plenary Paper), February 26-March 2, Washington, D.C.

HUMAN SUBJECTS: No human subjects were included in this study. Informed consent was obtained for all participants enrolled in AoU. The AoU IRB follows the regulations and guidance of the National Institutes of Health Office for Human Research Protections for all studies, ensuring that the rights and welfare of research participants are overseen and protected uniformly. The described research adhered to the tenets of the Declaration of Helsinki.

No animal subjects were used in this study.

Author Contributions:

Conception and design: Aboobakar, Cruz, Kinzy, Segrè, Crawford, Wiggs, Cooke Bailey.

Analysis and interpretation: Aboobakar, Cruz, Kinzy, Luo, Nallapaneni, Do, Vy, Zhao, Tran, Hysi, Khawaja, Gharahkhani, Pasquale, Hauser, Segrè, Crawford, Wiggs, Cooke Bailey

Data collection: Aboobakar, Cruz, Hysi, Khawaja, Pasquale, Hauser, International Glaucoma Genetics Consortium, Segrè, Crawford, Wiggs, Cooke Bailey.

Obtained funding: Aboobakar, Cruz, Wiggs, Cooke Bailey

Overall responsibility: Aboobakar, Cruz, Pasquale, Segrè, Crawford, Wiggs, Cooke Bailey.

Abbreviations and Acronyms:
AFR = African; **AMR** = Latino/Admixed American; **AoU** = All of Us; **EHR** = electronic health record; **eQTL** = expression quantitative trait locus; **EUR** = European; **GGLAD** = Genetics of Glaucoma in People of African Descent; **GGLAD-Duke** = Genetics of Glaucoma in People of African Descent Consortium recruited at Duke University; **GWAS** = genome-wide association study; **HIF-1α** = hypoxia-inducible factor 1-alpha; **ICD** = International Classification of Diseases; **IGGC** = International Glaucoma Genetics Consortium; **MTAG** = multitrait analysis of genome-wide association study; **OR** = odds ratio; **POAG** = primary open-angle glaucoma; **WGS** = whole genome sequencing.

Keywords:
Glaucoma, Genetics, Genomics, GWAS, All of Us, Biobank.

Correspondence:
Jessica N. Cooke Bailey, PhD, MA, East Carolina University, 600 Moye Blvd, BSOM 6E 120C, Greenville, NC 27834. E-mail: cookebaileyj23@ecu.edu.

References

1. Tielsch JM, Sommer A, Katz J, et al. Racial variations in the prevalence of primary open-angle glaucoma. The Baltimore eye survey. *JAMA*. 1991;266:369−374.
2. Sommer A, Tielsch JM, Katz J, et al. Racial differences in the cause-specific prevalence of blindness in east Baltimore. *N Engl J Med*. 1991;325:1412−1417.
3. Kang JH, Wang M, Frueh L, et al. Cohort study of race/ethnicity and incident primary open-angle glaucoma characterized by autonomously determined visual field loss patterns. *Transl Vis Sci Technol*. 2022;11:21.
4. Quigley HA, West SK, Rodriguez J, et al. The prevalence of glaucoma in a population-based study of Hispanic subjects: Proyecto VER. *Arch Ophthalmol*. 2001;119:1819−1826.
5. Varma R, Wang D, Wu C, et al. Four-year incidence of open-angle glaucoma and ocular hypertension: the Los Angeles Latino eye study. *Am J Ophthalmol*. 2012;154:315−325.e1.
6. Aboobakar IF, Wiggs JL. The genetics of glaucoma: disease associations, personalised risk assessment and therapeutic opportunities-A review. *Clin Exp Ophthalmol*. 2022;50:143−162.
7. Gharahkhani P, Jorgenson E, Hysi P, et al. Genome-wide meta-analysis identifies 127 open-angle glaucoma loci with consistent effect across ancestries. *Nat Commun*. 2021;12:1258.
8. Han X, Gharahkhani P, Hamel AR, et al. Large-scale multi-trait genome-wide association analyses identify hundreds of glaucoma risk loci. *Nat Genet*. 2023;55:1116−1125.
9. Bonnemaijer PWM, Iglesias AI, Nadkarni GN, et al. Genome-wide association study of primary open-angle glaucoma in continental and admixed African populations. *Hum Genet*. 2018;137:847−862.
10. Choquet H, Paylakhi S, Kneeland SC, et al. A multiethnic genome-wide association study of primary open-angle

glaucoma identifies novel risk loci. *Nat Commun*. 2018;9:2278.
11. Genetics of Glaucoma in People of African Descent Consortium, Hauser MA, Allingham RR, et al. Association of genetic variants with primary open-angle glaucoma among individuals with African ancestry. *JAMA*. 2019;322:1682−1691.
12. Li Z, Allingham R, Nakano M, et al. A common variant near TGFBR3 is associated with primary open angle glaucoma. *Hum Mol Genet*. 2015;24:3880−3892.
13. Verma SS, Gudiseva HV, Chavali VRM, et al. A multi-cohort genome-wide association study in African ancestry individuals reveals risk loci for primary open-angle glaucoma. *Cell*. 2024;187:464−480.e10.
14. Lo Faro V, Bhattacharya A, Zhou W, et al. Novel ancestry-specific primary open-angle glaucoma loci and shared biology with vascular mechanisms and cell proliferation. *Cell Rep Med*. 2024;5:101430.
15. Ceballos FC, Hazelhurst S, Ramsay M. Assessing runs of homozygosity: a comparison of SNP array and whole genome sequence low coverage data. *BMC Genomics*. 2018;19:106.
16. Das S, Abecasis GR, Browning BL. Genotype imputation from large reference panels. *Annu Rev Genomics Hum Genet*. 2018;19:73−96.
17. Pei YF, Li J, Zhang L, et al. Analyses and comparison of accuracy of different genotype imputation methods. *PLoS One*. 2008;3:e3551.
18. Schwarze K, Buchanan J, Taylor JC, Wordsworth S. Are whole-exome and whole-genome sequencing approaches cost-effective? A systematic review of the literature. *Genet Med*. 2018;20:1122−1130.
19. Cai CX, Halfpenny W, Boland MV, et al. Advancing toward a common data model in ophthalmology: gap analysis of general eye examination concepts to standard observational medical outcomes partnership (OMOP) concepts. *Ophthalmol Sci*. 2023;3:100391.
20. All of Us Research Program, I. The "All of Us" research program. *N Engl J Med*. 2019;381:668−676.
21. All of Us Research Program Genomics, I. Genomic data in the all of us research program. *Nature*. 2024;627:340−346.
22. Willer CJ, Li Y, Abecasis GR. METAL: fast and efficient meta-analysis of genomewide association scans. *Bioinformatics*. 2010;26:2190−2191.
23. Magi R, Horikoshi M, Sofer T, et al. Trans-ethnic meta-regression of genome-wide association studies accounting for ancestry increases power for discovery and improves fine-mapping resolution. *Hum Mol Genet*. 2017;26:3639−3650.
24. Boughton AP, Welch RP, Flickinger M, et al. LocusZoom.js: interactive and embeddable visualization of genetic association study results. *Bioinformatics*. 2021;37:3017−3018.
25. Consortium GT. The GTEx consortium atlas of genetic regulatory effects across human tissues. *Science*. 2020;369:1318−1330.
26. Kwong A, Boughton AP, Wang M, et al. FIVEx: an interactive eQTL browser across public datasets. *Bioinformatics*. 2022;38:559−561.
27. Tarhan L, Bistline J, Chang J, et al. Single cell portal: an interactive home for single-cell genomics data. *bioRxiv*. 2023.
28. Albert FW, Kruglyak L. The role of regulatory variation in complex traits and disease. *Nat Rev Genet*. 2015;16:197−212.
29. Raunio H, Rautio A, Pelkonen O. The CYP2A subfamily: function, expression and genetic polymorphism. *IARC Sci Publ*. 1999;197-207.
30. Koskela S, Hakkola J, Hukkanen J, et al. Expression of CYP2A genes in human liver and extrahepatic tissues. *Biochem Pharmacol*. 1999;57:1407−1413.
31. Germeys C, Vandoorne T, Davie K, et al. Targeting EGLN2/PHD1 protects motor neurons and normalizes the astrocytic interferon response. *Cell Rep*. 2024;43:114719.
32. Zhang R, Lai L, He J, et al. EGLN2 DNA methylation and expression interact with HIF1A to affect survival of early-stage NSCLC. *Epigenetics*. 2019;14:118−129.
33. Zhang J, Wang C, Chen X, et al. EglN2 associates with the NRF1-PGC1alpha complex and controls mitochondrial function in breast cancer. *EMBO J*. 2015;34:2953−2970.
34. Monavarfeshani A, Yan W, Pappas C, et al. Transcriptomic analysis of the ocular posterior segment completes a cell atlas of the human eye. *Proc Natl Acad Sci U S A*. 2023;120:e2306153120.
35. Sirugo G, Williams SM, Tishkoff SA. The missing diversity in human genetic studies. *Cell*. 2019;177:1080.
36. Verlouw JAM, Clemens E, de Vries JH, et al. A comparison of genotyping arrays. *Eur J Hum Genet*. 2021;29:1611−1624.
37. Kwon D, Kim SM, Correia MA. Cytochrome P450 endoplasmic reticulum-associated degradation (ERAD): therapeutic and pathophysiological implications. *Acta Pharm Sin B*. 2020;10:42−60.
38. Sollis E, Mosaku A, Abid A, et al. The NHGRI-EBI GWAS catalog: knowledgebase and deposition resource. *Nucleic Acids Res*. 2023;51:D977−D985.
39. Vasiliou V, Gonzalez FJ. Role of CYP1B1 in glaucoma. *Annu Rev Pharmacol Toxicol*. 2008;48:333−358.
40. Yang L, Tan P, Zhou W, et al. N-acetylcysteine protects against hypoxia mimetic-induced autophagy by targeting the HIF-1alpha pathway in retinal ganglion cells. *Cell Mol Neurobiol*. 2012;32:1275−1285.
41. Gao XR, Chiariglione M, Arch AJ. Whole-exome sequencing study identifies rare variants and genes associated with intraocular pressure and glaucoma. *Nat Commun*. 2022;13:7376.
42. Beall CM. Two routes to functional adaptation: tibetan and Andean high-altitude natives. *Proc Natl Acad Sci U S A*. 2007;104(Suppl 1):8655−8660.
43. Piel FB, Patil AP, Howes RE, et al. Global distribution of the sickle cell gene and geographical confirmation of the malaria hypothesis. *Nat Commun*. 2010;1:104.
44. Ng S, March S, Galstian A, et al. Hypoxia promotes liver-stage malaria infection in primary human hepatocytes in vitro. *Dis Model Mech*. 2014;7:215−224.
45. Genovese G, Friedman DJ, Ross MD, et al. Association of trypanolytic ApoL1 variants with kidney disease in African Americans. *Science*. 2010;329:841−845.