# Distribution and Heritability of Intraocular Pressure in Chinese Children: The Guangzhou Twin Eye Study

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**Purpose.** To assess the distribution and heritability of intraocular pressure (IOP) in Chinese children.

**Methods.** Twins aged 8 to 16 years were recruited from the Guangzhou Twin Registry. IOP was measured in each twin and co-twin together, with a handheld tonometer by the same operator. Zygosity was determined based on genotyping with 16 polymorphic markers in all same-sex twin pairs. Heritability was estimated with a univariate variance component model.

**Results.** Four hundred seventy-three twin pairs (309 monozygotic [MZ] and 164 dizygotic [DZ] twins) were available for data analyses. The mean IOP was 14.2 (SD 2.3) mm Hg. Neither age nor sex was correlated with IOP. Phenotypic correlation was 0.68 (95% confidence interval [CI], 0.62–0.74) in MZ twins and 0.40 (95% CI, 0.26–0.52) in DZ twins. A genetic model involving additive genetic and unique environmental effects was the best fit. Heritability was estimated as 66.5% (95% CI, 60.6%–71.6%).

**Conclusions.** IOP is not correlated with age and sex in young children. Similar to the European population, the variation of IOP in healthy Chinese children is mainly attributable to additive genetic effects. (*Invest Ophthalmol Vis Sci.* 2009;50: 2040–2043) DOI:10.1167/iovs.08-3082

Cross-sectional evidence demonstrates that IOP is lower in East Asians than in Europeans.[1] Data from Africa-Americans, Caucasians, and Iranians show that IOP increases with age, whereas data from East Asians indicate that IOP decreases or is not associated with age.[2–7] These differences suggest that the determinants of IOP may differ in terms of genetic, lifestyle, and other environmental effects in various ethnic groups.

As a major and modifiable risk factor for glaucoma, the genetic determinants of IOP have been investigated in extended pedigree studies in the Beaver Dam and Salisbury cohorts.[8–10] Familial aggregation analyses have consistently shown that the heritability of IOP is around 0.30 to 0.40. Segregation analysis has further demonstrated a mode of polygenic inheritance of IOP.[11] Aggregation analysis based on extended families, however, is tempered by the fact that the environmental factors, particularly those that are not measurable, are often diversified to an unknown extent across generations or even among siblings when they are not at the same age. This difficulty makes the environmental effects difficult to adjust for.

Twin studies offer a unique opportunity to decompose the genetic and environmental effects in phenotypic variance.[12] A comparison of similarities of phenotypes between monozygotic (MZ) and dizygotic (DZ) twins allows for the estimation of heritability when the pair-wise familial environmental variation is assumed to be the same between MZ and DZ twins. As far as we know, both a Finnish elderly twin cohort study and a U.K. adult twin study have documented very similar heritability of IOP.[13,14] However, no heritability study in East Asian populations is available.

The purpose of this analysis was to describe the distribution and further explore the heritability of intraocular pressure in a Chinese young twin cohort identified from a population-based twin registry. The use of healthy young subjects offers an advantage that the IOP may be less affected by diversified environmental factors usually seen in adults, such as systematic diseases and hypertension medication use.

## Materials and Methods

The twins in this report were recruited from the Guangzhou Twin Registry. The details of the twin registry are described elsewhere.[15] In brief, this registry was established in Guangzhou City, China in 2005 to 2006. All twins born between 1987 and 2000 were identified by using the official Household Registry of Guangzhou and followed by a door-to-door verification. In 2006, 705 twin pairs living in two districts were invited for baseline data collection. Of these, 563 pairs have been successfully contacted and examined. In 2007, these twins (at the time, aged from 8 to 16 years) were invited for more phenotypic collections, including the IOP measurement. Twin pairs were excluded from this present analysis if one or both twins had pathologic changes (i.e., retinopathy of prematurity), recent orthokeratology contact lens correction, or previous laser treatment of myopia.

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

Zygosity of all same-sex twin pairs was determined by molecular methods based on genotyping of 16 multiplex STR (PowerPlex 16 system; Promega, Madison, WI)[16] at Forensic Medical Department of Sun Yat-sen University. Zygosity in opposite-sex twin pairs was classified as dizygotic without additional genotyping.

The twins and their co-twins were requested to present together for IOP measurement. IOP was measured with a handheld tonometer (Tonopen; Mentor, Norville, MA) in a similar fashion after instilling topical anesthesia (0.4% Oxybuprocaine; Santen, Osaka, Japan) by the same examiner (FX). The measurement was repeated when the SE was

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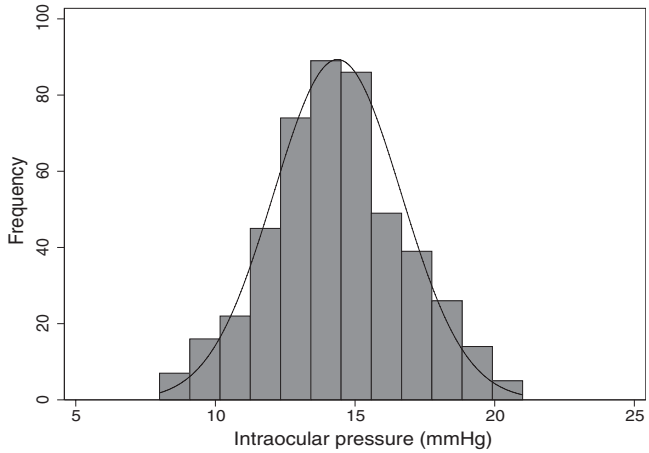


**FIGURE 1.** Distribution of IOP in the first-born twins.

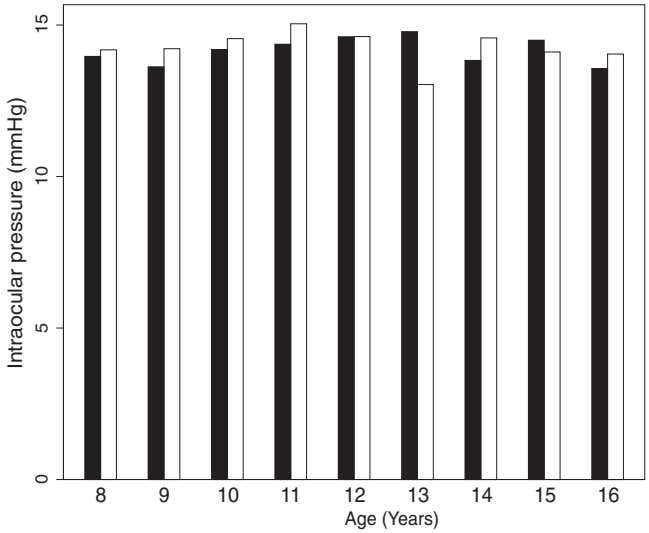


**FIGURE 2.** The mean IOP by age and sex in the first-born twins in the Guangzhou Twin Eye Study. (■) boys; (□) girls.

>5%. The tonometer was calibrated before use every day, according to the manufacturer's instructions.

The IOP in the right eye was used for analysis as it is similar to the IOP in the left eye (correlation coefficient = 0.86; $P < 0.001$). To avoid dependence on co-twin data, data on the first-born twins were used for descriptive analysis.

IOP was treated as quantitative traits in quantitative genetic modeling. The estimation of heritability in twin studies is based on the assumption that MZ twins share 100% of their genes, whereas DZ twins, on average, share only half. Assuming that two types of twins share the same environmental factors, greater similarities in phenotypes of MZ represent additional gene sharing.[17]

The Mx program was used for genetic modeling based on the phenotypic correlation in MZ and DZ twins.[18] In the full variance component model, the total phenotypic variance is decomposed into additive (A) genetic, dominant (D) genetic, common (C) environment, and unique (E) environment variances. The E component also includes measurement errors. Age and sex were treated as covariates in the model. The A variance represents the sum of the average effect of all alleles that influence a trait and correlates as 1.0 for MZ and 0.5 for DZ twins. The D variance reflects the genetic factors that result from a deviation of heterozygotes from an additive model and correlates as 1.0 for MZ and 0.25 for DZ twins. The E variance is the environmental factors that are unique to each member of a twin pair, and measurement error therefore does not contribute to the twin similarity. Because the C and D effects are confounded by each other and therefore cannot be tested in the same model, given that the intraclass correlation coefficient in DZ ($r = 0.40$) is greater than one half of the ones in MZ ($r = 0.68$), the model fitting starts from the ACE model. The determination of the best-fit reduced model was based on the $\chi^2$ test and principles of parsimony: A significant change in $\chi^2$ between the full and reduced models suggested that reduction was not acceptable, whereas a nonsignificant change in $\chi^2$ suggested that the reduced model should be chosen as the best fit to achieve the best parsimony.

## RESULTS

Four hundred seventy-three pairs of Chinese twins (309 MZ, 164 DZ) were involved in the data analysis after excluding 9 pairs with pathologic changes and 2 pairs with missing data in one of the twins. The mean age was 11.7 ± 2.5 years and 51.0% of the subjects were girls. MZ and DZ twins were of similar age (11.7 ± 2.6 years, MZ; 11.8 ± 2.4 years, DZ; *t*-test, $P = 0.495$). No difference in IOP was found between the MZ and DZ twins (14.2 ± 2.3 mm Hg, MZ; 14.2 ± 2.2 mm Hg, DZ; $P = 0.866$), and between the first- and second-born twins (14.2 ± 2.3 mm Hg, first-born; 14.4 ± 2.3 mm Hg, second-born; $P = 0.06$). IOP had an approximately normal distribution (Fig. 1). Table 1 and Figure 2 illustrate the distribution of IOP against age and sex. Multiple linear regression of IOP with age and sex in the first-born twin ($R^2 = 0.0007$, $P = 0.8433$) suggested that IOP was independent of age ($P = 0.897$) and sex ($P = 0.564$).

Figure 3 shows scatterplots of the correlations of IOP between twins in MZ and DZ pairs. The intraclass correlation coefficient (ICC, equivalent to the pair-wise correlation coefficient) was 0.68 (95% confidence interval [CI], 0.62–0.74) in MZ twins and 0.40 (95% CI, 0.26–0.52) in DZ twins. As ICC in DZ twins is two times higher than the one in MZ, the full model started from the ACE model. In maximum-likelihood genetic modeling, when we removed the common environment effect (from ACE to AE model), it did not yield a significant change in the model, based on the $\chi^2$ test, $P = 0.111$). On the other hand, the removal of the additive genetic effect (from the AE to the E model) created significant worsening of the model ($\chi^2$ test, $P < 0.001$). Therefore, the AE model was identified as the best fit, in which the additive genetic effect (A) explained 66.5% (95% CI, 60.6%–71.6%) of phenotypic

**TABLE 1.** Age- and Sex-Specific Distribution of IOP in the Right Eye in the First-Born Twins

| | Boys | | | Girls | | | Both Sexes | | |
|---|---|---|---|---|---|---|---|---|---|
| **Age (y)** | **Mean** | **Median** | ***n*** | **Mean** | **Median** | ***n*** | **Mean** | **Median** | ***n*** |
| 8–10 | 13.8 (2.2) | 14 | 66 | 14.2 (1.6) | 14 | 54 | 14.0 (2.0) | 14 | 120 |
| 11–13 | 14.4 (2.4) | 14 | 87 | 14.7 (2.4) | 15 | 82 | 14.5 (2.4) | 14 | 169 |
| 14–16 | 14.2 (2.5) | 14 | 82 | 14.0 (2.2) | 14 | 102 | 14.1 (2.3) | 14 | 184 |
| All ages | 14.2 (2.4) | 14 | 235 | 14.3 (2.2) | 14 | 238 | 14.2 (2.3) | 14 | 473 |

Data are expressed as the mean (±SD) and median IOP (mm Hg).

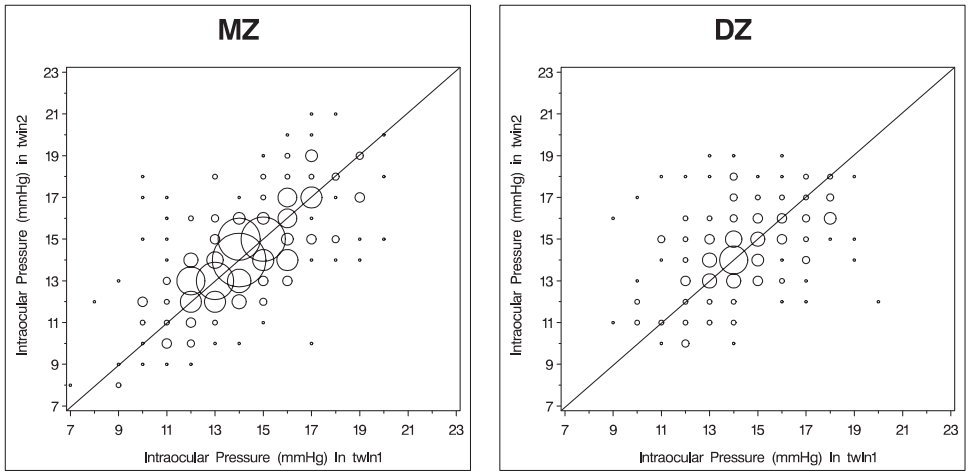


**FIGURE 3.** IOP in MZ and DZ twin pairs in the Guangzhou Twin Eye Study. *Small open circle*: one observation; *large open circle*: multiple observations. The circle size is proportional to the number of overlapped observations.

variances and unique environment (E) effect explained the remaining 33.5% (95% CI, 28.4%–39.4%; Table 2).

## DISCUSSION

Studies in European, Turkish, Indian, and Chinese populations have collected IOP data in children by using different measurement devices, with mean IOP reading ranging from 12.0 to 17.5 mm Hg.[19–26] The Singapore Cohort Study of Risk Factors for Myopia (SCORM) study reported that in Singapore Chinese children aged 9 to 12 years, the mean IOP was 16.6 ± 2.7 mm Hg when measured with a noncontact tonometer.[20] In another study of Chinese children (mean age, 14.7 years) in rural China, the mean IOP was 17.0 ± 3.4 mm Hg with an ocular response analyzer (ORA).[22] These studies showed somewhat higher mean IOP readings than our study. There is no clear explanation for this discrepancy, although differences in methodology and population structure could be the contributing factors. Despite the fact that twins and singletons are generally similar in many traits and diseases, whether our findings can be generalized to the population at large requires additional investigation.

The association of IOP with age in children is not consistent across studies. Sihota et al. [23] reported an increasing trend of IOP with age in Indian children, whereas the COMET study reported a decreasing trend in children with black, Hispanic, white, and mixed ethnicities.[26] Ethnic differences could be an explanation for this discrepancy. Another source of difference is that their study involved children at very young ages (0–12 years), whereas the COMET study participants were mainly myopic children (6–11 years). Of interest, the SCORM study in Singapore has demonstrated that IOP is not correlated with age.[20] The study involves Chinese Singaporean children at ages similar to those of our twins. It is therefore not surprising that this study demonstrates similar variations in IOP, not only with age but also with gender, compared with our findings.

To our best knowledge, we are the first to estimate genetic influences on IOP in Chinese. In a study of 61 MZ (mean age, 51.0 years) and 32 DZ (mean age, 38.8 years) twin pairs attending a twins festival in the United States, the ICC for IOP was 0.735 for MZ and 0.407 for DZ twins.[27] This is consistent with the considerable genetic contribution to IOP, although heritability was not estimated. In an elderly Finnish twins cohort (94 MZ and 96 DZ female twins) aged 63 to 76 years, measured with a noncontact tonometer, the heritability of IOP was 0.64 (95% CI, 0.53–0.71), with common and unique environmental factors explaining 0.18 (95% CI, 0.11–0.27) and 0.18 (95% CI, 0.15–0.23) of remaining variances, respectively.[13] In another study in the United Kingdom, with 211 MZ and 211 DZ adult twins (predominately Caucasians), the heritability of IOP was 0.62 (95% CI, 0.54–0.69), 0.63 (95% CI, 0.53–0.71), and 0.74 (95% CI, 0.67–0.76) with Goldmann applanation tonometry (GAT), dynamic contour tonometry (DCT), and ocular response analysis (ORA), respectively.[14] Despite ethnic variations of IOP in diverse populations and different measurement devices being used, our heritability estimate of IOP (0.67; 95% CI, 0.61–0.72) in Chinese children is very similar to these findings. That IOP is a dynamic measure that tends to fluctuate during the day partially explains relatively lower heritability estimation in comparison with other biometric traits (such as axial length) because the E component also includes other random effects including measurement errors. However, the fact that the IOP heritability is reasonably high across different ethnic populations, not only in elderly but also in young cohort, indicates evidence of genetic

**TABLE 2.** Genetic and Environmental Effects of IOP in Twin Data

| Models | Variables | | | −2 LL | *df* | $\Delta\chi^2$ | $\Delta df$ | $P^*$ |
|---|---|---|---|---|---|---|---|---|
| | A (95% CI) | C (95% CI) | E (95% CI) | | | | | |
| ACE | 0.4365 (0.1936–0.6958) | 0.2245 (0.0000–0.4504) | 0.3390 (0.2858–0.4013) | 4039.204 | 940 | | | |
| AE | 0.6650 (0.6056–0.7163) | — | 0.3350 (0.2837–0.3944) | 4041.748 | 941 | 2.544 | 1 | 0.111 |
| E | — | — | 1.0000 (1.0000–1.0000) | 4260.206 | 942 | 221.001 | 2 | <0.001 |

−2 LL, twice the negative log-likelihood, $\Delta\chi^2$, difference in $\chi^2$ values; $\Delta df$: difference in degrees of freedom; *P*, $\chi^2$ test result in model fitting. AE was the best fit.

* *P* statistics when the model is reduced.

influences for IOP and strongly supports the attempt to map the genes for IOP.

Three recent publications have provided insights into the underlying genetic mechanisms for IOP. Based on an extended primary open-angle glaucoma pedigree, multipoint linkage analyses have identified significant linkage (LOD score = 3.3, $P = 0.00015$) on 10q22 for maximum IOP.[28] In 244 sibling pairs with type 2 diabetes in West Africa, genome-wide linkage scan for IOP revealed suggestive linkages on 5q22 (LOD = 2.50, nominal $P = 0.0003$ and empiric $P = 0.0004$) and 14q22 (LOD = 2.95, nominal $P = 0.0001$ and empiric $P = 0.0003$).[29] In the Beaver Dam Eye Study, a genome-wide scan of 486 pedigrees have identified seven linkage regions, of which the short arm of chromosome 19 showed an empiric multipoint $P = 6.1 \times 10^{-5}$.[30] It should be noted that some of these regions are also identified in linkage studies for systemic hypertension.[28,30] Further investigations are needed to confirm genetic sharing of IOP and blood pressure.

Our twin sample was enrolled from a population-based twin registry, and therefore selection bias commonly seen in volunteer-based attendance was reduced.[31] Zygosity was determined by molecular methods based on genotyping of 16 microsatellite markers, thus minimizing the likelihood of misclassification introduced by zygosity questionnaire. The twins and their co-twins were measured together for IOP so that the measurement error due to IOP fluctuation was minimized. Given that healthy young twins are in general free of systematic and environmental influence on IOP and glaucoma, such as medication use for hypertension and glaucoma, the results may allow more accurate estimation on heritability. However, limitations should be noted as well. Our twins were healthy and aged from 8 to 16 years at the time of IOP measurement, and therefore these heritability estimates could not be directly applied to hypertensive children and adults. Furthermore, the use of the handheld tonometer (Tonopen; Mentor) for IOP measurement may introduce some measurement errors.[32]

In summary, IOP measured with this tonometer did not correlate with age and sex in the Chinese children. Our study confirmed strong genetic influences of IOP in a Chinese young twin cohort.

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