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African Ancestry Is Associated with Higher Intraocular Pressure in Latinos

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Purpose: Intraocular pressure (IOP) is a major risk factor, as well as the only modifiable risk factor, for glaucoma. Racial differences have been observed in IOP measurements with individuals of African descent experiencing the highest IOP when compared with other ethnic groups. The purpose of this study was to examine the relationship between genetic ancestry and IOP in Latinos.

Design: Population-based genetic association study.

Participants: A total of 3541 participants recruited from the Los Angeles Latino Eye Study.

Methods: Study participants were genotyped using the Illumina OmniExpress BeadChip (~730K markers). We used STRUCTURE to estimate individual genetic ancestry. Simple and multiple linear regression, as well as quantile regression, analyses were performed to investigate the relationship between genetic ancestry and IOP.

Main Outcome Measures: The relationship between genetic ancestry and IOP in Latinos.

Results: African ancestry was significantly associated with higher IOP in Latinos in our simple linear regression analysis ($P = 0.002$). After adjusting for age, gender, body mass index, systolic blood pressure, central corneal thickness, and type 2 diabetes, this association remained significant ($P = 0.0005$). The main association was modified by a significant interaction between African ancestry and hypertension ($P = 0.037$), with hypertensive individuals experiencing a greater increase in IOP with increasing African ancestry.

Conclusions: To our knowledge, we demonstrate for the first time that African ancestry and its interaction with hypertension are associated with higher IOP in Latinos. *Ophthalmology 2016;123:102-108 © 2016 by the American Academy of Ophthalmology.*

Supplemental material is available at www.aaojournal.org.

Elevated intraocular pressure (IOP) is a major and established risk factor for glaucoma, with increased levels of IOP associated with increased risk of glaucoma.[1] In addition, IOP is the only modifiable risk factor for glaucoma, and lowering IOP has been shown to delay the progression of glaucoma.[2] Therefore, it is important to identify factors that influence IOP for better prediction of IOP.

Several risk factors for IOP have been identified. These previously reported factors include older age, female gender, higher body mass index (BMI), higher systolic blood pressure (SBP) and diastolic blood pressure, faster pulse, elevated glycosylated hemoglobin, and thicker central corneal thickness (CCT).[3] Additionally, diabetic Latinos have been reported to have higher IOP compared with those without diabetes.[3,4] Racial differences in IOP have also been reported with individuals of African descent exhibiting the highest IOP levels when compared with non-Hispanic Whites, Asians, and Latinos.[3–7] Furthermore, racial differences in hypertension, a significant contributor to the variation in IOP, have been reported.[8]

According to the 2010 census, the increase in the Latino population between 2000 and 2010 represented more than half of the growth in the total population of the United States.[9] As one of the largest minority groups in the United States, and with an expected increase in the number of individuals affected by glaucoma, understanding the relationship between genetic ancestry and IOP in Latinos may help to elucidate racial differences and identify public health strategies to prevent and forestall the development of glaucoma. Moreover, Latinos are traditionally an understudied population. As such, there is a public health need to investigate the role genetics has on IOP in this population.

Despite the Latino population being categorized traditionally as a single ethnic group in the census, there is great variation in genetic ancestry at the individual level according to recent genetic studies.[10–12] Latinos are considered to be an admixed population of African, European, and Native American ancestries, with varying proportions of each ancestry.[11,13] Recently, the proportion of Native American ancestry was found to be associated with severe diabetic retinopathy in a Latino population.[12] Given the heterogeneity in genetic ancestry, as well as the fact that Latinos are a traditionally understudied population, determining whether or not there is an association between genetic ancestry and IOP in Latinos may further elucidate the racial differences in IOP. The purpose of this study was to examine the association between IOP and

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genetic ancestry among Latinos using data collected from the Los Angeles Latino Eye Study (LALES), the largest population-based epidemiology study of ophthalmic diseases in Latinos.[14] To our knowledge, we are the first to report on the association between genetic ancestry and IOP in a Latino population.

Methods

Ethics Statement

This research was approved by the University of Illinois at Chicago, the University of Southern California Health Sciences Campus, and the Los Angeles Biomedical Research Institute at Harbor-University of California, Los Angeles (UCLA) institutional review boards. All clinical investigation was conducted according to the principles outlined in the Declaration of Helsinki.

Intraocular Pressure Measurement and Study Subjects

All study participants underwent a detailed ophthalmologic examination. During the examination, 3 IOP measurements were obtained in each eye by Goldmann applanation tonometry (Haag-Streit, Bern, Switzerland). The average of the 3 measurements yielded a single IOP measurement for each eye. The average IOP measurement for the right and left eye was taken to yield the IOP measurement for each subject. If measurements from only 1 eye were available, the average IOP for this eye was used as the surrogate for the final IOP measurement. If IOP measurements were available during a second clinical visit, the IOP from the first and second visits were averaged to obtain the final IOP measurement. The distribution of IOP measurements is shown in Figure 1 (available at www.aaojournal.org). All subjects included in this study were ≥40 years of age and written, informed consent was obtained from each study participant.

Genotyping and Quality Control

We genotyped 3929 Latinos through LALES and the Mexican American Glaucoma Genetic Study (MAGGS) using the Illumina OmniExpress BeadChip Kit (730, 525 markers; Illumina, Inc., San Diego, CA). The Genotyping Laboratory of the Institute for Translational Genomics and Population Sciences at the Los Angeles Biomedical Research Institute at Harbor-UCLA performed the genotyping for this study. The software Illumina GenomeStudio (v2011.1) was used to call single nucleotide polymorphisms (SNPs). Study participants were excluded from further analysis if the genotyping call rate was <97%. We used PLINK (v1.07) to perform quality control on the genotype data.[15] We removed all duplicates, subjects with gender inconsistency between the reported and genetically inferred gender, any subjects with missing IOP values, and subjects receiving glaucoma medical treatment or IOP-lowering medication. SNPs were excluded if the call rate of <95%, a minor allele frequency of <1%, or if the Hardy-Weinberg equilibrium P values were $<10^{-6}$. After the above quality control, 619 712 SNPs in 3541 study participants remained for further analysis.

Estimation of Genetic Ancestry

We used STRUCTURE, a Bayesian clustering approach using a Marko Chain Monte Carlo method, to infer genetic ancestry for each study participant.[16,17] To make inferences based on populations of known ancestry, we included 3 reference panels, that is, unrelated individuals from West Africa (Yoruba in Ibadan, Nigeria; n = 88) and Northern Europeans from Utah, US; (n = 87) from the 1000 Genomes Project,[18] and Native Americans (n = 105).[13] We randomly selected 5000 autosomal SNPs to estimate genetic ancestry after merging the datasets. Randomly selected SNPs have been shown to estimate sufficiently the genetic ancestry of different ancestral populations.[19] For running STRUCTURE, we used 10 000 burn-in and 10 000 iterations. Additionally, we specified the prior information of the 3 reference panels when running STRUCTURE. The output for each individual from STRUCTURE included the estimated proportions of African, European, and Native American ancestry. The summation of the proportions of genetic ancestry for an individual equals 1. We repeated this procedure 5 times and used the average of each inferred ancestry for downstream analysis.

Table 1. Study Sample Characteristics and Simple Linear Regression Results

Characteristic	Participants (n = 3541)	P Value
IOP, mmHg	14.6 (2.8)	—
Age, y	54.9 (10.5)	<0.0001
Gender, male	40.6%	<0.0001
BMI, kg/m^2	31.0 (5.6)	<0.0001
SBP, mmHg	124.0 (19.0)	<0.0001
CCT, μm	550.3 (33.7)	<0.0001
T2D, yes	28.3%	<0.0001
Smoking status		0.006
Never	62.2%	
Former	24.6%	
Current	13.2%	
Education level, y		0.72
≤6	44.6%	
7–11	21.9%	
≥12	33.5%	
Income level*		0.045
<$20 000	50.1%	
$20 000–$40 000	35.8%	
>$40 000	14.1%	
NA ancestry, %	44.1 (14.7)	0.96
African ancestry, %	3.1 (4.1)	0.002

BMI = body mass index; CCT = central corneal thickness; IOP = intraocular pressure; NA = Native American; SBP = systolic blood pressure; T2D = type 2 diabetes.
All statistics shown for participants are mean and standard deviation except for gender, type 2 diabetes, smoking status, education level, and income level which are shown as percentages.
*Data missing for 440 study participants.

Statistical Analysis

Univariate analyses were performed to obtain summary statistics on the following variables: IOP, age, gender, BMI, SBP, CCT, type 2 diabetes (T2D), smoking status, education level, income, proportion of Native American ancestry, and proportion of African ancestry. European ancestry was not included because it is equal to 1 minus the proportions of Native American ancestry and African ancestry. To examine the association between IOP and the variables included in this analysis, simple and multiple linear regression analyses were performed. Clinical variables (i.e., age, gender, BMI, SBP, CCT, and T2D) were included in this analysis owing to previous associations with IOP and the remaining variables (smoking status, education level, and income) were included as