

Heritability of Anterior Chamber Depth as an Intermediate Phenotype of Angle-Closure in Chinese: The Guangzhou Twin Eye Study

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PURPOSE. To assess the heritability of anterior chamber depth (ACD) and relative anterior chamber depth (ACD/axial length, rACD) in Chinese in a classic twin study.

METHODS. Twins aged 7 to 15 years living in two local districts were recruited from the Guangzhou Twin Registry. Anterior chamber depth and axial length were measured by partial coherence laser interferometry. Zygosity in all same-sex twin pairs was confirmed by genotyping with 16 polymorphic markers. The phenotypes of the right eyes were used in analysis. Heritability was assessed by structural variance component genetic modeling.

RESULTS. In total, 1126 twin participants were available for analysis, including 357 monozygotic (MZ) and 206 dizygotic (DZ) twin pairs. ACD increased with age (0.036 mm per year, $P < 0.001$) and 0.09 mm shallower in the girls than in the boys ($P < 0.001$). Age- and sex-adjusted intraclass correlation coefficients (ICCs) for ACD were 0.92 for the MZ and 0.50 for the DZ twins; those for rACD were 0.89 for the MZ and 0.52 for the DZ twins. The best-fitting model yielded 90.1% (95% CI: 88.2%–91.7%) of additive genetic and 9.9% (95% CI: 8.3%–11.8%) of unique environmental effects for ACD and 89.2% (95% CI: 87.1%–90.9%) of additive genetic and 10.8% (95% CI: 9.1%–12.9%) of unique environmental effects for rACD.

CONCLUSIONS. Additive genetic effects appear to be the major contributor to the variation of ACD and rACD in Chinese population. High heritability remained even when the data were corrected for the influence of myopia. (*Invest Ophthalmol Vis Sci.* 2008;49:81–86) DOI:10.1167/iovs.07-1052

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Population-based studies suggest that the prevalence of primary angle-closure (PAC) is higher in East Asians than European and Africans.^{1,2} Racial difference in the prevalence of PAC appears consistent with the anatomic variation of the anterior segment of the eye in the populations of Greenlandic and Canadian Inuit, Chinese, Mongolians, and people with European origin.^{3–5}

The observed ethnic differences in prevalence of PAC, and their underlying anatomic basis, have led to considerable interest in identifying a genetic basis of the disease. A positive family history has long been recognized as predisposing to angle-closure.^{6–8} The similarity of ocular biometry in first-degree relatives of patients appears to suggest that these PAC-related anatomic characteristics are heritable.^{8–10} Furthermore, molecular genetic studies have identified linkage of nanophthalmos to a locus on chromosome 11 but were not able to replicate linkage after stipulating a more stringent phenotype of angle-closure glaucoma or occludable drainage angles.¹¹ Another group has mapped recessive nanophthalmos to a unique locus at 11q23.3 and identified four independent mutations in the *MFRP* gene.¹² An association between a single nucleotide polymorphism in the *MMP-9* gene, and acute PAC has recently been reported, but this has yet to be confirmed.¹³ However, the genetic mechanism of angle closure remains elusive and controversial. Lowe identified only three acute, two chronic, and one subacute case of angle closure in 778 siblings of 200 PAC probands.⁸ Angle closure is a dichotomous phenotype, often of late-onset, and highly age dependent and subject to environmental influence. This phenotypic heterogeneity hinders the accurate phenotyping across generations and further gene-searching efforts.

Using a quantitative trait as an intermediate phenotype has been adopted increasingly in familial aggregation studies and gene mapping in complex traits. An “ideal intermediate phenotype” should be heritable and stable, closely associated with the disease or biological phenomenon, and relatively easy to quantify.^{14,15} A shallow anterior chamber, short axial length, small corneal diameter and steep corneal curvature, shallow limbal chamber depth, and a thick, relatively anteriorly positioned lens are all associated with PAC.¹⁶ Among these, anterior chamber depth (ACD) has been recognized as the cardinal anatomic risk factor for angle closure. We have reported a direct association between ACD and drainage angle width in a Chinese population, and an association between angle width and the rate of peripheral anterior synechiae (PAS, permanent synechiae between iris and drainage channels—a hallmark of angle closure).^{17,18} ACD is highly heritable and can be measured with high reproducibility using partial-coherence laser interferometry.¹⁹ Therefore, ACD is used as an intermediate phenotype in the present study.

Twin studies have been widely used to determine heritability—the proportion of the total phenotypic variation attributable to genetic variance.²⁰ A comparison of similarities of phenotypes between monozygotic and dizygotic twins allows for the estimation of heritability when the environmental im-

pacts are assumed to be very similar between both types of twin pairs. The purpose of this analysis was to estimate the heritability of ACD, as an intermediate phenotype for PAC, in a Han ethnic Chinese population in a classic twin study design.

MATERIALS AND METHODS

Participants

The study participants were recruited from the Guangzhou Twin Registry, which has been described elsewhere.²¹ In brief, the Registry was established in Guangzhou City. To date, more than 9700 pairs of twins born from 1987 to 2000 have been enrolled in an official Household Registry of Guangzhou and followed-up by a door-to-door verification. We recruited all twins aged 7 to 15 years (defined at the date of July 1, 2006) living in two districts neighboring to the Zhongshan Ophthalmic Center, where the examination station was setup, for baseline data collection. The biological parents of these twin children were also invited to participate. The parents and twin children were requested to attend examination together. Written, informed consent was obtained for all participants from either parents or guardians of the participating children after careful explanation of the study in detail, including the discussion and specific consent for the use of DNA information. Ethical committee approval was obtained from the Zhongshan University Ethical Review Board and Ethics Committee of Zhongshan Ophthalmic Center. The study was conducted in accordance with the tenets of the World Medical Association's Declaration of Helsinki. Zygosity of all same-sex twin pairs was determined by 16 multiplex short tandem repeats (STRs; PowerPlex 16 system, Promega, Madison, USA.)²² at the Forensic Medicine Department of Sun Yat-Sen University. Zygosity in opposite-sex twin pairs was considered as dizygotic without a need for genotyping.

Examination

Axial length and ACD were both measured by noncontact partial-coherence laser interferometry (IOLMaster, Carl Zeiss Meditec, Oberkochen, Germany), in a dark room before pharmacologic dilation of the pupils. The displayed results were compatible with the ultrasonic immersion measurement of axial length when an internal statistically verified calculation algorithm has been integrated in the device. A mean of 5 measurements generated by the device represented the adjusted axial length. Poor measurements with signal-to-noise ratio (SNR) <2.0 (displayed as borderline SNR or Error) or results of one measurement that differed from the others by >0.1 mm (displayed as Evaluation!) were deleted and remeasured.

ACD was measured after the keratometry module of the interferometer (IOLMaster; Carl Zeiss Meditec), as the system requires automatic usage of the measured corneal radius for the calculation of ACD. The fixation point was aligned between the images and the cornea and the lens, close, but not within, the optical section of the lens. A mean of five measurements were taken. Measurements with displayed error messages were deleted and remeasured. The ACD was measured as the

distance between the anterior lens surface and corneal epithelium illumination and therefore included the thickness of the cornea.

Twin pairs were excluded from the present analysis if one or both twins had pathologic changes or recent orthokeratology contact lens correction, or previous myopia laser treatment.

Fifty participants aged 7 to 15 years from the twin clinic were measured on two separate occasions on the same day during a pilot study. For the right eye measurement, the test-retest difference for ACD was -0.004 ± 0.034 mm (paired *t*-test, *P* = 0.86), 95% limit of agreement: -0.015 to $+0.008$ mm. The test-retest difference on axial length was -0.008 ± 0.035 mm (paired *t*-test, *P* = 0.387), 95% CI: -0.019 to $+0.004$ mm.

Data Analysis and Genetic Modeling

The right eye was selected to represent the phenotypic characteristics of the specific individual in the data analysis given the readings on right and left eyes were similar (correlation coefficient for ACD = 0.97, *P* < 0.0001). ACD and relative (r)ACD were treated as quantitative traits and analyzed by quantitative genetic modeling. rACD was calculated by using ACD divided by axial length. The estimation of heritability in twin studies is based on concordance comparison of phenotypes between monozygotic (MZ) and dizygotic (DZ) twin pairs. MZ twins share 100% of their genes, whereas DZ twins, on average, share only half. Assuming that the two types of twins share the same extent of environmental factors, greater similarities in phenotypes of MZ than in DZ twins can be attributed to the additional gene sharing.

The variance component model used in the present study included the additive genetic (A) variance and the common (C) and unique (E) environmental variances. The E component also included measurement error. This model assumed that all genetic effects for ACD and rACD were additive. The best-fitting model was determined based on the maximum-likelihood test and χ^2 test. A significant change in χ^2 value between the full and the reduced model would indicate 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 of the model. To control for the main effects of age and sex, the model treated the age and sex variable as covariates. Special software (Mx; Statistical Modeling, Richmond, VA)²³ was used for model-fitting analyses.

RESULTS

Of the total 705 pairs of eligible twins invited, 563 twin pairs (357 MZ, 206 DZ) aged 7 to 15 years were available for the data analysis after excluding 12 twin pairs with pathologic conditions (10 retinopathy of prematurity, 1 congenital cataract, 1 optic nerve atrophy) and five with missing ACD data on either twin. The response rate was 82.3% (580/705), and the reasons for the failure of attendance were refusal (*n* = 97 pairs), unable to contact (*n* = 18) and other (*n* = 10). Table 1 shows the

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

	<i>N</i>	Age	ACD (mm)	AL (mm)	rACD (ACD/AL)
Monozygotic twin					
Male-male	168	10.6 (2.7)	3.50 (0.25)	23.75 (1.00)	0.1473 (0.0092)
Female-female	189	10.9 (2.6)	3.42 (0.28)	23.24 (1.15)	0.1471 (0.0093)
Total	357	10.8 (2.6)	3.46 (0.27)	23.48 (1.11)	0.1472 (0.0092)
Dizygotic twin					
Male-male	61	10.6 (2.5)	3.51 (0.25)	23.76 (1.02)	0.1478 (0.0092)
Female-female	45	11.0 (2.4)	3.41 (0.25)	23.34 (1.07)	0.1463 (0.0079)
Opposite sex	100	11.1 (2.4)	3.48 (0.28)	23.55 (1.13)	0.1476 (0.0098)
Total	206	10.9 (2.4)	3.47 (0.26)	23.57 (1.09)	0.1474 (0.0092)

Descriptive data were presented based on the right eyes of first-born twin and are expressed as the mean \pm SD. AL, axial length.

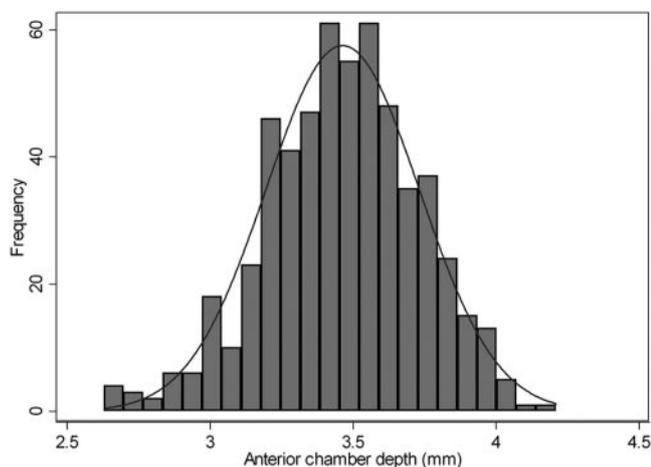


FIGURE 1. Distribution of ACD in the right eyes of first-born twin.

characteristics of the demographic and phenotypes of interest in the MZ and DZ twins. The ages of the MZ (10.8 ± 2.6 years) and the DZ (10.9 ± 2.4) pairs were not significantly different (*t*-test, $P > 0.05$). No significant differences in ACD were identified between the MZ (3.46 ± 0.27 mm) and the DZ (3.47 ± 0.26 mm) twins ($P = 0.51$). rACD was not different between the MZ (0.1472 ± 0.0092 arbitrary units) and the DZ (0.1474 ± 0.0092 , $P = 0.92$) pairs.

ACD had an approximately normal distribution with mild skew toward lower values (S-K test for normality, ACD: P for skewness = 0.008, P for kurtosis = 0.515; rACD: P for skewness = 0.587, P for kurtosis = 0.411, Fig. 1). The mean ACDs for the boys and girls were significantly different: 3.50 (SD: 0.26) mm and 3.43 (0.28) mm, respectively (*t*-test, $P = 0.0009$). Multiple linear regression of ACD with age and sex ($R^2 = 0.12$, $P < 0.0001$) suggested that mean ACD increased by 0.36 mm per decade ($P < 0.001$) and was 0.09 mm ($P < 0.001$) shallower in the girls than in the boys (adjusted for age). However, rACD was no longer significantly different between the boys and girls (boys: 0.1475 ± 0.0006 , girls: 0.1471 ± 0.0005 arbitrary units, $P = 0.499$). Multiple linear regression of rACD on age suggested that mean rACD increased by 0.0004 arbitrary units per decade ($P = 0.011$) when adjusted for gender.

Intraclass correlation coefficients (ICCs, equivalent to a pair-wise correlation coefficients) between twin pairs were found to be 0.92 in MZ pairs for both ACD and axial length (AL), whereas ICC for rACD was 0.89 (Table 2). ICCs in DZ twins were consistently found to be approximately 0.50 in both ACD and rACD. The pair-wise correlation in the MZ and DZ twins are demonstrated in scatterplots in Figure 2. In maximum-likelihood modeling, the full model started from ACE, as the ICC in DZ was greater than one-half of the ICC in the MZ pairs. Statistical modeling suggested the AE model

(additive genes and unique environment) best fit both the ACD and the rACD data, whereas the effect of C (common environment) was dropped (reduced model, χ^2 test, $P = 0.637$ for ACD, $P = 0.140$ for rACD). Table 3 shows the goodness-of-fit parameters in the best-fitting models for both ACD and rACD. Additive genetic effect (A) explained 90.1% (95% CI: 88.2%–91.7%), equivalent to heritability here, and unshared environment (E) explained the remaining 9.9% (95% CI: 8.3%–11.8%) of variance in ACD phenotype. In the case of rACD, in which the effect of axial length (probably myopia) was de-emphasized, the heritability decreased but remained high (89.2%, 95% CI: 87.1%–90.9%), with unshared environment explaining the remaining 10.8% (95% CI: 9.1%–12.9%).

DISCUSSION

This is the first study that specifically explored the heritability of ACD in a population-based twin cohort in a large group of Chinese people. The concept of rACD, a ratio of ACD and AL, was introduced to adjust the effect of AL, and to de-emphasize the influence of myopia on the ACD trait. Our study confirmed that a large proportion of ACD variance was attributable to genetic effects; the heritability remained high, even after adjustment for myopic effects.

This twin cohort was enrolled from a population-based twin registry and therefore the concordance-dependent bias in this study should have been minimized.²⁴ Although comparable ACD data in a young population are not available in the literature, the refractive error (spherical equivalent) distribution in our twin cohort was found to be comparable to a general population sample.²⁵ This further suggests that our twin cohort is representative and that the results should be generalizable to the entire population.

Two published twin studies reported the heritability of refractive error as well as the that of ocular biometry parameters, including ACD.^{26,27} The study in Danish twins used handheld ultrasound for the ACD measurement, which may be subject to significant measurement error, particularly for the ACD measurement, due to the inadvertent indentation of the cornea.²⁷ We used noncontact laser interferometry for ACD measurement in this study, a method that has been widely used and found to have good diagnostic efficacy in the detection of angle closure.²⁸ The study by Lyhne et al.²⁷ in 53 MZ and 61 DZ Danish twin pairs (age, 20–45 years) identified 88% heritability of ACD,²⁷ a study with larger sample size and wider age range found 51% heritability in male and 78% in females in Australia twins (345 MZ and 267 DZ, age 18–88 years).²⁶ Our data identified a slightly higher level of heritability (90.1%, 95% CI: 88.2%–91.7%) for ACD in a Chinese sample, although the rate of myopia was much higher in this Chinese cohort. When reporting heritability separately for the boys and girls, we did not identify differences in heritability between genders (boys: 90.6%, 95% CI: 87.9%–92.7%; girls: 89.7%, 95% CI: 86.9%–91.9%, χ^2 test, $P = 0.142$). Looking further into the ICCs

TABLE 2. Intraclass Correlation Coefficients for ACD and rACD

Twin Pairs	ACD	AL	rACD
MZ male	0.91 (0.89–0.94)	0.90 (0.87–0.93)	0.88 (0.84–0.91)
MZ female	0.92 (0.89–0.94)	0.92 (0.90–0.94)	0.91 (0.88–0.93)
MZ all	0.92 (0.90–0.93)	0.92 (0.90–0.93)	0.89 (0.87–0.91)
DZ male	0.49 (0.26–0.66)	0.49 (0.26–0.66)	0.63 (0.45–0.76)
DZ female	0.64 (0.42–0.78)	0.49 (0.23–0.68)	0.47 (0.20–0.67)
DZ opposite	0.46 (0.29–0.60)	0.45 (0.28–0.59)	0.48 (0.32–0.62)
DZ all	0.50 (0.39–0.60)	0.47 (0.36–0.57)	0.52 (0.42–0.62)

Data are the ICC (95% CI). Comparison between twin pairs is based on the right eyes.

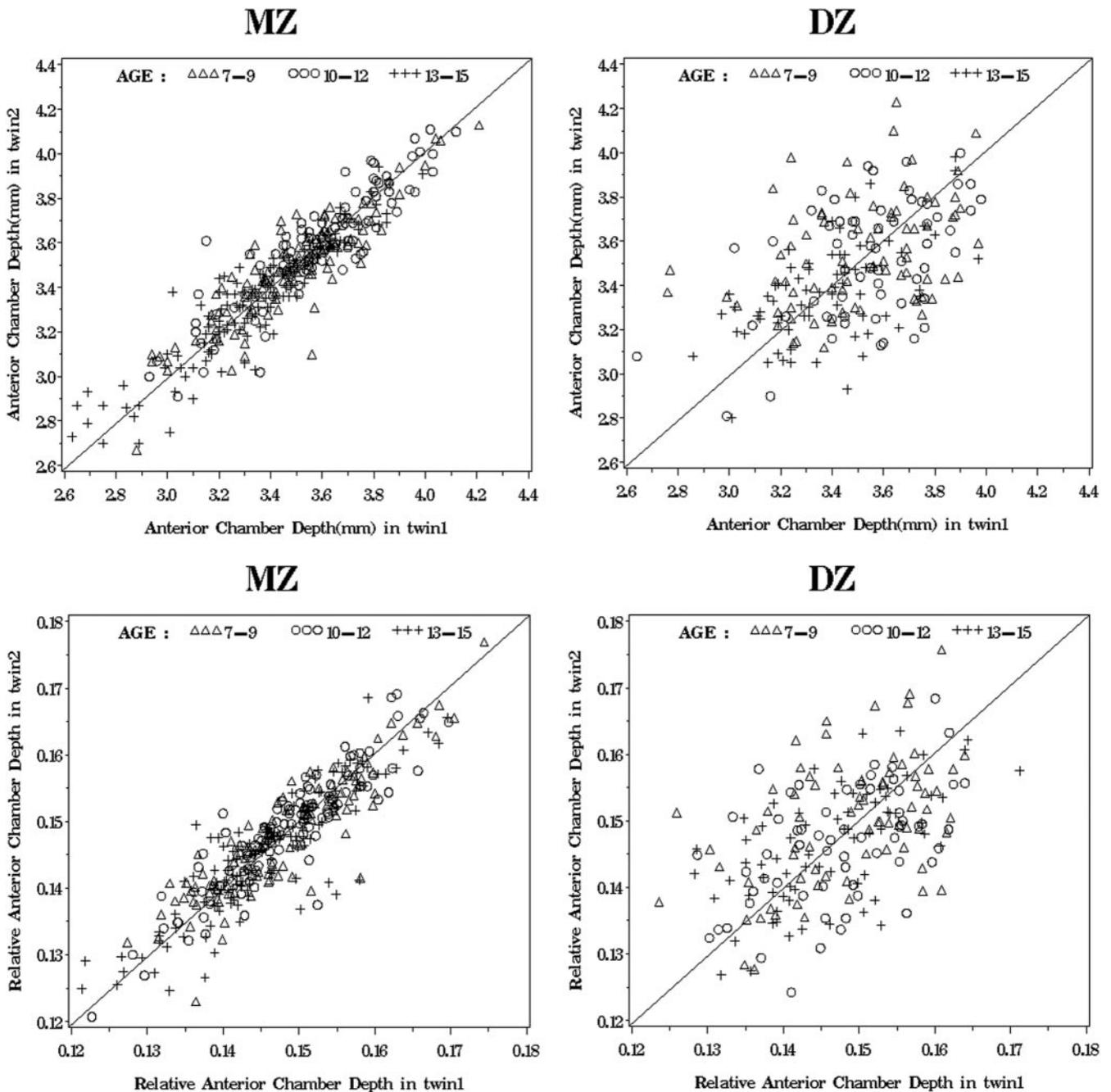


FIGURE 2. Intrapair correlation for ACD and rACD in MZ and DZ twin pairs in the Guangzhou Twin Eye Study.

reported in Australia twins and our twin cohort, the ICCs in the Australian (0.46–0.62 for MZ, 0.26–0.37 for DZ) are lower than that in our Chinese twins (0.92 for MZ, 0.50 for DZ) although the ratios between the MZ and DZ twin pairs are quite similar between the Australia and Chinese samples. The twin studies in Denmark and Australia recruited twins in adulthood, and the environmental effect should therefore be greater than that on younger twins and tends to be diversified between twins in a pair. Nevertheless, it is intriguing to find that our heritability findings are compatible with those in a family study (involving the siblings and children of a PAC proband) in Eskimos where heritability of ACD was estimated as approximately 70% with additive polygenic inheritance when the effects from age and gender variations were adjusted by a lineal regression model.²⁹

It is interesting to find that ICCs and heritability remained high when rACD was considered as the parameter of interest, and the effect of myopia was de-emphasized. The high heritability of rACD appears to suggest the genetic determinant of anterior positioning of the iridolenticular diaphragm in addition to the ACD variation secondary to AL changes. The concept of rACD is similar but not the same as the relative lens position (RLP) proposed by Lowe, where $RLP = (ACD + \frac{1}{2} \text{ lens thickness}) / \text{axial length}$.³⁰

The results of the present study must be taken within the context of limitations. First, the impact of environmental exposures on observed phenotypes in different populations vary according their relative exposures. However, the similarity of our findings with those from Australia and Denmark suggest that this is not a major impediment to the use of twin data.

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

Variables/ Models	A (95% CI)	C (95% CI)	E (95% CI)	-2LL	df	$\Delta\chi^2$	Δdf	P*
ACD (mm)								
ACE	0.853 (0.673, 0.916)	0.049 (0, 0.230)	0.099 (0.083, 0.118)	-606.772	1120			
AE	0.901 (0.882, 0.917)	—	0.099 (0.083, 0.118)	-606.55	1121	0.222	1	0.637
CE	—	0.745 (0.706, 0.779)	0.255 (0.221, 0.294)	-412.873	1121	193.90	1	<0.001
E	—	—	1.000	42.471	1122	649.24	2	<0.001
rACD (AU)								
ACE	0.745 (0.579, 0.904)	0.148 (0, 0.314)	0.107 (0.090, 0.128)	7530.462	1120			
AE	0.892 (0.871, 0.909)	—	0.108 (0.091, 0.129)	7532.642	1121	2.18	1	0.140
CE	—	0.754 (0.717, 0.788)	0.246 (0.212, 0.284)	7687.389	1121	156.93	1	<0.001
E	—	—	1.000					

A, additive genetic; C, common environment; E, unique environment; df, degree of freedom; -2LL, twice the negative log-likelihood; $\Delta\chi^2$, difference of χ^2 values; Δdf , difference of degree of freedom; P, χ^2 test in model fitting.

* These reflect the statistics when the model is reduced.

Second, ACD and rACD data were treated as intermediate phenotypes for angle closure, given that their anatomic characteristics are associated with established disease. The continuous distribution of ACD (quantitative trait) was used to estimate the importance of genes and environment. However, our study participants were healthy young people in whom angle-closure is extremely uncommon. As far as we are aware, there were no cases of angle-closure among our participants. Consequently, the results are only applicable to Chinese children. Our inference that our findings are relevant to future risk of angle-closure depends on the assumption that shallow ACD in childhood indicates a propensity to a shallow ACD in later life. On the other hand, limited data suggest that PAC develops over a 5- to 10-year period in only a fraction (between 10% and 20%) of people with narrow angles.^{31,32} This suggests that, while there may be strong genetic control over the anatomic characteristics associated with angle-closure, there may well be other factors (either genetic or environmental) that determine individual predisposition to angle-closure glaucoma in which iridotrabeal contact causes elevated intraocular pressure leading to loss of vision.

We believe our findings have relevance for the understanding of the mechanisms controlling ocular development and particularly that of the anterior segment. In addition, it helps to clarify the factors that determine the risk of angle-closure glaucoma in a population with high rates of this disease in adulthood. It remains possible but unproven that identification of genetic factors may have a role in risk profiling for angle-closure glaucoma.

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