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 266 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: 87.1%–90.9%) of additive genetic and 10.8% (95% CI: 11.8%) of unique environmental effects for ACD and 88.2% (95% CI: 86.3%–91.7%) of additive genetic and 9.9% (95% CI: 8.3%–11.5%) 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 Ophtalmol Vis Sci. 2008;49:81–86) DOI:10.1167/iovs.07-1052

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 1q23.3 and identified four independent mutations in the MFRP gene.12 An association between a single nucleotide polymorphism in the MMP9 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-

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messages were deleted and remeasured. The ACD was measured as the fixation point was aligned between the images and the cornea and the usage of the measured corneal radius for the calculation of ACD. The Evaluation! were deleted and remeasured.

**TABLE 1.** Phenocharacteristics of Twin Pairs by Zygosity and Gender

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Age (mm)</th>
<th>ACD (mm)</th>
<th>AL (mm)</th>
<th>rACD (ACD/AL)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Monzygotic twin</strong></td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Male–male</td>
<td>168</td>
<td>10.6 (2.7)</td>
<td>3.50 (0.25)</td>
<td>23.75 (1.00)</td>
<td>0.1473 (0.0092)</td>
</tr>
<tr>
<td>Female–female</td>
<td>189</td>
<td>10.9 (2.6)</td>
<td>3.42 (0.28)</td>
<td>23.24 (1.15)</td>
<td>0.1471 (0.0095)</td>
</tr>
<tr>
<td>Total</td>
<td>357</td>
<td>10.8 (2.6)</td>
<td>3.46 (0.27)</td>
<td>23.48 (1.11)</td>
<td>0.1472 (0.0092)</td>
</tr>
<tr>
<td><strong>Dizygotic twin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male–male</td>
<td>61</td>
<td>10.6 (2.5)</td>
<td>3.51 (0.25)</td>
<td>23.76 (1.02)</td>
<td>0.1478 (0.0092)</td>
</tr>
<tr>
<td>Female–female</td>
<td>45</td>
<td>11.0 (2.4)</td>
<td>3.41 (0.25)</td>
<td>23.34 (1.07)</td>
<td>0.1463 (0.0079)</td>
</tr>
<tr>
<td>Opposite sex</td>
<td>100</td>
<td>11.1 (2.4)</td>
<td>3.48 (0.28)</td>
<td>23.55 (1.13)</td>
<td>0.1476 (0.0098)</td>
</tr>
<tr>
<td>Total</td>
<td>206</td>
<td>10.9 (2.4)</td>
<td>3.47 (0.26)</td>
<td>23.57 (1.09)</td>
<td>0.1474 (0.0092)</td>
</tr>
</tbody>
</table>

Descriptive data were presented based on the right eyes of first-born twin and are expressed as the mean ± SD. AL, axial length.
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: 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 (R² = 0.12, P < 0.0001) suggested that mean ACD increased by 0.56 mm per decade (P < 0.001) and was 0.09 mm (P < 0.001) shallower in the girls than in the boys (adjusted for gender). 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 both ACD and rACD. The pair-wise correlation coefficients between twin pairs were 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 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, χ² 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%).

**Table 2. Intraclass Correlation Coefficients for ACD and rACD**

<table>
<thead>
<tr>
<th>Twin Pairs</th>
<th>ACD</th>
<th>AL</th>
<th>rACD</th>
</tr>
</thead>
<tbody>
<tr>
<td>MZ male</td>
<td>0.91 (0.89–0.94)</td>
<td>0.90 (0.87–0.95)</td>
<td>0.88 (0.84–0.91)</td>
</tr>
<tr>
<td>MZ female</td>
<td>0.92 (0.89–0.94)</td>
<td>0.92 (0.90–0.94)</td>
<td>0.91 (0.88–0.93)</td>
</tr>
<tr>
<td>DZ male</td>
<td>0.49 (0.26–0.66)</td>
<td>0.49 (0.26–0.66)</td>
<td>0.65 (0.45–0.76)</td>
</tr>
<tr>
<td>DZ female</td>
<td>0.64 (0.42–0.78)</td>
<td>0.49 (0.23–0.68)</td>
<td>0.47 (0.20–0.67)</td>
</tr>
<tr>
<td>DZ opposite</td>
<td>0.46 (0.29–0.60)</td>
<td>0.45 (0.28–0.59)</td>
<td>0.48 (0.32–0.62)</td>
</tr>
<tr>
<td>DZ all</td>
<td>0.50 (0.39–0.60)</td>
<td>0.47 (0.36–0.57)</td>
<td>0.52 (0.42–0.62)</td>
</tr>
</tbody>
</table>

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

**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. 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. 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. 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. We used non-contact 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. The study by Lyhne et al. in 53 MZ and 61 DZ Danish twin pairs (age 20–45 years) identified 88% heritability of ACD; 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). 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%, χ² test, P = 0.142). Looking further into the ICCs
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 adult-
hood, 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 approxi-
mately 70% with additive polygenic inheritance when the ef-
ffects 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 herita-
bility of rACD appears to suggest the genetic determinant of
anterior positioning of the iridolenticular diaphragm in addi-
tion to the ACD variation secondary to AL changes. The con-
cept of rACD is similar but not the same as the relative lens
position (RLP) proposed by Lowe, where $RLP = \frac{ACD + \frac{1}{2}}{lens \ thickness}/axial \ length$.30

The results of the present study must be taken within the
context of limitations. First, the impact of environmental ex-
posures 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.

![Figure 2. Intrapair correlation for ACD and rACD in MZ and DZ twin pairs in the Guangzhou Twin Eye Study.](image-url)
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.

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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References


