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Association of Genetic Variants With Primary Open-Angle Glaucoma Among Individuals With African Ancestry

The Genetics of Glaucoma in People of African Descent (GGLAD) Consortium

IMPORTANCE Primary open-angle glaucoma presents with increased prevalence and a higher degree of clinical severity in populations of African ancestry compared with European or Asian ancestry. Despite this, individuals of African ancestry remain understudied in genomic research for blinding disorders.

OBJECTIVES To perform a genome-wide association study (GWAS) of African ancestry populations and evaluate potential mechanisms of pathogenesis for loci associated with primary open-angle glaucoma.

DESIGN, SETTINGS, AND PARTICIPANTS A 2-stage GWAS with a discovery data set of 2320 individuals with primary open-angle glaucoma and 2121 control individuals without primary open-angle glaucoma. The validation stage included an additional 6937 affected individuals and 14 917 unaffected individuals using multicenter clinic- and population-based participant recruitment approaches. Study participants were recruited from Ghana, Nigeria, South Africa, the United States, Tanzania, Britain, Cameroon, Saudi Arabia, Brazil, the Democratic Republic of the Congo, Morocco, Peru, and Mali from 2003 to 2018. Individuals with primary open-angle glaucoma had open iridocorneal angles and displayed glaucomatous optic neuropathy with visual field defects. Elevated intraocular pressure was not included in the case definition. Control individuals had no elevated intraocular pressure and no signs of glaucoma.

EXPOSURES Genetic variants associated with primary open-angle glaucoma.

MAIN OUTCOMES AND MEASURES Presence of primary open-angle glaucoma. Genome-wide significance was defined as $P < 5 \times 10^{-8}$ in the discovery stage and in the meta-analysis of combined discovery and validation data.

RESULTS A total of 2320 individuals with primary open-angle glaucoma (mean [interquartile range] age, 64.6 [56-74] years; 1055 [45.5%] women) and 2121 individuals without primary open-angle glaucoma (mean [interquartile range] age, 63.4 [55-71] years; 1025 [48.3%] women) were included in the discovery GWAS. The GWAS discovery meta-analysis demonstrated association of variants at amyloid-β A4 precursor protein-binding family B member 2 (*APBB2*; chromosome 4, rs59892895T>C) with primary open-angle glaucoma (odds ratio [OR], 1.32 [95% CI, 1.20-1.46]; $P = 2 \times 10^{-8}$). The association was validated in an analysis of an additional 6937 affected individuals and 14 917 unaffected individuals (OR, 1.15 [95% CI, 1.09-1.21]; $P < .001$). Each copy of the rs59892895*C risk allele was associated with increased risk of primary open-angle glaucoma when all data were included in a meta-analysis (OR, 1.19 [95% CI, 1.14-1.25]; $P = 4 \times 10^{-13}$). The rs59892895*C risk allele was present at appreciable frequency only in African ancestry populations. In contrast, the rs59892895*C risk allele had a frequency of less than 0.1% in individuals of European or Asian ancestry.

CONCLUSIONS AND RELEVANCE In this genome-wide association study, variants at the *APBB2* locus demonstrated differential association with primary open-angle glaucoma by ancestry. If validated in additional populations this finding may have implications for risk assessment and therapeutic strategies.

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Supplemental content

Author/Group Information: The Genetics of Glaucoma in People of African Descent (GGLAD) Consortium members appear at the end of the article.

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Primary open-angle glaucoma affects millions of people worldwide and is a leading cause of irreversible blindness.[1,2] Genome-wide association studies (GWASs) have identified more than 15 genetic loci associated with increased risk of primary open-angle glaucoma in populations with European or Asian ancestry,[3,4] and these results have been supported by analyses of glaucoma-associated quantitative traits, such as intraocular pressure (IOP) and vertical cup-to-disc ratio.[5] In contrast, although GWASs of individuals of African ancestry have been performed,[6,7] no genome-wide significant loci have been identified to date in this disproportionately affected population. Studies have shown that while individuals of European ancestry older than 40 years exhibit a disease prevalence of 1%, the prevalence is markedly higher in individuals with African ancestry older than 40 years (up to 6.8%).[2,8,9] Primary open-angle glaucoma also has earlier onset and is more severe in individuals of African ancestry.[10-12] A 2018 GWAS examining primary open-angle glaucoma in a multiethnic sample, the Genetic Epidemiology Research on Adult Health and Aging cohort, confirmed that there is a higher prevalence of primary open-angle glaucoma in individuals of African ancestry (16.1%) compared with individuals of East Asian (9.9%) and European (7.4%) ancestry.[13]

The objective of this study was to address this disparity in genomic science research by performing a GWAS of primary open-angle glaucoma via a multicenter research partnership to obtain biological insights into disease pathogenesis in individuals with African ancestry.

Key Points

Question Are there differences in genetic risk factors for primary open-angle glaucoma based on ancestry?

Findings In this multistage, case-control, genome-wide association study that included 26 295 participants, the amyloid-β A4 precursor protein-binding family B member 2 (*APBB2*) locus was significantly associated with primary open-angle glaucoma among individuals of African ancestry (odds ratio, 1.19 per copy of the risk allele for single-nucleotide polymorphism rs59892895T>C), but not of European or Asian ancestry.

Meaning This study identified a single-nucleotide polymorphism that demonstrated differential association with primary open-angle glaucoma by ancestry.

Methods

Study Populations

The study populations comprised 2 groups: the GWAS discovery stage followed by a validation stage. The validation stage included 2 separate meta-analyses. All participants were recruited using the same criteria in both stages. Individuals with primary open-angle glaucoma, control individuals without primary open-angle glaucoma, and eye and brain tissue donors (or family members of deceased donors) were enrolled after written informed consent was obtained from each participant, in full adherence to the Declaration of Helsinki. All relevant local and hospital institutional review boards approved the study. Participant ancestry was self-reported.

For the GWAS discovery stage, study participants of African ancestry were recruited from Ghana, Nigeria, South Africa, and Duke University (Durham, NC), where the same phenotype definition was applied to diagnose primary open-angle glaucoma.[3,14,15] Individuals with primary open-angle glaucoma were defined by the presence of glaucomatous optic neuropathy (defined as loss of neuroretinal rim with a vertical cup-to-disc ratio of >0.7 or an intereye asymmetry >0.2 and/or notching attributable to glaucoma) with compatible visual field loss, open angles on gonioscopy, and absence of secondary causes of glaucomatous optic neuropathy. Elevation of IOP was not a criterion in inclusion or exclusion of patients. Patients who were unable to give informed consent or those with secondary glaucoma due to trauma, uveitis, neovascularization, exfoliation syndrome, or pigment dispersion were excluded. Control individuals were recruited in a hospital-based or population-based manner. Hospital-based control individuals were older than 40 years and were confirmed to have no sign of glaucoma or other major eye diseases. These participants had an IOP of less than 21 mm Hg with open angles at the time of recruitment, healthy optic nerves, normal visual fields, and no family history of glaucoma. Population-based control individuals were matched by hospital and ancestry and were healthy individuals older than 40 years. The participating institutions are listed in the eAppendix in the Supplement. The sample collections from the discovery GWAS analysis were ascertained or reexamined between January 1, 2012, and December 31, 2017.

The study design and genotyping method for the 7 sample collections analyzed in the first validation meta-analysis have been previously described.[6,7,13,16-18] The study names of these collections are listed in the eAppendix in the Supplement. The sample collections were ascertained or reexamined between January 1, 2003, and December 31, 2018.

The second validation meta-analysis included individuals with primary open-angle glaucoma and matched control individuals from Mali, Cameroon, Nigeria (Lagos, Kaduna, and Enugu), Brazil, Saudi Arabia, the Democratic Republic of the Congo, Morocco, and Peru. The participating hospital institutions are listed in the eAppendix in the Supplement. These sample collections were ascertained or reexamined between January 1, 2015, and December 31, 2018.

Genotyping and Quality Control Procedures

For the GWAS discovery stage, genome-wide genotyping was performed using the Illumina OmniExpress beadchip, which directly assessed more than 700 000 single-nucleotide polymorphism (SNP) markers across the human genome. This genotyping array has been successfully used in multiple genome-wide scans,[19,20] including scans for primary open-angle glaucoma and other forms of glaucoma.[14,21] Further details on GWAS genotyping and quality control procedures are included in the eAppendix in the Supplement.

The first validation meta-analysis for amyloid-β A4 precursor protein-binding family B member 2 (*APBB2*; Refseq NM_004307) rs59892895 was performed with genome-wide genotyping data from previously described matched primary open-angle glaucoma case-control data sets. The second validation meta-analysis for *APBB2* rs59892895 was performed with the Sequenom MassArray primer extension system, with the genotypes further verified with Applied Biosystems Taqman assays.

Fine-scale imputation analysis using the 1000 Genomes Project cosmopolitan reference panel was performed to increase the density of the discovery GWAS. The IMPUTE version 2 software package was used to perform the imputation.[22] Stringent quality control was applied on the imputed data by only including imputed genotypes with an information score of at least 0.95 and by only including SNPs with minor allele frequency of at least 1%. The imputation accuracy of *APBB2* rs59892895T>C was validated with direct genotyping using the MassArray (Sequenom) and Taqman (Applied Biosystems) systems (with >99% concordance).

Immunohistochemistry and Image Analysis of *APBB2* and β-Amyloid in Donor Retina Tissues

APBB2 was shown to increase β-amyloid flux through both the amyloidogenic and nonamyloidogenic pathways of amyloid precursor protein (APP) processing.[23] Donor eyes were selected from a tissue collection obtained from the Iowa Lions Eye Bank within 8 hours after death (eTable 1 in the Supplement). Retinal tissue sections from the donor eyes were assessed for *APBB2* and β-amyloid expression using immunohistochemistry and image analysis. Further details on the experimental methods are included in the eAppendix in the Supplement.

Immunohistochemistry and Image Analysis of *APBB2* and β-Amyloid in Primary Visual Cortex Tissues

All donor samples (eTable 2 in the Supplement) were obtained from the Duke Kathleen Price Bryan Brain Bank and Biorepository and were matched for age and Alzheimer disease severity stage using the Braak classification.[24,25] Sections from the primary visual cortex of the donor samples were assessed for *APBB2* and β-amyloid expression using immunohistochemistry and image analysis. Further details on the experimental methods are included in the eAppendix in the Supplement.

Statistical Analysis

An analysis of the discovery GWAS and follow-up validation stages were prespecified. The evaluation of previously described loci and their consequences on primary open-angle glaucoma risk in the cohort of participants with African ancestry as well as studies exploring potential pathogenic mechanisms related to *APBB2* were undertaken in an exploratory, post hoc manner.

For the discovery GWAS analysis, the association between individual SNP genotypes and primary open-angle glaucoma risk was modeled additively for each copy of the minor allele using logistic regression adjusted for the top 3 principal components of population stratification using PLINK, version 1.9 (details on principal component analysis are included in the eAppendix in the Supplement).[26] For imputed genotypes, the information content for allele dosage (range, 0-1; 1 indicates perfect information) were included into the association test model to account for and average across imputation uncertainty. The assumptions of this logistic regression model were that the effective sample size was sufficiently large to allow for χ^2-distributed test statistics (eg, the Wald statistic for logistic regression) to be valid, for the observations to be independent of one another, and for only a low degree of collinearity to exist between the independent variables. The model assumptions were all met.

Genomic inflation (λgc) in the GWAS discovery stage was estimated using the median regression test statistic. The genomic inflation factor is presented for each of the 4 GWAS discovery sites as well as for the GWAS discovery meta-analysis in eFigure 1 in the Supplement. For the GWAS discovery analysis, $P < 5 \times 10^{-8}$ (2-sided test) was considered statistically significant. In the validation stages, the association between *APBB2* rs59892895 and primary open-angle glaucoma risk was measured using logistic regression for an additive model. Because only 1 SNP (*APBB2* rs59892895) was tested in the first and second validation stages, $P < .05$ (2-sided test) was considered statistically significant for each validation stage. Meta-analyses were conducted using the inverse-variance fixed-effects method (eAppendix in the Supplement).[27] Intercohort heterogeneity was assessed for the GWAS discovery and validation stages.

Previous case-control studies of primary open-angle glaucoma in individuals with European and Asian ancestry have robustly implicated at least 26 SNPs mapping to 15 distinct gene loci (*TMCO1*, *FMNL2*, *CADM2*, *AFAP1*, *THSD7A*, *CAV1-CAV2*, *ANGPT1*, *CDKN2B-AS*, *ABCA1*, *LMX1B*, *PLCE1*, *TMTC2*, *SIX6*, *TCF12*, and *GAS7*), accompanied by validation in at least 2 independent studies.[3,13,14,28-31] The association between these 26 SNPs and primary open-angle glaucoma risk were tested using logistic regression in the collections from individuals with African ancestry, which included 5153 affected individuals and 10 014 unaffected individuals with available genotyping data. An inverse-variance, fixed-effects meta-analysis was conducted to summarize the estimates.

A case-only quantitative trait locus analysis was performed between *APBB2* rs59892895T>C and 2 clinical parameters: maximum IOP and vertical cup-to-disc ratio at the time of examination (using the mean ratio if available for both eyes). The association between *APBB2* rs59892895T>C and the clinical parameters was assessed using linear regression with sex and age as covariates. The fluorescence intensity data from the immunohistochemical analysis (eAppendix in the Supplement) of retina and primary visual cortex tissues were analyzed with regards to *APBB2* rs59892895T>C carrier status using a linear mixed model incorporating additional random effect terms for individual (for both retina and visual cortex data) and Braak stage (for visual cortex data only).

Table. Summary of Case-Control Collections in a Study of the Association of Genetic Variants With Primary Open-Angle Glaucoma Among Individuals With African Ancestry

Sample Collection[a]	rs59892895*C Present, %		Sample Size, No.	
	Individuals With Primary Open-Angle Glaucoma	Control Individuals Without Primary Open-Angle Glaucoma	Individuals With Primary Open-Angle Glaucoma	Control Individuals Without Primary Open-Angle Glaucoma
GWAS Discovery				
Ghana	26.9	23.3	833	896
Nigeria	30.4	22.6	554	348
South Africa	31.1	22.9	228	269
United States	26.1	21.7	705	608
Total			2320	2121
First Validation				
Women's Health Initiative	23.1	20.8	1720	6067
Kaiser Permanente GERA	23.3	18.4	300	2700
ADAGES	24.3	21.4	1890	2205
South Africa	13.0	14.4	297	147
Tanzania	30.1	28.3	366	329
United States	23.6	22.6	450	1350
South London	26.6	21.6	378	217
Total			5401	13 015
Second Validation				
Cameroon	31.3	29.0	56	57
Nigeria	28.6	26.2	231	61
Nigeria (Kaduna)	29.2	30.2	99	88
Nigeria (African Glaucoma Genetics Project)	32.6	31.0	131	71
Saudi Arabia	5.5	3.1	276	655
Brazil	8.8	4.5	399	460
The Democratic Republic of the Congo	37.7	33.9	124	120
Morocco	6.8	3.5	37	130
Peru	2.0	1.2	51	128
Mali	27.3	23.4	132	132
Total			1536	1902
All validation			6937	14 917
Total samples			9257	17 038

Abbreviations: ADAGES, African Descent and Glaucoma Evaluation Study; GERA, Genetic Epidemiology Research on Adult Health and Aging; GWAS, genome-wide association study.

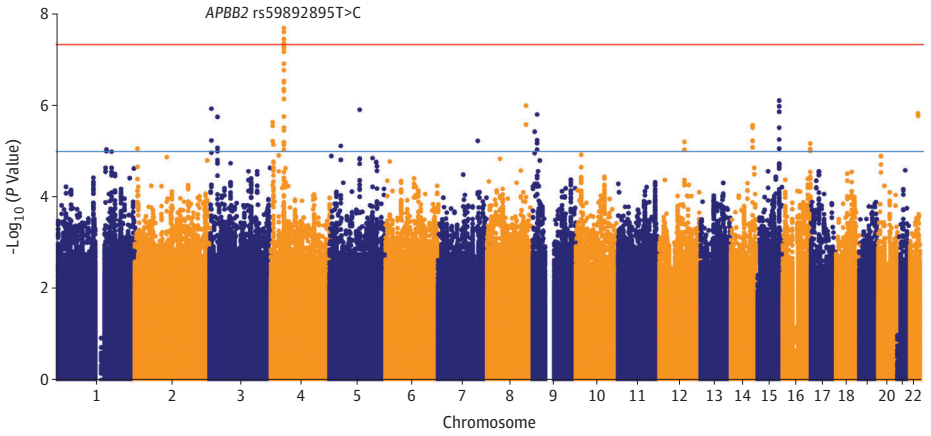
[a] The study site (country) or name of the study that the sample collection was taken from. More information on the sample collections can be found in the eAppendix in the Supplement.

Results

A total of 26 295 individuals were included in the study. The number of individuals with primary open-angle glaucoma and control individuals analyzed in the GWAS and validation stages are presented in the **Table** (quality control results and handling of population stratification can be found in the eAppendix and eFigures 1, 2, and 3 in the Supplement). The discovery meta-analysis identified a genome-wide significant association at 1 locus on chromosome 4, characterized by multiple SNP markers showing high pairwise linkage disequilibrium (**Figure 1**; summary statistics for the GWASs are publicly available per the data sharing statement). The association mapped to the *APBB2* rs59892895T>C locus (**Figure 2**), whereby the minor C allele was observed to be associated with increased risk of primary open-angle glaucoma (per-allele odds ratio [OR], 1.32 [95% CI, 1.20-1.46]; $P = 2 \times 10^{-8}$).

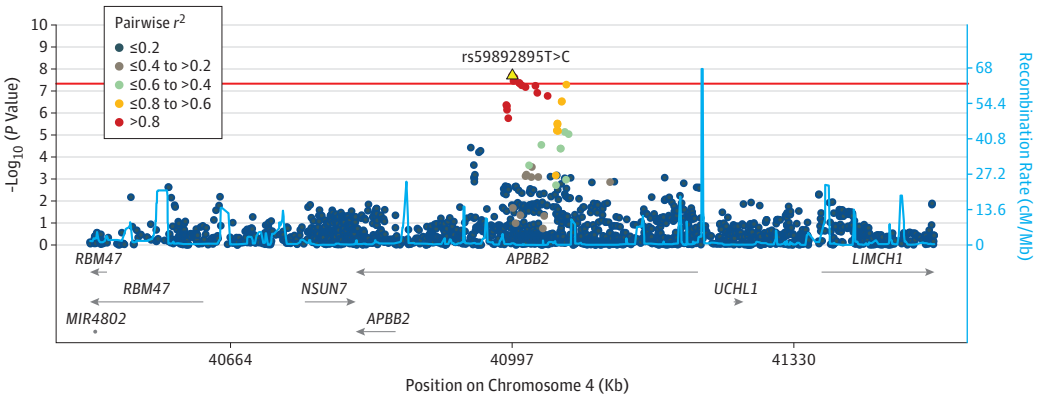
The *APBB2* rs59892895 association was tested in the first validation meta-analysis comprising 7 independently ascertained sample collections from participants with African ancestry (Table). This first validation data set with prior genome-wide genotyping data available for 5401 individuals with primary open-angle glaucoma and 13 015 individuals without primary open-angle glaucoma had greater than 90% statistical power to validate an SNP with a minor allele frequency as low as 20% and an OR as low as 1.10 at a 2-sided *P* value less than .05.[32] The association at *APBB2* rs59892895 was validated, with the risk C allele associated with increased risk of primary open-angle glaucoma (OR, 1.13 [95% CI, 1.07-1.20]; $P < .001$; **Figure 3**). There was no significant heterogeneity across all sites analyzed (*P* value for heterogeneity = .15).

Figure 1. Discovery Analysis of 2320 Individuals With Primary Open-Angle Glaucoma and 2121 Age-Matched Control Individuals



Single-nucleotide polymorphisms (SNPs) were only considered if they were assessed across all 4 genome-wide association discovery study sites. A total of 6 734 161 SNPs are included in this figure. The blue horizontal line indicates a threshold for suggestive statistical significance commonly used in genome-wide association studies ($P = 10^{-5}$) and the red horizontal line indicates the threshold for genome-wide significance ($P = 5 \times 10^{-8}$). Multiple SNPs at the gene encoding for amyloid-β A4 precursor protein-binding family B member 2 (*APBB2*) have a significant association with primary open-angle glaucoma disease risk.

Figure 2. Association at the Amyloid-β A4 Precursor Protein-Binding Family B Member 2 (*APBB2*) Locus on Chromosome 4



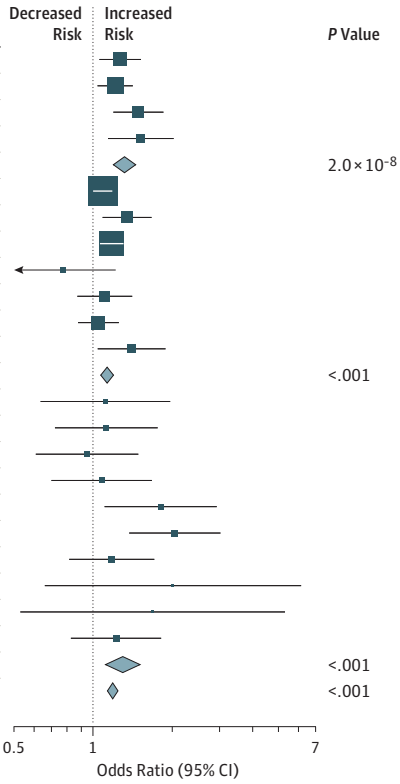
The association between single-nucleotide polymorphisms (SNPs) and primary open-angle glaucoma were plotted by genomic position on chromosome 4 and degree of statistical significance. The horizontal line shows the threshold for genome-wide significance, $P = 5 \times 10^{-8}$. The dots indicate the extent of linkage disequilibrium (LD) between each tested SNP with rs59892895 (based on pairwise r^2 values calculated from the discovery analysis). LD refers to the association between alleles of SNPs located close to one another on the same chromosome; SNPs in strong LD can serve as proxies for one another. Estimated recombination rates were plotted in light blue to reflect the LD structure in individuals with African ancestry. The estimated recombination rate shows the average frequency in which recombination occurs at a particular location. The extent of LD drops with increasing recombination rate. The horizontal lines accompanied by arrows in the lower panel of the plot reflect the genes mapping to the given genomic locations. The arrows indicate the direction of transcription of the genes. The horizontal lines labeled *APBB2* and *RBM47* reflect 2 different gene transcripts of different lengths for both genes.

A second validation meta-analysis for this association was completed with an additional 1536 affected individuals and 1902 unaffected individuals with African ancestry (Table). A significant association between the rs59892895*C allele and increased risk of primary open-angle glaucoma was observed (OR, 1.30 [95% CI, 1.12-1.51]; $P < .001$; Figure 3), with no significant heterogeneity across all 10 sites analyzed (P value for heterogeneity = .27). An overall meta-analysis of rs59892895*C involving the 9257 individuals with primary open-angle glaucoma and 17 038 individuals without primary open-angle glaucoma from all cohorts showed consistent association with primary open-angle glaucoma risk (OR, 1.19 [95% CI, 1.14-1.25]; $P < .001$) (Figure 3). The rs59892895*C allele was observed to not be significantly associated with IOP and vertical cup-to-disc ratio ($P = .62$) in an analysis of 6179 individuals of African ancestry with available data.

Only individuals of African ancestry or individuals with African ancestry admixture (eg, Brazil, Morocco, Peru, and Saudi Arabia; Table) were polymorphic at *APBB2* rs59892895—the rs59892895*C risk allele was not present in European, South Asian, or East Asian individuals (eFigure 4 in the Supplement). The sources of data accessed to ascertain the frequency of rs59892895 in participants with other ancestries were from the 1000 Genomes Project browser[33] (eFigure 5 in the Supplement), the Genome Aggregation Database (gNOMAD; eTable 3 in the Supplement),[34] as well as previously published GWAS data sets of European[3] (eAppendix in the Supplement) and Asian individuals.[15,35] No SNP within the broad *APBB2* locus was

Figure 3. Association Between Amyloid-β A4 Precursor Protein-Binding Family B Member 2 (*APBB2*) rs59892895 and Primary Open-Angle Glaucoma Risk

Collection	No. of Samples Genotyped		*APBB2* rs59892895*C Risk Alleles/No. Total Alleles		Odds Ratio (95% CI)	*P* Value
	Affected Individuals	Unaffected Individuals	Affected Individuals	Unaffected Individuals		
GWAS United States	694	596	362/1388	259/1192	1.27 (1.06-1.53)	
GWAS Ghana	821	884	442/1642	411/1768	1.22 (1.04-1.42)	
GWAS Nigeria	547	345	332/1094	156/690	1.49 (1.20-1.86)	
GWAS South Africa	222	256	138/444	117/512	1.52 (1.14-2.03)	
GWAS discovery summary					1.32 (1.20-1.46)	2.0×10^{-8}
Women's Health Initiative	1720	6067	794/3440	2523/12 134	1.09 (1.00-1.19)	
Kaiser Permanente	300	2700	140/600	991/5400	1.35 (1.09-1.67)	
ADAGES	1890	2205	918/3780	942/4410	1.18 (1.06-1.31)	
South Africa	297	146	77/594	42/292	0.77 (0.49-1.22)	
Tanzania	366	329	220/732	186/658	1.11 (0.87-1.41)	
United States	450	1350	212/900	610/2700	1.05 (0.88-1.26)	
South London	378	215	201/756	93/430	1.40 (1.04-1.89)	
First validation meta-analysis					1.13 (1.07-1.20)	<.001
Cameroon	56	57	35/112	33/114	1.12 (0.63-1.97)	
Nigeria	231	61	132/462	32/122	1.12 (0.72-1.77)	
Nigeria (Kaduna)	96	86	56/192	52/172	0.95 (0.61-1.49)	
Nigeria (AGGP)	129	71	84/258	44/142	1.08 (0.70-1.68)	
Saudi Arabia	275	600	30/550	37/1200	1.81 (1.11-2.97)	
Brazil	399	447	70/798	40/894	2.05 (1.38-3.07)	
The Democratic Republic of the Congo	122	118	92/244	80/236	1.18 (0.81-1.71)	
Morocco	37	130	5/74	9/260	2.02 (0.66-6.22)	
Peru	51	128	2/102	3/256	1.69 (0.53-5.40)	
Mali	132	128	72/264	60/256	1.23 (0.82-1.82)	
Second validation meta-analysis					1.30 (1.12-1.51)	<.001
All samples					1.19 (1.14-1.25)	<.001



The oblong data markers represent odds ratios, with the height of the data markers being inversely proportional to the standard error of the odds ratio. The diamonds represent the odds ratios after the meta-analysis, with the width representing the 95% CIs. Collections from the United States were taken from an African American population and the collection from South London was taken from a West African population. ADAGES indicates African Descent and Glaucoma Evaluation Study; AGGP, African Glaucoma Genetics Project; GWAS, genome-wide association study.

significantly associated with primary open-angle glaucoma in previously studied European or Asian ancestry case-control collections (eFigure 6 in the Supplement). *APBB2* rs59892895T>C was not observed to be in linkage disequilibrium (defined as pairwise $r^2 > 0.8$) with other coding genetic variants or with potentially functional regulatory elements (eFigure 7 in the Supplement).

Post Hoc Evaluation of Previously Described Loci and Their Consequences on Risk in the Cohorts

Analysis of 26 well-validated primary open-angle glaucoma SNPs from studies of individuals of European and Asian ancestry showed that for 23 of the 26 SNPs, the ORs in participants with African ancestry were smaller than in individuals with European ancestry. Heterogeneity tests showed 19 of the SNPs had *P* values for heterogeneity of less than .05 in support of a smaller OR in participants with African ancestry compared with European individuals (eTable 4 and eFigure 8 in the Supplement). Assessment of the relationship between IOP loci[13,30] and primary open-angle glaucoma risk showed a weak correlation between IOP and primary open-angle glaucoma risk in individuals with African ancestry (eTable 5 and eFigure 9 in the Supplement). Assessment of the relationship between vertical cup-to-disc ratio loci[36] and primary open-angle glaucoma risk showed that all previously reported loci for vertical cup-to-disc ratio were not associated with primary open-angle glaucoma risk in participants with African ancestry (eTable 6 in the Supplement).

Post Hoc Studies Exploring Potential Pathogenic Mechanisms Related to *APBB2*

All donor retina tissues were from individuals of African ancestry. For primary visual cortex tissues, carriers of the *APBB2* rs59892895*C risk allele were of African ancestry, whereas 3 of the 4 individuals with the *APBB2* rs59892895*TT homozygous baseline genotype were of European ancestry to match for the Braak stage of Alzheimer disease diagnosis (eTable 2 in the Supplement). Exploratory analyses using immunohistochemistry on donor retina and primary visual cortex tissues (eTable 1 and eTable 2 in the Supplement) suggested that participants carrying the rs59892895*C risk allele had associated higher *APBB2* expression as well as associated increased staining

for β-amyloid compared with participants homozygous for the baseline rs59892895*T nonrisk allele (eFigures 10, 11, and 12 in the Supplement).

Discussion

This study of 26 295 individuals found a genetic variant in the *APBB2* gene that was associated with a higher risk of primary open-angle glaucoma. The genetic association between primary open-angle glaucoma and *APBB2* was observed only in individuals of African ancestry. The level of genetic diversity in participants of African ancestry was higher than in individuals of European or Asian ancestry, and the functional risk alleles in *APBB2* may not be present in these other populations. The increased risk associated with the *APBB2* allele appeared not to be mediated via increased IOP or optic nerve neuropathy associated with an increasing vertical cup-to-disc ratio, thus suggesting a new insight to primary open-angle glaucoma disease pathogenesis.

Because the odds ratio of the *APBB2* rs59892895*C risk allele on primary open-angle glaucoma appeared to be larger in populations with African ancestry admixture, such as in Saudi Arabia, Brazil, Peru, and Morocco, this raised the possibility that estimates from these 4 populations could have been confounded by population stratification. However, principal component analysis of ancestry-informative markers from Brazil, Peru, and Morocco, which had sufficient DNA to allow assessment of these additional markers, revealed little evidence of population stratification between affected and unaffected individuals (eFigure 13 in the Supplement).

Because *APBB2* was shown to be involved in the amyloidogenic pathway of APP processing, an exploratory analysis of human retinal and primary visual cortex tissues suggested a potential relationship between the *APBB2* rs59892895*C risk allele, increased *APBB2* expression, and associated increased β-amyloid plaque deposition. Primary open-angle glaucoma neurotoxicity may result from incomplete clearance of amyloid β and other neurotoxins from the interstitial space of the optic nerve.[37] However, there has been no conclusive evidence that these pathways contribute to primary open-angle glaucoma in humans.

The present analysis suggests that the majority of open-angle glaucoma genetic loci described in individuals of European or Asian ancestry have a much more modest effect in individuals of African ancestry. Also, in contrast to studies of European individuals, the present data on individuals of African ancestry showed a much weaker correlation between genetic factors contributing to increased IOP and primary open-angle glaucoma risk. It is possible that these differences in genetic architecture are, at least in part, responsible for the increased prevalence and severity of primary open-angle glaucoma in African ancestry populations.

Limitations

This study has several limitations. First, despite the moderately large sample size of participants of African ancestry, there was only sufficient statistical power to detect associations with common genetic variants. Second, although all study sites used well-established clinical protocols to diagnose primary open-angle glaucoma, the heterogeneity of the primary open-angle glaucoma phenotype may have limited the ability to detect some genetic associations by biasing the effect estimates toward the null. Third, while the association observed between *APBB2* rs59892895 and primary open-angle glaucoma risk was statistically significant, the causal mechanisms of association have yet to be elucidated. Fourth, because the observations from human retinal and visual cortex tissues in this report are based on limited sample sizes, they are interpreted here as exploratory and hypothesis generating, and would require further validation through future research.

Conclusions

In this GWAS, variants at the *APBB2* locus demonstrated differential association with primary open-angle glaucoma by ancestry. If validated in additional populations this may have implications for risk assessment and therapeutic strategies.

ARTICLE INFORMATION

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