Distribution and Heritability of Iris Thickness and Pupil Size in Chinese: The Guangzhou Twin Eye Study

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Purpose. To investigate the distribution and heritability of iris thickness and pupil diameter measured by anterior segment optical coherence tomography (ASOCT) in a classic twin study.

Methods. Twins aged 8 to 16 years were enrolled from the Guangzhou Twin Registry. ASOCT was used to obtain one horizontal scan, and the images were analyzed with custom software. Iris thickness was measured at 750 μm (IT750) and 2000 μm (IT2000) from the scleral spur, as well as cumulative iris area (IAREA). Pupil diameter in millimeters (PDMM) was measured between the most central points of the iris at the nasal and temporal sides. Zygosity was confirmed by genotyping in all same-sex twin pairs. Heritability was assessed by structural variance component genetic modeling after adjustment for age and sex with the Mx program.

Results. Participating in the analysis were 309 monozygotic (MZ) and 165 dizygotic (DZ) twin pairs. The mean IT750, IT2000, and IAREA were 0.406 $\pm$ 0.075 (SD) mm, 0.514 $\pm$ 0.075 mm, and 1.169 $\pm$ 0.184 mm^2, whereas the PDMM was 5.600 $\pm$ 0.0821 mm. The intraclass correlation coefficients for the IT750, IT2000, IAREA, and PDMM were 0.53, 0.54, 0.61, and 0.63 for MZ pairs and 0.29, 0.11, 0.35, and 0.34 for DZ pairs, respectively. A model with additive genetic and unique environmental effect was the most parsimonious, and the heritability was approximately 60% for iris thickness and pupil diameter.

Conclusions. Iris thickness is thinner in girls but is not associated with age in children. The variation is largely attributable to additive genetic effects. (*Invest Ophthalmol Vis Sci.* 2009;50: 1593–1597) DOI:10.1167/iovs.08-2735

East Asian populations have consistently been thought to be prone to primary angle closure (PAC) by both cross-sectional and incidence data.[1] The anatomic variation of the anterior segment of the eye is considered as a major factor in this ethnic variation. Optical pachymetry measurements of axial anterior chamber depth have been found to be inversely associated with the prevalence of angle-closure in European, Mongolian, Chinese, and Inuit populations.[2–5]

This ethnic difference in anterior chamber anatomy and prevalence findings has led to considerable interest in identifying a genetic mechanism of angle closure. Our population-based twin study has suggested that the variation of axial anterior chamber depth and degree of angle width are predominately attributable to additive genetic effects, with a small proportion of the variation due to unique environmental influences.[6,7]

Although population-based comparable data are not available, the Chinese and African irises are believed to be thicker, and thus YAG is often less effective on them.[8,9] Furthermore, peripheral iris thickening has been considered to be one of the anatomic features in the “non–pupil block” mechanism for angle closure.[10–12] The thick brown iris in the East Asian eye occupies a larger proportion of the anterior chamber volume in the angle recess area than does a thin blue iris. With dilation of the pupil, the thickening of the peripheral iris will become even more pronounced and may come into contact with the trabecular meshwork and dramatically increase the risk of angle closure. Therefore, the thickness of the iris is an important trait directly relevant to angle closure. If the heritability can be proven as reasonably high, it will support the genetic etiology and justify gene mapping efforts on this quantitative trait. The genes being identified will help understand the genetic mechanism of the pathway that eventually leads to angle closure.

The recently available anterior segment optical coherence tomography (ASOCT) system is a fast, non–contact method for imaging the anterior chamber. A single-image scan reveals the entire anterior chamber, including the anterior and posterior iris surfaces, with high enough quality to allow for measurement of both iris thickness and cumulative iris cross-sectional area.[13]

Twin studies have been used widely to estimate the contribution of genetic and environmental effects in particular traits or disease. In a classic twin design, a greater phenotypic similarity in monozygotic (MZ) twin pairs than in dizygotic pairs (DZ) suggests additional gene sharing, given that the MZ pairs share 100%, whereas DZ pairs share on average 50% of their genes and that pair-wise environmental similarities are independent of zygosity.

The purpose of this analysis was to describe the distribution and estimate the heritability of iris thickness in a population-based twin cohort. Given that pupil size is an important factor influencing the iris, we also report the distribution and heritability of pupil diameter.

Materials and Methods

Participants

The study participants were recruited from the Guangzhou Twin Registry, which has been described in detail elsewhere.[14] In brief, this registry was established in Guangzhou City, China by our research group. Since 2006, we have annually invited to participate all twins

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aged 7 to 15 years (defined at July 1, 2006) living in two districts neighboring the Zhongshan Ophthalmic Center, where the examination station was established. The participation rate has been approximately 82.3%.

The ASOCT imaging was obtained from all twins who participated in our second annual examination performed between July and August of 2007. The twins ranged between 8 and 16 years of age at the time of the examination. Twin pairs were excluded from the present analysis after one or twins had pathologic changes (10 retinopathy of prematurity, 1 congenital cataract, and 1 optic nerve atrophy).

Zygosity of all same-sex twin pairs (466 pairs of same-sex twins) was determined by 16 multiplex STRs (PowerPlex 16 system; Promega, Madison, WI)[15] at the Forensic Medicine Department of Sun Yat-Sen University after the first examination in 2006. Opposite-sex twin pairs were considered to be DZ and thereby did not require genotyping.

Written informed consent was obtained for all participants from either their parents or legal guardians. Ethics approval was obtained from the Zhongshan University Ethics Review Board and the Ethics Committee of Zhongshan Ophthalmic Center. This study was conducted in accordance with the tenets of the World Medical Association's Declaration of Helsinki.

Examination and Measurement

ASOCT imaging (Visante; Carl Zeiss Meditec, Dublin, CA) was performed with the participants in the seated position. The images were acquired in a dark room (<5 lux) before pharmacologic dilation of the pupil. The refractive correction (as determined by autorefractor) was used to adjust the internal fixation target to achieve a nonaccommodated state. One scan was taken on the horizontal meridian (0–180°), centered on the pupil. The scan on vertical direction was not attempted because of the difficulties of obtaining and analyzing the vertical-scan images. The scan direction was aligned until a full corneal reflection was achieved (indicated on the real-time ASOCT screen by an interference flare on the axis of the anterior chamber). The horizontal fixation angle was adjusted to correct any lateral gaze. The image with the highest quality was selected and saved for each eye.

The software and algorithms used for the image analysis have been described in detail elsewhere.[13] In brief, the ASOCT images were taken from the device's output function as 816 × 636-pixel JPEG (lossless compression) files. Custom software, the Zhongshan Angle Assessment Program (ZAAP, Guangzhou, China), automatically extracted a 600 × 300 8-bit grayscale (intensities from 0 to 255) image from the JPEG file and performed noise and contrast conditioning. Algorithms automatically defined the borders of the corneal epithelium and endothelium, anterior and posterior surfaces of the iris, and anterior surface of the lens.

A trained ophthalmologist (DW) identified the scleral spurs nasally and temporally, and the parameters were then automatically calculated by the software (Fig. 1). The iris thickness was measured at 750 μm (IT750) and 2000 μm (IT2000) from the scleral spur (i.e., toward the pupil), as well as the cumulative cross-sectional area of the full length (from spur to pupil) of the iris (IAREA). The locations for iris thickness measurement were adjusted from the Ishikawa protocol.[16] Pupil diameter in millimeters (PDMM) was automatically measured as the distance between the most central points of the nasal and temporal iris.

Forty consecutive participants from the twin cohort were selected to assess reproducibility. ASOCT images were captured on two separate occasions, 5 to 10 minutes apart. The images were later analyzed by the same masked grader using the ZAAP software. The agreement between two independent image acquisitions was assessed by mean ± SD of the difference and 95% limits of agreement. The test–retest differences for IT750, IT2000, and IAREA were 0.005 ± 0.034 mm (paired *t*-test, $P = 0.346$), 0.007 ± 0.031 mm^2 (paired *t*-test, $P = 0.192$), and 0.008 ± 0.085 mm^2 (paired *t*-test, $P = 0.568$), respectively. Limits of agreement were −0.016 to 0.006 mm for IT750, −0.017 to 0.003 mm for IT2000, and −0.035 to 0.020 mm^2 for IAREA.

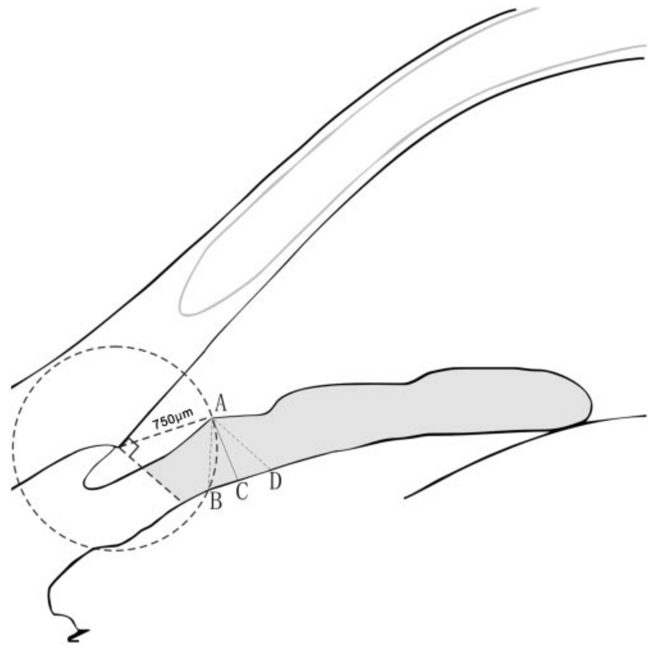

Figure 1. The principles used in the measurement of iris thickness. A circle with radius of 750 μm was drawn, with the scleral spur used as the center. The point of intersection at the anterior surface of the iris was identified (point A). The point (C) on the posterior iris surface that was the shortest distance from point A is identified and then the linear distance from points A to C was calculated as iris thickness at 750 μm (IT750). The same method was used for IT2000. IAREA was defined as the cumulative area of the iris bordered by a line perpendicular to the trabecular surface at the scleral spur.

Data Analysis and Genetic Modeling

The right eye was arbitrarily selected to represent the phenotypic characteristics of the specific individual in the data analysis. An average of the measurements of both temporal and nasal quadrants in one meridian scan was used for the analysis. The estimation of heritability in our study was based on model-fitting analyses as well as on the comparison of correlations of iris parameters between MZ and DZ twins.

The Mx program was used for model-fitting variance component analyses.[17] The total phenotypic variance was decomposed into additive (A) and dominance (D) genetic variances as well as common (C) and unique (E) environmental variances. The E components include measurement error. As the C and D components confound each other when pairs of twins are reared together, the twin model allows only one of these two to be included in the one modeling session. If the DZ pair-wise correlation is less than half of the correlation in MZ pairs, it suggests a contribution of genetic dominance. In this case the model is fitted with an ADE model; otherwise, the model is fitted with an ACE model. In addition, the raw data option in Mx calculates twice the negative log-likelihood (−2LL) of the modeling data. As the difference in −2LL between the two nested models has a χ^2 distribution, the likelihood ratio χ^2 test was used to select the best-fitting model from alternative models. A significant change between the full and reduced model indicates that the parameter removed from the full model was significant and therefore should be retained in the model. In contrast, a nonsignificant change in χ^2 suggests that the parameter eliminated from the full model was not significant and therefore should be dropped to achieve parsimony.[17] To control for the effects of age and sex, the model treated the age and sex variables as covariates.[17]

Results

A total of 474 twin pairs (309 MZ, 165 DZ) aged between 8 and 16 years were available for the analysis after excluding 10 pairs

TABLE 1. Phenotypic Characteristics of Twin Pairs by Zygosity and Sex

	n	Age (y)	IT750 (mm)	IT2000 (mm)	ITmean (mm)	IAREA (mm^2)	PD (mm)
Monozygotic twin							
Male–male	143	11.5 (2.7)	0.416 (0.056)	0.517 (0.074)	0.467 (0.054)	1.208 (0.172)	5.609 (0.867)
Female–female	166	11.8 (2.5)	0.393 (0.064)	0.505 (0.074)	0.449 (0.057)	1.122 (0.163)	5.576 (0.754)
Total	309	11.7 (2.6)	0.403 (0.062)	0.511 (0.074)	0.457 (0.056)	1.161 (0.172)	5.591 (0.807)
Dizygotic twin							
Male–male	48	11.5 (2.5)	0.416 (0.058)	0.537 (0.086)	0.477 (0.062)	1.210 (0.222)	5.640 (0.860)
Female–female	34	12.2 (2.4)	0.412 (0.052)	0.514 (0.064)	0.461 (0.048)	1.119 (0.184)	5.586 (0.735)
Opposite sex	83	11.9 (2.4)	0.409 (0.056)	0.514 (0.074)	0.461 (0.054)	1.196 (0.201)	5.620 (0.896)
Total	165	11.8 (2.4)	0.412 (0.056)	0.521 (0.076)	0.466 (0.056)	1.185 (0.205)	5.619 (0.851)
Age (y)							
8–10	179	9.1 (0.8)	0.400 (0.055)	0.508 (0.073)	0.452 (0.055)	1.165 (0.191)	5.517 (0.950)
11–13	162	12.0 (0.8)	0.414 (0.063)	0.526 (0.075)	0.469 (0.056)	1.162 (0.173)	5.728 (0.665)
14–16	133	15.0 (0.8)	0.410 (0.060)	0.509 (0.078)	0.459 (0.056)	1.185 (0.188)	5.558 (0.793)
Sex							
Male	234	11.5 (2.6)	0.416 (0.057)	0.523 (0.076)	0.470 (0.056)	1.209 (0.185)	5.622 (0.845)
Female	240	11.9 (2.5)	0.397 (0.061)	0.505 (0.073)	0.451 (0.054)	1.131 (0.176)	5.580 (0.799)
Total	474	11.7 (2.5)	0.406 (0.060)	0.514 (0.075)	0.459 (0.056)	1.169 (0.184)	5.600 (0.821)

Descriptive data are presented as the mean ± SD, based on the right eye of first-born twins.

with missing OCT data or iris parameters that were not analyzable. Table 1 summarizes the demography and phenotypes of interest in our study cohort. The ages of MZ pairs (11.7 ± 2.6 years) and DZ pairs (11.8 ± 2.4) were not significantly different (*t*-test, $P = 0.833$). In 474 first-born twins (234 boys and 240 girls), the mean IT750 and IT2000 micrometers from the scleral spur was 0.406 ± 0.060 (SD) and 0.514 ± 0.075 mm, whereas IAREA was 1.169 ± 0.184 mm^2 and PD was 5.601 (0.821) mm. Figure 2 illustrates the distribution of the mean of IT750 and IT2000. Linear regression ($R^2 = 0.07$, $P < 0.001$) showed that iris thickness did not differ significantly between people of different age groups ($P = 0.108$); however, the girls had irises that were approximately 19 μm thinner than those of the boys ($P < 0.001$). Adjusted for age and sex, iris thickness was not associated with axial length ($P = 0.204$) or weight (0.366) but was marginally significant with height ($P = 0.015$). In addition, as expected, we found that the iris thickness increased by 0.027 mm for every 1 mm increase in pupil size ($P < 0.001$).

No significant differences between MZ and DZ twins were identified in IT750 (0.403 ± 0.062 mm for MZ, 0.412 ± 0.056 mm for DZ, $P = 0.135$), IT2000 (0.511 ± 0.074 mm vs. 0.521 ± 0.076 mm, $P = 0.168$), IAREA (1.161 ± 0.172 mm^2 vs. 1.185 ± 0.205 mm^2, $P = 0.196$), or PD (5.591 ± 0.807 mm vs. 5.619 ± 0.851 mm, $P = 0.727$). The sex- and age-adjusted intraclass correlation (ICC, equivalent to pair-wise correlation coefficient) was 0.60 and 0.20 for mean iris thickness in MZ and DZ pairs, respectively. The variation of ICC values was significantly greater in DZ pairs (indicated by 95% CI). IT750 and IT2000 correlations in MZ pairs were more than twice that of DZ pairs, whereas IAREA and pupil diameter correlations in MZ and DZ pairs were more similar (Table 2).

A series of model comparisons suggested that the one with AE (additive genes and unique environmental) components for iris thickness, cumulative iris area, and pupil diameter was the most parsimonious (Table 3). Dominant genetic effects (D) or common environmental effects (C) were not significant for any of these three variables of interest and were consequently dropped. Table 3 also reveals the parameter estimates in the best-fitting models for ITmean, IAREA, and PD.

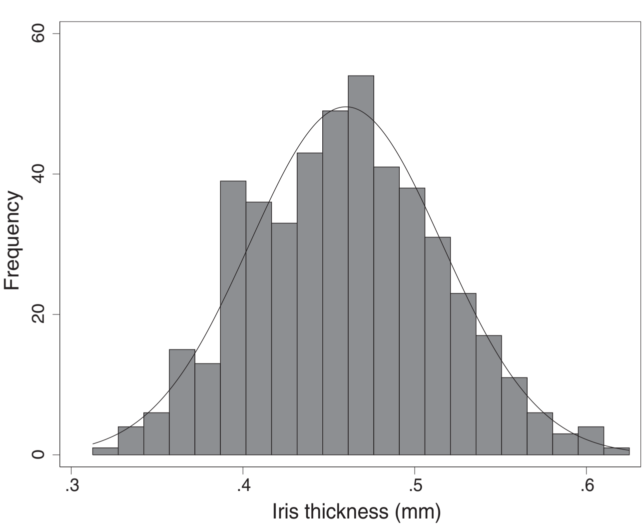

FIGURE 2. Distribution of average iris thickness at 750 μm and 2000 μm (ITmean) from the scleral spur in first-born twins. ITmean is approximately normally distributed (SK test, *P* for skewness = 0.205; *P* for kurtosis = 0.216).

DISCUSSION

This is the first study conducted specifically to investigate the distribution and heritability of iris thickness parameters and pupil diameter measured by ASOCT using a large population-based twin cohort. The results of our study are consistent with an important role for genetic factors in the variation of these iris parameters in this population of Chinese twins. We found that genetic influences account for approximately 60% of the variation in iris and pupil parameters.

The recruited subjects are from a population-based twin registry and therefore the selection bias and its effect on the heritability findings in this study are likely to be minimal.[18] Zygosity was determined by microsatellite polymorphic markers in all same-sex twins, and therefore the misclassification of zygosity is extremely unlikely.

Reproducible measurement of iris thickness could have been difficult without the ASOCT device. A single ASOCT scan reveals the entire cornea, both angles on the meridian, and the anterior portion of the lens. It provides good definition of the iris surface and angle structures such as the scleral spur, which is used as a reference point for iris thickness measurements. Iris thickness can be altered by illumination and accommodation, yet ASOCT allows measurement in nonaccommodative status and standard dark illumination, effectively limiting these

Table 2. ICC for Anterior Chamber Depth and Relative Anterior Chamber Depth (ACD/Axial Length)

	IT750 (mm)	IT2000 (mm)	ITmean (mm)	ITAREA (mm²)	PD (mm)
Twin pairs					
MZ male	0.49 (0.36–0.61)	0.50 (0.36–0.61)	0.53 (0.39–0.64)	0.68 (0.58–0.76)	0.63 (0.51–0.72)
MZ female	0.53 (0.40–0.63)	0.58 (0.47–0.68)	0.64 (0.54–0.72)	0.53 (0.41–0.64)	0.63 (0.53–0.71)
MZ all	0.53 (0.44–0.61)	0.54 (0.45–0.61)	0.60 (0.52–0.66)	0.61 (0.53–0.68)	0.63 (0.55–0.69)
DZ male	0.31 (0.01–0.55)	−0.09 (−0.37–0.21)	0.12 (−0.17–0.40)	0.41 (0.13–0.63)	0.38 (0.10–0.60)
DZ female	0.25 (−0.11–0.55)	0.30 (−0.06–0.59)	0.29 (−0.07–0.58)	0.55 (0.22–0.76)	0.33 (−0.02–0.61)
DZ opposite	0.30 (0.08–0.48)	0.17 (−0.05–0.37)	0.21 (−0.01–0.41)	0.22 (0.00–0.41)	0.32 (0.11–0.50)
DZ all	0.29 (0.14–0.43)	0.11 (−0.0–0.26)	0.20 (0.05–0.35)	0.35 (0.20–0.48)	0.34 (0.19–0.47)

* Comparison between twin-pairs was based on right eye.

sources of variation. In the iris thickness data, even when we adjusted for the pupil size in a linear regression model, the distribution and heritability results did not change significantly (data not shown). Furthermore, based on an algorithm we developed, the software allows an automatic measurement of the iris that requires the operator to identify only the scleral spur. However, as found in our previous study, subjective operator definition and location of the scleral spur reference point may introduce variation in iris measurements.[13] The correlation coefficients we found in both MZ and DZ pairs were significantly lower than what have been found in operator-free measurements, such as anterior chamber depth and corneal thickness within the same cohort, supporting that the relatively lower heritability may also be in part explained by the measurement errors: these measurement errors may inflate the individual environment (E) component and therefore lead to underestimation of the heritability.

The heritability of iris thickness and pupil diameter, to our knowledge, has not before been reported. We previously reported a 70% to 90% heritability for the angle closure–related traits such as anterior chamber depth and iridotrabecular angle width.[6,7] The high heritability of anterior chamber depth is similar to the reports in Caucasian populations.[19,20] Clearly, the proximity of the peripheral iris and the trabecular meshwork, quantified as iridotrabecular angle width, is central to the understanding of angle closure. Nevertheless, variation in the thickness and profile of the iris could be the major variables determining the nature of this relationship.[11,21] In the present study, we identified high heritability in all iris thickness parameters. Given that the traits are also measurable in a reproducible fashion, iris thickness could be treated as an intermediate phenotype[22] for angle closure in the understanding of genetic and environmental effects that are driving the pathways to angle closure glaucoma.

Although the Chinese are believed to have a thicker iris, we could not find ethnicity-specific distribution or normative data on this anatomic feature. Using an identical definition of an "occludable" angle, studies in Mongolia and Singapore found similar rates of occludable angles (6.3%–6.4%), although the Singaporeans had significantly deeper anterior chambers. The authors made the anecdotal observation that iris thickness (observed when performing laser iridotomies) appears greater among Singaporeans and therefore may counterbalance the effect of a deeper anterior chamber in Singaporean Chinese.[23,24] This may underscore the importance of quantifying iris thickness in the mechanism of angle closure. The present study found that iris thickness had an approximately normal distribution. Although it does not vary significantly with age, it

Table 3. Genetic and Environmental Effects Estimated by an Age- and Sex-Adjusted Maximum Likelihood Model

Variables/ Models	A (95% CI)	D (95% CI)	C (95% CI)	E (95% CI)	−2LL	*df*	$\Delta\chi^2$	Δdf	*P*
ITmean (mm)									
ADE	0.193 (0–0.634)	0.403 (0–0.658)		0.405 (0.341–0.474)	−2764.86	910			
AE	0.586 (0.509–0.653)			0.414 (0.347–0.491)	−2762.91	911	1.95	1	0.163
E				1	−2629.98	912	134.9	2	<0.001
IAREA (mm²)									
ACE	0.623 (0.362–0.691)		0.006 (0–0.240)	0.3707 (0.3090–0.4454)	−650.918	890			
AE	0.630 (0.557–0.691)			0.3704 (0.3089–0.4427)	−650.915	891	0.003	1	0.96
CE			0.496 (0.423–0.563)	0.5039 (0.4372–0.5769)	−627.481	891	23.44	1	<0.001
E				1	−500.913	892	150.0	2	<0.001
PD (mm)									
ACE	0.623 (0.358–0.692)		0.010 (0–0.253)	0.367 (0.308–0.438)	2170.217	920			
AE	0.633 (0.565–0.692)			0.367 (0.308–0.436)	2170.223	921	0.005	1	0.94
CE			0.517 (0.447–0.580)	0.484 (0.420–0.553)	2193.853	921	23.64	1	<0.001
E				1	2337.531	922	167.3	2	<0.001

95% CI, 95% confidence interval; −2LL, twice the negative log-likelihood; $\Delta\chi^2$, difference of χ^2 values; Δdf, difference of degree of freedom; *P*, *P* of χ^2 test in model fitting.

* These reflect the statistics when the model is reduced from an ACE (or ADE) model to an AE model.

was consistently thinner in the girls. The nondependence on age was also identified in pupil diameter. However, given that this observation is based on a cohort of children aged 8 to 16 years, further investigation is needed in adults aged 50 years and older, where angle closure is more commonly developed.

In summary, we found a heritability of approximately 60% for iris thickness and pupil size. These findings suggest an important role for iris parameters and a genetic contribution in the etiology of PAC. The data on distribution and heritability may need to be further confirmed in older populations and other ethnic groups.

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