Genetic African Ancestry Is Associated With Central Corneal Thickness and Intraocular Pressure in Primary Open-Angle Glaucoma

Pieter W. M. Bonnemaijer,[1,2] Colin Cook,[3] Abhishek Nag,[4,5] Christopher J. Hammond,[4,5] Cornelia M. van Duijn,[2] Hans G. Lemij,[6] Caroline C. W. Klaver,[1,2,7] and Alberta A. H. J. Thiadens[1,2]

[1]Department of Ophthalmology, Erasmus MC, Rotterdam, The Netherlands
[2]Department of Epidemiology, Erasmus MC, Rotterdam, The Netherlands
[3]Division of Ophthalmology, University of Cape Town, Cape Town, South Africa
[4]Department of Twin Research and Genetic Epidemiology, King's College London, London, United Kingdom
[5]Department of Ophthalmology, King's College London, London, United Kingdom
[6]Glaucoma Service, The Rotterdam Eye Hospital, Rotterdam, The Netherlands
[7]Department of Ophthalmology, Radboud University Medical Center, Nijmegen, The Netherlands

Correspondence: Alberta A.H.J. Thiadens, Erasmus MC, Department of Ophthalmology and Epidemiology, Room NA 28-08, P.O. Box 2040, 3000 CA Rotterdam, The Netherlands;
a.thiadens@erasmusmc.nl.

Submitted: February 20, 2017
Accepted: April 23, 2017

Citation: Bonnemaijer PWM, Cook C, Nag A, et al. Genetic African ancestry is associated with central corneal thickness and intraocular pressure in primary open-angle glaucoma. *Invest Ophthalmol Vis Sci*. 2017;58:3172–3180. DOI:10.1167/iovs.17-21716

Purpose. To unravel the relationship between African ancestry, central corneal thickness (CCT), and intraocular pressure (IOP) by estimating the genetic African ancestry (GAA) proportion in primary open-angle glaucoma (POAG) patients and controls from an admixed South African Colored (SAC) and a South African Black (SAB) population.

Methods. In this case-control study, 268 POAG patients and 137 controls were recruited from a university clinic in Cape Town, South Africa. All participants were genotyped on the Illumina HumanOmniExpress beadchip or HumanOmni2.5Exome beadchip. ADMIXTURE was used to infer participant's GAA among 86,632 SNPs. Linear and logistic regression models were used to assess the relation between GAA, POAG, CCT, and IOP.

Results. The median proportion of GAA was 60% in the study population. GAA was significantly associated with thinner CCT ($P < 0.001$) and IOP ($P = 0.034$) in POAG patients. The effect of GAA on CCT was marginally different among POAG patients versus controls ($P = 0.066$). In POAG patients, the CCT was significantly thinner compared to controls after adjusting for age and sex ($P = 0.016$). In a stratified analysis in participants with >60% GAA, CCT was not associated with POAG ($P = 0.550$).

Conclusions. This study demonstrated that a higher proportion of GAA was associated with a thinner CCT and a higher IOP in POAG patients. Remarkably, at higher proportions of GAA, the difference in CCT between POAG and controls was reduced. This suggests that thinner CCT is not associated with POAG in Africans.

Keywords: genetic African ancestry, glaucoma, central corneal thickness, intraocular pressure

Primary open-angle glaucoma (POAG) is the predominant type of glaucoma worldwide and a leading cause of irreversible blindness.[1,2] In African populations, the prevalence is approximately three times higher compared to European populations and it runs a more severe course with higher intraocular pressure (IOP).[3–9] The IOP is a major risk factor for POAG and the only one that can be modified therapeutically to alter the progression rate of the disease. Therefore, it is essential that it is measured accurately. The reliability of IOP measurements, especially Goldmann applanation tonometry (GAT), is confounded by variations in central corneal thickness (CCT), which affects the rigidity of the cornea.[10] Not only does CCT affect the accuracy of GAT, but CCT also is reported to be a strong predictor of the development of POAG in ocular hypertensive patients, even when IOP is corrected for CCT.[11] Moreover, in the Early Manifest Glaucoma Trial, CCT was reported to be an independent predictive factor for longer-term progression of POAG in patients with higher baseline IOP.[12]

Nevertheless, whether the effect of CCT on glaucoma is only due to its effects on IOP measurement error or whether an independent relationship between CCT and glaucoma truly exists remains controversial.[11–15] Large population-based studies could not find any association of CCT with POAG. Other studies suggest that CCT is correlated with scleral and lamina cribrosa thickness, which affects the properties and vulnerability of the optic nerve and, therefore, increases the risk of glaucoma. However, histomorphometric studies in humans and monkeys could not confirm this correlation.[16,17] Other biomechanical characteristics have been suggested to link CCT with POAG, such as the viscoelasticity of the cornea or corneal hysteresis. Lower corneal hysteresis has been associated with an increased risk of glaucoma and glaucoma progression.[18–22]

CCT follows a diurnal rhythm and is affected by sex, age, and ethnicity.[23–27] The ethnic variation of CCT has

been studied widely. A meta-analysis including 53 studies showed that African individuals have a 20 to 30 μm thinner CCT compared to Europeans, Hispanics, and East Asians.[28] However, the possible relationship between a thinner CCT in individuals of African ancestry and their observed increased POAG risk has not been addressed sufficiently.

The purpose of this study was to disentangle the relationships between African ancestry, CCT, and IOP in POAG patients and controls. To overcome inaccuracy due to reporting bias and to study the effect of African ancestry quantitatively, we assessed each participant's biogeographic ancestry by inferring the genetic African Ancestry (GAA) rather than the self-reported ancestry.

Methods

Study Population

The Genetics in Glaucoma patients of African descent study (GIGA study) is a case-control study comprising open-angle glaucoma patients and healthy controls from South Africa. All participants ($n = 405$) provided a written informed consent in accordance with the ethical standards as stated in the Declaration of Helsinki. The institutional review boards of the Erasmus MC and the University of Cape Town granted ethical approval. Participants were ascertained at the ophthalmology outpatient department of the Groote Schuur Hospital in Cape Town, South Africa. In total, 268 POAG patients met the inclusion criteria of the study. Inclusion criteria were participants of South African Black (SAB) or admixed South African Colored (SAC)[29] descent, over 35 years of age, and diagnosed with either POAG or normal tension glaucoma (NTG). All other types of glaucoma, including secondary causes or narrow/closed angle glaucoma, were excluded. Inclusion criteria for controls ($n = 137$) were persons aged over 55 years, of SAB or SAC descent, without a diagnosis of any form of glaucoma, and without a family history (first degree relatives) of glaucoma. All participants were examined by a local glaucoma specialist.

Ophthalmic Examination

The complete eye examination included visual acuity (VA) by using a Snellen or Tumbling E chart at 6 m with and without correction, refraction, IOP measurement with GAT, slit-lamp examination including peripheral anterior chamber depth assessment by the Van Herick method, indirect gonioscopy, funduscopy for optic nerve head examination, and digital fundus photography centered on the optic nerve by means of a Canon CF-60DSi fundus camera.

CCT was measured after topical instillation of lidocaine anesthetics with an ultrasonic A-scan/pachymeter OcuScan RxP (Alcon Laboratories, Inc., Ft. Worth, TX, USA). Ten readings were automatically captured in both eyes.

Visual field testing was performed with the Humphrey Field Analyzer 24-2 Sita Fast (Carl Zeiss Meditec, Inc., Dublin, CA, USA) strategy. A definite visual field defect consistent with glaucoma was defined if the glaucoma hemifield test graded "outside normal limits" and if a cluster of 3 contiguous points was observed at the 5% level of the pattern deviation plot, including at least 1 of these points <1%. Field defects were not attributed to glaucoma in the presence of media opacities or nonglaucomatous optic nerve disease that could explain the visual field abnormality.

Inclusion Criteria

All patients were categorized as glaucomatous according to the ISGEO classification for open-angle glaucoma.[30] After preliminary screening by local glaucoma specialists, and grading of fundus photographs by one senior ophthalmologist and one trained research grader, detailed grading was performed independently by one general ophthalmologist (AAT) and one glaucoma specialist (HGL). They interpreted fundus images and visual field results independently while being masked for other clinical information. In case of any discrepancy between the two graders, adjudication was solved by consensus. If no consensus was reached, participants were excluded. Category 1 or 2 ISGEO criteria had to be met to diagnose glaucoma. The highest level of evidence (category 1) requires a definite visual field defect, as mentioned above, and loss of the neuroretinal rim with a Vertical Cup Disc Ratio (VCDR) ≥ 0.7, or VCDR asymmetry ≥ 0.2 (both values represented the $\geq$97.5th percentile for the normal SAB population[31]). Visual field testing results with less than 8% false-positive and false-negative responses, and less than 10% fixation losses were considered reliable. Category 2 requires a severely damaged optic disc, that is, a VCDR > 0.8 or VCDR asymmetry > 0.2 (both values determined by $\geq$99.5th percentile for the normal SAB population[31]) in the absence of a satisfactory visual field test.

In addition, patients with POAG demonstrated an open angle on gonioscopy. Nonglaucomatous participants were those who met the following criteria in both eyes: IOP ≤ 21 mm Hg, a nonglaucomatous optic disc with VCDR < 0.5, and an intereye variation in VCDR <0.2.

Estimation of Genetic Ancestry

Participants were genotyped on the Illumina HumanOmniExpressExome beadchip ($n = 137$) and the Illumina HumanOmni2.5Exome beadchip ($n = 244$). Before combining both genotype datasets, PLINK(v1.07) was used to perform extensive quality control checks.[32] No within sample cryptic relatedness was observed during QC. To make inferences based on populations of known ancestry, we merged the combined dataset with 3 reference populations from Africa (Yoruba in Ibadan, Nigeria, and Luhya in Webuye, Kenya), East-Asia (Japanese in Tokyo, Japan, Southern Han Chinese, and Han Chinese in Beijing, China) and Europe (Utah Residents [CEPH] with Northern and Western Ancestry, Tuscany in Italy, Finnish in Finland, British in England and Scotland, and Iberian in Spain) appearing in the 1000 Genomes Project.[33] PLINK then was used to perform linkage disequilibrium pruning on the merged genotype data to produce a reduced set of unlinked single nucleoside polymorphism (SNPs) (–indep-pairwise 50 10 0.1); 86,632 autosomal SNPs with an SNP call rate of 100% were selected from the merged datasets to estimate biogeographic ancestry (BGA). First we examined the genetic clustering by visualizing the principal components calculated in PLINK (Supplementary Fig. S1). The program ADMIXTURE v1.23 then was used to estimate the ancestral fractions of the three putative ancestral populations—African, Asian, and European—among the study samples.[34] ADMIXTURE was run with default settings and $K = 3$ ancestral populations.

Statistical Analysis

Since the mean CCTs of right and left eyes were not statistically different (mean difference, 1.1 μm; $P = 0.242$; Pearson

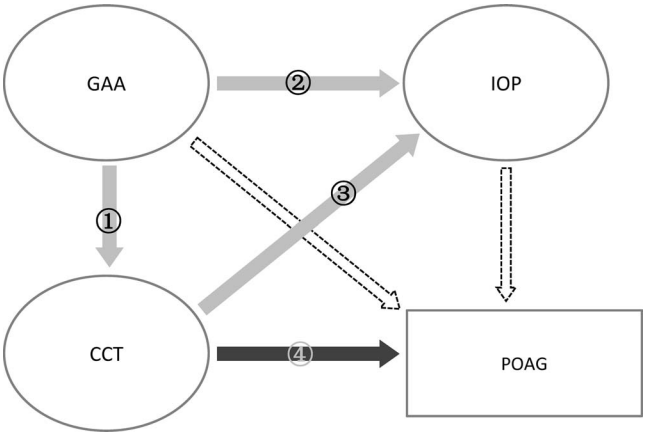

FIGURE 1. Directed acyclic graph (DAG) depicting the interrelationships among GAA, CCT, IOP, and POAG. *Black arrow* represent the relationship between the primary independent variables (i.e., risk factors) and the outcome (i.e., POAG). *Gray arrows* represent the relationships between the independent variables (i.e., risk factors). *Dashed arrows* represent relationships that were not further studied because of the study design.

correlation = 0.90), we only present the results of the right eye analyses. If measurements from the right eye were not available, then data from the left eye were used instead. In total, 383 right eyes and 22 left eyes were available for analysis. The average of the first 5 CCT readings was used in the analysis. The independent samples Student's *t*-test was used to compare continuous variables among ethnic and diagnostic groups. We performed χ^2 tests on categorical variables. GAA fractions inferred from SNP data were used instead of self-reported ethnicity to determine any association with African ancestry. We studied four interrelationships among POAG, GAA, CCT, and IOP as depicted in Figure 1. Univariable and multivariable linear regression models, adjusting for age and sex, were applied to test the association between GAA and CCT, GAA and IOP, and CCT and IOP. Univariable and multivariable logistic regression models, adjusting for age and sex, were used to test the association of CCT with POAG. Also, effect modification of CCT by GAA was tested in the association of CCT with POAG by adding the multiplicative interaction term to the adjusted model. All statistical analyses were performed in SPSS (version 21.0; IBM Corp. Armonk. NY, USA) and R studio (R Core Team [2014]; R Foundation for Statistical Computing, Vienna, Austria).

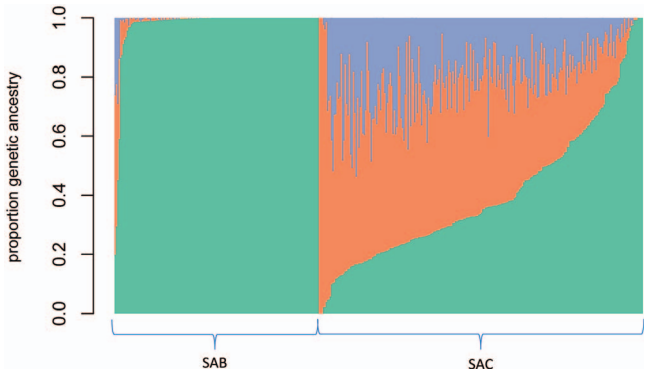

FIGURE 2. Distribution of African (*green*), European (*orange*), and Asian (*blue*) genetic ancestry per individual. Every individual is represented by a *vertical bar* which is composed of three colors corresponding to their proportion genetic ancestry from these ancestral populations. The *x*-axis denotes individuals of self-reported SAB descent and SAC descent. The *y*-axis denotes individual proportions of genetic ancestry.

RESULTS

Demographics and Clinical Characteristics

The demographic and clinical characteristics of the 268 POAG patients and 137 controls are given in Table 1. In the control group, there were significantly more women, and controls had undergone more ocular surgery (in particular cataract extraction) compared to the POAG patients. In the POAG patients, the untreated IOP was statistically significantly higher ($P < 0.001$) and the CCT was statistically significantly thinner than in control participants ($P = 0.019$). There was no statistically significant difference in mean CCT among participants with and without ocular surgery when adjusted for age, sex, and POAG status (surgery, 507.1 ± 40.5 μm, $n = 194$; no surgery, 504.5 ± 36.0, $n = 211$; $P = 0.460$). The CCT did not significantly vary with age (–0.23 μm per year; 95% confidence interval [CI], –0.57–0.11; $P = 0.188$). All CCT measurements had been performed during daytime (9 AM to 5 PM), and there was no association between CCT and the time of examination. The distribution of self-reported ethnicity/race was similar for POAG patients and controls. This was confirmed by an equal median percentage GAA (Mann-Whitney *U* Test, $P = 0.750$) for 381 participants that were genotyped successfully. Figure 2 and Supplementary Table S1 present the distribution of the percentage genetic Asian, African, and European ancestry across SAB and SAC. The median proportion of GAA was significantly different in SAC participants compared to SAB participants (Mann-Whitney *U* Test, $P < 0.001$). One individual

TABLE 1. Demographic and Clinical Characteristics

Demographic and Clinical Characteristics	POAG, $n = 268$	Controls, $n = 137$	*P* Value*
Median age, y (IQR)	68.0 (20)	66.0 (12)	0.828
Female, *n* (%)	144 (53.7)	91 (66.4)	0.019
Ocular surgery, *n* (%)	110 (41.0)	84 (61.3)	<0.001
IOP (untreated), mm Hg ± SD	28.61 ± 9.73	14.20 ± 2.89	<0.001
CCT, μm ± SD	502.53 ± 37.00	511.92 ± 39.82	0.019
Median VCDR (IQR)	0.90 (0.15)	0.30 (0.20)	<0.001
Median proportion GAA, % (IQR)	61.24 (71.94)	55.37 (67.66)	0.750

IQR, interquartile range.

* *P* value obtained from a Student's *t*-test for continuous variables and with χ^2 test for categorical variables. For median age and median VCDR and median proportion GAA, *P* values were obtained with the Mann-Whitney *U* test.

Table 2. Association of GAA, CCT, IOP, and POAG as Graphically Depicted in the Directed Acyclic Graph (Fig. 1)

	Univariable Regression Model			Multivariable Regression Model*		
	β	95% CI	*P* Value	*β*	95% CI	*P* Value
1. CCT ~ GAA						
All, $n = 381$	−3.58	−4.65 to −2.51	<0.001	−4.42	−5.38 to −3.14	<0.001
Control, $n = 130$	−5.23	−7.10 to −3.36	<0.001	−5.41	−7.36 to −3.45	<0.001
POAG, $n = 251$	−2.80	−4.09 to −1.51	<0.001	−3.68	−5.06 to −2.30	<0.001
2. IOP ~ GAA						
Control, $n = 129$	−0.14	−0.29 to 0.01	0.069	−0.12	−0.28 to 0.04	0.131
POAG, $n = 200$	0.63	0.24 to 1.02	0.002	0.46	0.05 to 0.87	0.029
3. IOP ~ CCT						0.204
Control, $n = 136$	0.09	−0.04 to 0.21	0.174	0.08	−0.04 to 0.20	
POAG, $n = 214$	0.00	−0.35 to 0.36	0.991	−0.05	−0.40 to 0.30	0.767
4. POAG ~ CCT, $n = 405$	1.067†	1.01 to 1.13	0.020	1.07†	1.01 to 1.13	0.019

β = effect per 10% increase in GAA or 10 μm decrease in CCT.
* Multivariable regression model adjusted for age and sex.
† Odds ratio. Corresponds to the effect of 10 μm decrease in CCT.

of self-reported SAB descent had less than 25% GAA according to the ADMIXTURE results, while 17 self-reported SAC individuals (7%) had more than 80% GAA; three self-reported SAC individuals (1.2%) did not have any GAA.

The results of the single exploratory analysis of the interrelationships between GAA, IOP, CCT and POAG, as graphically depicted in Figure 1, are presented in Table 2.

1. Relationship of CCT and GAA

For the relationship between CCT and GAA, we found a statistically significant, negative association in the univariable and multivariable regression model for controls and POAG patients together ($P_{univariable} < 0.001$, $P_{multivariable} < 0.001$). For every 10% increase in GAA, CCT showed a mean decrease of 4.4 μm (95% CI, −5.4 to −3.1). The regression lines for CCT as a function of GAA in POAG patients and controls separately are illustrated in Figure 3. For every 10% increment in GAA, the CCT in the controls decreased by 5.4 μm, on average. In the POAG patients, a 10% increase in GAA was associated with a 3.7 μm decrease in CCT. As an effect of the differences in the slope for controls and POAG patients, the difference in CCT between controls and POAG cases narrowed as the regression lines converged.

2. Relationship of IOP and GAA

In the POAG patients, GAA was significantly associated with IOP ($P < 0.029$), as shown in the multivariable regression model. As such, for every 10% increase in GAA in POAG patients IOP increased by 0.46 mm Hg. In controls, GAA was not associated with IOP ($P = 0.131$).

3. Relationship of IOP and CCT

We examined the association between CCT and IOP for POAG patients and controls separately. In none of the groups there was a statistically significant relationship between CCT and IOP in a multivariable regression model adjusting for sex and age ($P_{POAG} = 0.767$; $P_{control} = 0.204$).

4. Relationship of POAG and CCT

Logistic regression analysis showed that a thinner CCT was associated with an increased likelihood of POAG ($P_{univariable} < 0.02$, $P_{multivariable} < 0.019$). A 10 μm decrease in CCT was associated with approximately 7% higher odds of POAG after adjusting for sex ($P = 0.017$; odds ratio [OR], 0.59; 95% CI, 0.38–0.91), and age (age per year, $P = 0.694$; OR, 1.0; 95% CI, 0.97–1.02). To test if the relationship between CCT and POAG was modified by GAA, we tested for effect modification by adding the multiplicative interaction term between GAA and CCT to the multivariable regression model. In addition, a stratified analysis for median GAA (i.e., below and above the median GAA value of 59.6%) was performed. No statistically significant interaction between GAA and CCT was observed (*P*-interaction = 0.112). When the data were stratified by median GAA, the CCT was associated only with POAG for individuals with a GAA less than 59.6% ($P = 0.044$; Table 3). Since NTG (untreated IOP < 21 mm Hg) is found more commonly in non-Africans and has been associated previously with a thinner CCT, we performed a sensitivity analysis by removing all NTG patients ($n = 28$) from our analyses. Excluding the NTG patients from the main analysis did not change the association between CCT and POAG ($P = 0.02$; OR, 1.07; 95% CI, 1.01–1.13); similarly, the multiplicative interaction between GAA and CCT ($P = 0.102$) did not change.

Discussion

In this study, we found a statistically significant association between GAA, CCT, and IOP in the South African study population. Participants with a higher proportion of GAA had a thinner CCT. African ancestry also was associated with higher IOP in POAG patients. In the total study population, the POAG patients had a significantly thinner CCT, but the association of POAG and CCT was not statistically modified by differences in GAA. However, when stratified by median GAA, only an association between CCT and POAG for individuals with <60% GAA remained statistically significant. This suggests that genetic ancestry may have a role in the association between POAG and CCT.

To our knowledge, this study is the first to investigate the variation in CCT across different ethnic/racial groups in an African population and its association with GAA. Only recently have studies started to investigate the CCT in populations from Sub-Saharan Africa, of which most are from West Africa (i.e., Ghana and Nigeria).[35–38] In comparison with other African studies, the mean CCT found for control participants in this

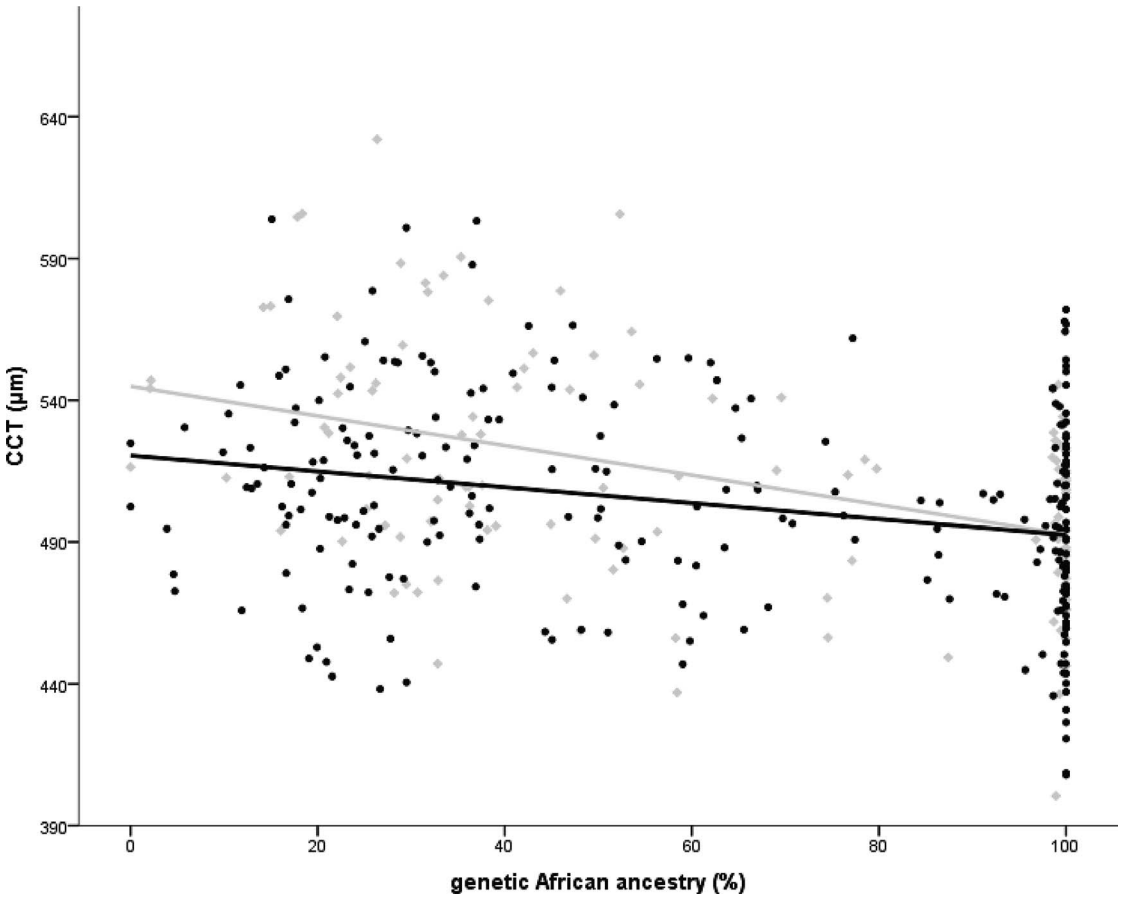

FIGURE 3. Scatter plot depicting the relation between GAA and CCT. *Black dots* represent POAG patients, every *gray diamonds* represent controla. The *black line* is the linear regression adjusted for sex and age for POAG patients ($CCT_{POAG} = 563.2–0.37*GAA$). The *gray line* is the linear regression adjusted for sex and age for controls ($CCT_{controls} = 584.0–0.54*GAA$).

South African population was considerably thinner; it was even the thinnest in any African study performed by means of ultrasound pachymetry to date (i.e., 512 ± 39.8; Fig. 4).[28,35–46] Associations between GAA and CCT have been studied previously in African Americans and Europeans in the ADAGES study.[47] This study found a similar correlation for CCT and GAA in the entire group. However, a significant association between GAA and CCT in the African American subgroup could not be detected due to a limited degree of admixture in this group.

The association between IOP and GAA has been studied in Latinos in the LALES study.[48] This population-based study found that IOP increases by 0.38 mm Hg for every 10% increase in GAA. Although West Coast Latinos have a modest contribution of GAA, our study found similar results, that is, a 0.46 mm Hg increase per 10% increase in GAA, for POAG patients. For controls, we did not find any association between GAA and IOP. This could be explained by selection bias that was induced by selecting only controls with an IOP < 21 mm Hg. We did not observe a significant linear correlation between IOP and CCT in either POAG patients or controls. Although most population-based studies find a correlation between IOP and CCT, case control studies could not always detect this association in POAG patients due to selection of severe cases with critical elevated IOP.

TABLE 3. Association of CCT With POAG Stratified by Median Proportion GAA

Strata	n_{POAG}; $n_{control}$	OR	95% CI	*P* Value*
< median GAA (<59.6%)	122; 69	1.09	1.00–1.18	0.044
≥ median GAA (≥59.6%)	129; 61	1.04	0.94–1.14	0.477

OR, odds ratio per 10 µm decrease in CCT.
* Multivariable regression model adjusted for age and sex.

Most of the studies investigating the relationship between glaucoma and CCT were based predominantly on European ancestral populations and focused on ocular hypertension and NTG patients. There have been conflicting reports about the CCT of POAG patients versus controls. Several studies did not find any statistically significant differences in CCT between these groups.[27,49–54] Yet, various other studies have, indeed, reported such differences.[26,55,56] A few studies have investigated this relationship in African populations.[26,35,37,44,46] Only one of these detected a statistically significantly thinner CCT in POAG patients, but this difference was only present in the left eye.[35] Also, the Barbados eye study found a thinner CCT in POAG patients, but this difference was not statistically significant ($P = 0.07$).[44] Recently, the Tema eye survey, the largest population-based study of CCT on the African continent, could not find an association between CCT and POAG as well.[38]

A novel finding of our study was that the difference in CCT between POAG patients and controls attenuated by increasing GAA (Fig. 3). This highlights that in individuals with a high percentage of African ancestry, differences in CCT are little, if at all, associated with POAG. This stresses the importance of anatomic variation between ethnic/racial groups and the

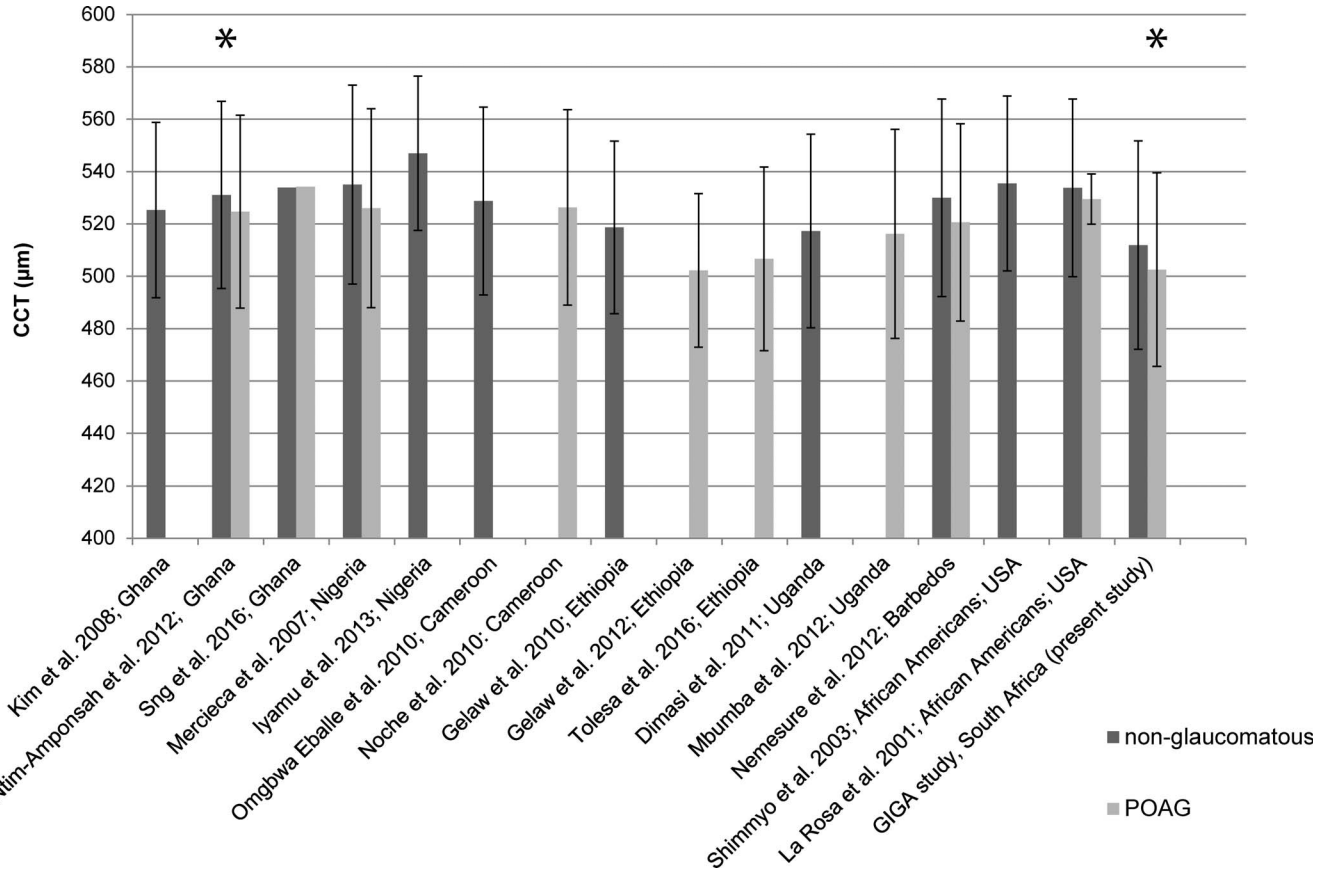

Figure 4. CCT in African POAG patients and non-glaucomatous African individuals. *Error bars*: Standard deviation. *Significant difference between POAG patients and controls; Sng et al., no standard deviation available.

possible susceptibility for development of POAG. Investigation into the racial and ethnic differences in the anatomy of the optic nerve head showed, for instance, a thicker retinal nerve fiber layer, and larger optic discs with deeper cups in African individuals.[57–61] In particular, a correlation between thinner CCT and larger optic discs seems to be present in POAG patients.[62,63] Larger optic disc diameters may be associated with increased vulnerability to pressure-induced deformation. Therefore, eyes with thinner corneas are more susceptible to glaucomatous damage in comparison with those having thicker corneas. This hypothesis may explain why African persons are more vulnerable to glaucomatous optic nerve head damage. Although conflicting evidence exists that CCT is associated with other disc topographic parameters (i.e., rim area, cup area and VCDR).[64–66] A new property of the cornea, corneal hysteresis, has shown to be a better predictor of glaucomatous damage.[15,21]

Our study has strengths and weaknesses. A strength of our study is that by applying BGA estimation, we were able to objectively measure variation in CCT and IOP related to ethnic/racial differences. Self-reported ethnicity/race frequently is used in epidemiologic studies to assess an individual's background origin. Often participants are asked to specify a single ethnic/racial group based on categories. This method can be unreliable, since these definitions can be imprecise and inconsistent over time.[67,68] Also, self-reported ethnicity/race can be based on subjective physical characteristics and intrinsic beliefs. Skin color, for example, often is used as surrogate of race, although visual classification of skin color can be interpreted differently.[69–71] Especially in complex admixed populations, such as SAC, self-reported ethnicity does not reveal the extent of admixture, which is because admixed individuals can have multiple ancestries, and these ancestry proportions can vary greatly per individual. Recent advances in genome-wide genotyping that allow the inference of BGA can set aside the use of proxy methods, such as self-reported ethnicity/race.[71]

The high degree of admixture in our study population also is a valuable asset of the study, since it enabled detailed evaluation of the differences in CCT and IOP in relation to African ancestry.

A limitation of this study is its relatively small sample size. As a result, this study had limited statistical power to find significant interaction between GAA and CCT when studying the association between CCT and POAG. Also, we performed several numbers of tests. Therefore, chance finding should be considered when interpreting the data. Post hoc power analysis showed that this study was sufficiently powered (power $> 80\%$; $P < 0.013$; considering four tests), for the multivariable associations in the POAG patients. We currently are extending our genotyping efforts in a Tanzanian population. As genotyping progresses, we will have more statistical power to detect any significant differences. Preliminary data from Tanzania strengthens our current findings and confirm that in this African black population CCT is not different among POAG patients and controls. Another limitation of this study includes potential selection bias. For selecting POAG patients based on functional damage (ISGEO category 1), we applied rather strict criteria for assessing the reliability of the visual fields. This might have led to a selection of super-test takers, and, therefore, an undercalling of POAG patients. It turned out, however, that 96% of the probable glaucoma cases

that failed our strict reliability criteria were later identified as glaucomatous, based on advanced structural optic nerve head damage (ISGEO category 2). Therefore, the effects of our strict visual field reliability criteria on our results probably were insignificant. In controls, the IOP cutoff for enrolment could have biased the associations in this group. Although high IOP is the main risk factor for POAG, we might have overlooked potentially healthy participants with elevated IOP.

In conclusion, this study shows that in African admixed individuals GAA measurement is an unprejudiced tool to distinguish associations with POAG and their endophenotypes. We found that a higher proportion of GAA is associated with a thinner CCT, and that an increase in GAA in POAG patients is associated with a higher IOP. Interestingly, our current study shows that the difference in CCT between POAG patients and controls is reduced at higher proportions of GAA. This confirms previous studies that did not find significant differences in CCT between POAG patients and controls in Africans.[26,37,38,44,46] Therefore, some biomechanical properties of the African eye may be different compared to those in other ethnic groups. However, it is not yet clear to what extent they relate to the increased glaucoma susceptibility of Africans.

Acknowledgments

The authors thank all the GIGA study participants for their cooperation. We acknowledge Suzanne van Schaik, Milou van Bruchem, Hannah Hardjosantoso, Katinka Snoek, Chawan Amin, Vicky Hokken, Corina Brussee, Magda Meester-Smoor, Suzanne van der Laar, and all ophthalmologist, residents, and nurses of the division of Ophthalmology from the Groote Schuur Hospital in Cape Town for their continuous efforts in the recruitment of participants.

Supported by grants to Stichting Combined Ophthalmic Research Rotterdam, The Netherlands; BrightFocus Foundation, USA; Algemene Nederlandse Vereniging ter Voorkoming van blindheid, The Netherlands; Landelijke Stichting voor Blinden en Slechtzienden, The Netherlands; Stichting Beheer het Schild, The Netherlands; Prof. Dr. Henkes Stichting, The Netherlands; Rotterdamse Stichting Blindenbelangen, The Netherlands; International Glaucoma Association, United Kingdom; National Institute of Health Research (NIHR) Senior Research Fellowship, United Kingdom; and Stichting Glaucoomfonds, The Netherlands.

Disclosure: **P.W.M. Bonnemaijer**, None; **C. Cook**, None; **A. Nag**, None; **C.J. Hammond**, None; **C.M. van Duijn**, None; **H.G. Lemij**, None; **C.C.W. Klaver**, None; **A.A.H.J. Thiadens**, None

References

1. Kapetanakis VV, Chan MP, Foster PJ, et al. Global variations and time trends in the prevalence of primary open angle glaucoma (POAG): a systematic review and meta-analysis. *Br J Ophthalmol*. 2016;100:86–93.
2. Tham YC, Li X, Wong TY, et al. Global prevalence of glaucoma and projections of glaucoma burden through 2040: a systematic review and meta-analysis. *Ophthalmology*. 2014; 121:2081–2090.
3. Cook C. Glaucoma in Africa: size of the problem and possible solutions. *J Glaucoma*. 2009;18:124–128.
4. Wormald R, Foster A. Clinical and pathological features of chronic glaucoma in north-east Ghana. *Eye (Lond)*. 1990;4: 107–114.
5. Verrey JD, Foster A, Wormald R, Akuamoa C. Chronic glaucoma in northern Ghana–a retrospective study of 397 patients. *Eye (Lond)*. 1990;4:115–120.
6. Mafwiri M, Bowman RJ, Wood M, Kabiru J. Primary open-angle glaucoma presentation at a tertiary unit in Africa: intraocular pressure levels and visual status. *Ophthalmic Epidemiol*. 2005;12:299–302.
7. Omoti AE, Osahon AI, Waziri-Erameh MJ. Pattern of presentation of primary open-angle glaucoma in Benin City, Nigeria. *Trop Doct*. 2006;36:97–100.
8. Abdull MM, Gilbert CC, Evans J. Primary open angle glaucoma in northern Nigeria: stage at presentation and acceptance of treatment. *BMC Ophthalmol*. 2015;15:111.
9. Kyari F, Abdull MM, Bastawrous A, et al. Epidemiology of glaucoma in sub-saharan Africa: prevalence, incidence and risk factors. *Middle East Afr J Ophthalmol*. 2013;20:111–125.
10. Goldmann H, Schmidt T. Applanation tonometry [in German]. *Ophthalmologica*. 1957;134:221–42.
11. Brandt JD, Gordon MO, Gao F, et al. Adjusting intraocular pressure for central corneal thickness does not improve prediction models for primary open-angle glaucoma. *Ophthalmology*. 2012;119:437–442.
12. Leske MC, Heijl A, Hyman L, et al. Predictors of long-term progression in the early manifest glaucoma trial. *Ophthalmology*. 2007;114:1965–1972.
13. Manni G, Oddone F, Parisi V, et al. Intraocular pressure and central corneal thickness. *Prog Brain Res*. 2008;173:25–30.
14. Medeiros FA, Weinreb RN. Is corneal thickness an independent risk factor for glaucoma? *Ophthalmology*. 2012;119: 435–436.
15. Carbonaro F, Hysi PG, Fahy SJ, et al. Optic disc planimetry, corneal hysteresis, central corneal thickness, and intraocular pressure as risk factors for glaucoma. *Am J Ophthalmol*. 2014;157:441–446.
16. Jonas JB, Holbach L. Central corneal thickness and thickness of the lamina cribrosa in human eyes. *Invest Ophthalmol Vis Sci*. 2005;46:1275–1279.
17. Jonas JB, Hayreh SS, Tao Y. Central corneal thickness and thickness of the lamina cribrosa and peripapillary sclera in monkeys. *Arch Ophthalmol*. 2009;127:1395–1396.
18. Mangouritsas G, Morphis G, Mourtzoukos S, Feretis E. Association between corneal hysteresis and central corneal thickness in glaucomatous and non-glaucomatous eyes. *Acta Ophthalmol*. 2009;87:901–905.
19. Kaushik S, Pandav SS, Banger A, et al. Relationship between corneal biomechanical properties, central corneal thickness, and intraocular pressure across the spectrum of glaucoma. *Am J Ophthalmol*. 2012;153:840–849.
20. Congdon NG, Broman AT, Bandeen-Roche K, et al. Central corneal thickness and corneal hysteresis associated with glaucoma damage. *Am J Ophthalmol*, 2006;141:868–875.
21. Medeiros FA, Meira-Freitas D, Lisboa R, et al. Corneal hysteresis as a risk factor for glaucoma progression: a prospective longitudinal study. *Ophthalmology*. 2013;120: 1533–1540.
22. Zhang C, Tatham AJ, Abe RY, et al. Corneal hysteresis and progressive retinal nerve fiber layer loss in glaucoma. *Am J Ophthalmol*. 2016;166:29–36.
23. Doughty MJ, Zaman ML. Human corneal thickness and its impact on intraocular pressure measures: a review and meta-analysis approach. *Surv Ophthalmol*. 2000;44:367–408.
24. Goldich Y, Barkana Y, Pras E, et al. Variations in corneal biomechanical parameters and central corneal thickness during the menstrual cycle. *J Cataract Refract Surg*. 2011; 37:1507–1511.
25. Fogagnolo P, Rossetti L, Mazzolani F, Orzalesi N. Circadian variations in central corneal thickness and intraocular pressure in patients with glaucoma. *Br J Ophthalmol*. 2006; 90:24–28.
26. Aghaian E, Choe JE, Lin S, Stamper RL. Central corneal thickness of Caucasians, Chinese, Hispanics, Filipinos, African

Americans, and Japanese in a glaucoma clinic. *Ophthalmology*. 2004;111:2211–2219.

27. Ventura AC, Bohnke M, Mojon DS. Central corneal thickness measurements in patients with normal tension glaucoma, primary open angle glaucoma, pseudoexfoliation glaucoma, or ocular hypertension. *Br J Ophthalmol*. 2001;85:792–795.
28. Dimasi DP, Hewitt AW, Kagame K, et al. Ethnic and mouse strain differences in central corneal thickness and association with pigmentation phenotype. *PLoS One*. 2011;6:e22103.
29. Adhikari M. *Not White Enough, Not Black Enough: Racial Identity in the South African Coloured Community*. Athens, OH: Ohio University Press; 2005.
30. Foster PJ, Buhrmann R, Quigley HA, Johnson GJ. The definition and classification of glaucoma in prevalence surveys. *Br J Ophthalmol*. 2002;86:238–242.
31. Rotchford AP, Kirwan JF, Muller MA, et al. Temba glaucoma study: a population-based cross-sectional survey in urban South Africa. *Ophthalmology*. 2003;110:376–382.
32. Purcell S, Neale B, Todd-Brown K, et al. PLINK: a tool set for whole-genome association and population-based linkage analyses. *Am J Hum Genet*. 2007;81:559–575.
33. The 1000 Genomes Project Consortium. A global reference for human genetic variation. *Nature*. 2015;526:68–74.
34. Alexander DH, Novembre J, Lange K. Fast model-based estimation of ancestry in unrelated individuals. *Genome Res*. 2009;19:1655–1664.
35. Ntim-Amponsah CT, Seidu AY, Essuman VA, et al. A study of central corneal thickness in glaucoma and nonglaucoma patients in a West African population. *Cornea*. 2012;31:1093–1096.
36. Kim HY, Budenz DL, Lee PS, et al. Comparison of central corneal thickness using anterior segment optical coherence tomography vs ultrasound pachymetry. *Am J Ophthalmol*. 2008;145:228–232.
37. Mercieca K, Odogu V, Fiebai B, et al. Comparing central corneal thickness in a sub-Saharan cohort to African Americans and Afro-Caribbeans. *Cornea*. 2007;26:557–560.
38. Sng C, Barton K, Kim H, et al. Central corneal thickness and its associations with ocular and systemic factors in an urban West African population. *Am J Ophthalmol*. 2016;169:268–275.
39. Iyamu E, Iyamu JE, Amadasun G. Central corneal thickness and axial length in an adult Nigerian population. *J Optom*. 2013;6:154–160.
40. Eballe AO, Koki G, Ellong A, et al. Central corneal thickness and intraocular pressure in the Cameroonian nonglaucomatous population. *Clin Ophthalmol*. 2010;4:717–724.
41. Noche CD, Eballe AO, Bella AL. Central corneal thickness in black Cameroonian ocular hypertensive and glaucomatous subjects. *Clin Ophthalmol*. 2010;4:1371–1377.
42. Tolesa K, Gessesse GW. Central corneal thickness in newly diagnosed glaucoma patients in South West Ethiopia: a cross-sectional study. *BMC Ophthalmology*. 2016;16:152.
43. Mbumba BF, Kagame K, Onyango J, Aliraki L. Characteristics of glaucoma in black African patients attending Ruharo Eye Centre, South Western Uganda. *East Afr J Ophthalmol*. 2012;16:4.
44. Nemesure B, Wu SY, Hennis A, et al. Corneal thickness and intraocular pressure in the Barbados eye studies. *Arch Ophthalmol*. 2003;121:240–244.
45. Shimmyo M, Ross AJ, Moy A, Mostafavi R. Intraocular pressure, Goldmann applanation tension, corneal thickness, and corneal curvature in Caucasians, Asians, Hispanics, and African Americans. *Am J Ophthalmol*. 2003;136:603–613.
46. La Rosa FA, Gross RL, Orengo-Nania S. Central corneal thickness of Caucasians and African Americans in glaucomatous and nonglaucomatous populations. *Arch Ophthalmol*. 2001;119:23–27.
47. Girkin CA, Nievergelt CM, Kuo JZ, et al. Biogeographic Ancestry in the African Descent and Glaucoma Evaluation Study (ADAGES): association with corneal and optic nerve structure. *Invest Ophthalmol Vis Sci*. 2015;56:2043–2049.
48. Nannini D, Torres M, Chen YD, et al. African ancestry is associated with higher intraocular pressure in Latinos. *Ophthalmology*. 2016;123:102–108.
49. Copt RP, Thomas R, Mermoud A. Corneal thickness in ocular hypertension, primary open-angle glaucoma, and normal tension glaucoma. *Arch Ophthalmol*. 1999;117:14–16.
50. Herndon LW, Choudhri SA, Cox T, et al. Central corneal thickness in normal, glaucomatous, and ocular hypertensive eyes. *Arch Ophthalmol*. 1997;115:1137–1141.
51. Argus WA. Ocular hypertension and central corneal thickness. *Ophthalmology*. 1995;102:1810–1812.
52. Morad Y, Sharon E, Hefetz L, Nemet P. Corneal thickness and curvature in normal-tension glaucoma. *Am J Ophthalmol*. 1998;125:164–168.
53. Bron AM, Creuzot-Garcher C, Goudeau-Boutillon S, d'Athis P. Falsely elevated intraocular pressure due to increased central corneal thickness. *Graefes Arch Clin Exp Ophthalmol*. 1999;237:220–224.
54. Liu X, Zeng YF, Huang JJ, et al. The measurement of central corneal thickness of normal subjects and glaucomatous patients with optical coherence tomography [in Chinese]. *Zhonghua Yan Ke Za Zhi*. 2006;42(3):199–203.
55. Bechmann M, Thiel MJ, Roesen B, et al. Central corneal thickness determined with optical coherence tomography in various types of glaucoma. *Br J Ophthalmol*. 2000;84:1233–1237.
56. Wolfs RC, Klaver CC, Vingerling JR, et al. Distribution of central corneal thickness and its association with intraocular pressure: the Rotterdam Study. *Am J Ophthalmol*. 1997;123:767–772.
57. Varma R, Tielsch JM, Quigley HA, et al. Race-, age-, gender-, and refractive error-related differences in the normal optic disc. *Arch Ophthalmol*. 1994;112:1068–1076.
58. Beck RW, Messner DK, Musch DC, et al. Is there a racial difference in physiologic cup size? *Ophthalmology*. 1985;92:873–876.
59. Chi T, Ritch R, Stickler D, et al. Racial differences in optic nerve head parameters. *Arch Ophthalmol*. 1989;107:836–839.
60. Girkin CA, Sample PA, Liebmann JM, et al. African Descent and Glaucoma Evaluation Study (ADAGES): II. Ancestry differences in optic disc, retinal nerve fiber layer, and macular structure in healthy subjects. *Arch Ophthalmol*. 2010;128:541–550.
61. Dandona L, Quigley HA, Brown AE, Enger C. Quantitative regional structure of the normal human lamina cribrosa. A racial comparison. *Arch Ophthalmol*. 1990;108:393–398.
62. Terai N, Spoerl E, Pillunat LE, et al. The relationship between central corneal thickness and optic disc size in patients with primary open-angle glaucoma in a hospital-based population. *Acta Ophthalmol*. 2011;89:556–559.
63. Pakravan M, Parsa A, Sanagou M, Parsa CF. Central corneal thickness and correlation to optic disc size: a potential link for susceptibility to glaucoma. *Br J Ophthalmol*. 2007;91:26–28.
64. Wu RY, Zheng YF, Wong TY, et al. Relationship of central corneal thickness with optic disc parameters: the Singapore Malay Eye Study. *Invest Ophthalmol Vis Sci*. 2011;52:1320–1324.
65. Prata TS, Lima VC, Guedes LM, et al. Association between corneal biomechanical properties and optic nerve head

Investigative Ophthalmology & Visual Science

morphology in newly diagnosed glaucoma patients. *Clin Exp Ophthalmol*. 2012;40:682–688.

66. Hawker MJ, Edmunds MR, Vernon SA, et al. The relationship between central corneal thickness and the optic disc in an elderly population: the Bridlington Eye Assessment Project. *Eye (Lond)*. 2009;23:56–62.
67. Ramos BR, D'Elia MP, Amador MA, et al. Neither self-reported ethnicity nor declared family origin are reliable indicators of genomic ancestry. *Genetica*. 2016;144:259–265.
68. Burnett MS, Strain KJ, Lesnick TG, et al. Reliability of self-reported ancestry among siblings: implications for genetic association studies. *Am J Epidemiol*. 2006;163:486–492.
69. Leite TK, Fonseca RM, de Franca NM, et al. Genomic ancestry, self-reported "color" and quantitative measures of skin pigmentation in Brazilian admixed siblings. *PLoS One*. 2011; 6:e27162.
70. Parra FC, Amado RC, Lambertucci JR, et al. Color and genomic ancestry in Brazilians. *Proc Natl Acad Sci U S A*. 2003;100: 177–182.
71. Mersha TB, Abebe T. Self-reported race/ethnicity in the age of genomic research: its potential impact on understanding health disparities. *Hum Genomics*. 2015;9:1.

Investigative Ophthalmology & Visual Science