Heritability of Myopia and Ocular Biometrics in Koreans: The Healthy Twin Study

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PURPOSE. To estimate the heritabilities of myopia and ocular biometrics among different family types among a Korean population.

METHODS. We studied 1508 adults in the Healthy Twin Study. Spherical equivalent, axial length, anterior chamber depth, and corneal astigmatism were measured by refraction, corneal topography, and A-scan ultrasonography. To see the degree of resemblance among different types of family relationships, intraclass correlation coefficients (ICC) were calculated. Variance-component methods were applied to estimate the genetic contributions to eye phenotypes as heritability based on the maximum likelihood estimation. Narrow sense heritability was calculated as the proportion of the total phenotypic variance explained by additive genetic effects, and linear and nonlinear effects of age, sex, and interactions between age and sex were adjusted.

RESULTS. A total of 240 monozygotic twin pairs, 45 dizygotic twin pairs, and 938 singleton adult family members who were first-degree relatives of twins in 345 families were included in the study. ICCs for spherical equivalent from monozygotic twins, pooled first-degree pairs, and spouse pairs were 0.83, 0.34, and 0.20, respectively. The ICCs of other ocular biometrics were also significantly higher in monozygotic twins compared with other relative pairs, with greater consistency and conformity. The estimated narrow sense heritability (95% confidence interval) was 0.78 (0.71–0.84) for spherical equivalent; 0.86 (0.82–0.90) for axial length; 0.83 (0.76–0.91) for anterior chamber depth; and 0.70 (0.63–0.77) for corneal astigmatism.

CONCLUSIONS. The estimated heritability of spherical equivalent and ocular biometrics in the Korean population suggests the compelling evidence that all traits are highly heritable.

Keywords: heritability, twin study, myopia

Myopia is the most common eye disorder worldwide, with a prevalence ranging from 20% to 25% in Western countries and up to 90% in East Asian countries such as Singapore and Taiwan. The development of myopia is complex and multifactorial, and there is substantial interest in understanding the roles of genetic and environmental factors in disease development. Twin studies have noted higher concordance in refractive error and refractive component parameters (axial length [AL], lens power, and corneal curvature) in monozygotic (MZ) twins compared with dizygotic (DZ) twins, with heritability estimates ranging from 50% to 90%. In 2008, Dirani et al. reported the first evidence for a genetic component in adult-onset myopia in a large cohort of twins of European descent, and He et al. estimated a high genetic contribution to axial length, anterior chamber depth (ACD), and angle opening distance in twins from the Guangzhou Twin Registry.

Despite the high prevalence of myopia in Asia, the evaluation of genetic and environmental factors for myopia in Asian populations is still limited, and findings from previous studies may require replications with increasing sample sizes or by adding extended family relationships. Classical twin studies, which compare the intraclass correlations between MZ and DZ, have the potential risk of inflating heritabilities since it is difficult to separate additive from dominant genetic effects in this design. Additionally, heritabilities of behavioral traits may be overestimated when the correlation of environmental effects shared by MZ twins is greater than that of DZ twins. Therefore, we conducted a twin and family study including different types of familial relationships to provide more accurate estimates of the heritabilities and intraclass correlations among different family types regarding a range of refractive errors and ocular biometrics in an Asian sample.
METHODS

Participants

We studied participants in the Healthy Twin Study, a prospective cohort study that has recruited Korean adult twins and their family members based on a nationwide registry through mailing and advertisements at public health agencies since 2005. Extensive eye exams were introduced in 2007 for newly recruited participants and for the follow-up visits of previously recruited participants in Seoul. In total, 1688 individuals (665 men and 1023 women) underwent detailed eye examinations in the Department of Ophthalmology at the Samsung Medical Center in Seoul, Korea, between 2007 and 2011. A more detailed description of the recruitment and protocols of the study is available elsewhere.\(^{13,14}\)

We excluded 180 participants who had ocular disorders such as strabismus, keratoconus, glaucoma, cataracts, retinopathy, or amblyopia, or who had undergone prior eye surgery. The final sample size was 1508 participants: 240 MZ twin pairs, 45 DZ twin pairs, and 938 singleton adult family members who were first-degree relatives of twins in 345 families; 48 orphan MZ cotwins and 12 orphan DZ cotwins were regarded as singletons, and spouses of twins were included only when their adult offspring participated as well.

The sample included 1361 parent-offspring pairs (235 father-son pairs, 304 father-daughter pairs, 349 mother-son pairs, and 473 mother-daughter pairs); 1407 sibling pairs (603 sister pairs, 303 brother pairs, and 501 sister-brother pairs); and 214 spouse pairs. For each trait, different numbers of participants were available: 1504 individuals for spherical equivalent (SE), 1450 individuals for axial length, 1335 individuals for anterior chamber depth and corneal astigmatism (CA). All participants provided written informed consent. The study protocol was approved by the institutional review board of the Samsung Medical Center, and the study was conducted in compliance with the Declaration of Helsinki.

The zygosities of participating twin pairs were identified by 16 short tandem repeat markers (15 autosomal markers and one sex-determining marker) in 67% of the twin pairs. For the remaining 33%, zygosity was determined based on a self-administered zygosity questionnaire, of which the positive predictive value was 97.2% for MZ and 95.0% for DZ.\(^{15}\)

Measurements

Participants underwent nondilated refraction measurements with an autorefractor (Topcon AT; Topcon Corp., Tokyo, Japan). A total of three readings were taken in each eye, and the average value for each eye was recorded. Refractive error was calculated as the mean SE for each eye measured in diopters (D) using the standard formula SE = spherical error + (cylindrical error/2). Myopia was defined as SE \(< -0.50 \text{ D} \) in at least one eye.

Computed corneal topographic analysis (Orbscan; Bausch + Lomb, Buffalo, NY) was performed to obtain keratometry and ACD. Corneal astigmatism was obtained by using a simulated keratometry value from the corneal topography. Axial length was measured by corneal touch A-scan ultrasonography (Model 820; Allergan-Humphrey, San Leandro, CA).

Statistical Analysis

All analyses were carried out using the average of both eyes for each parameter. Spherical equivalent, axial length, anterior chamber depth, and corneal astigmatism were analyzed as continuous variables. To determine the degree of resemblance among different types of family relationships, intraclass

\begin{table}
\centering
\begin{tabular}{|c|c|c|c|c|c|}
\hline
\textbf{Age Group, y} & \textbf{SE, D} & \textbf{AL, mm} & \textbf{ACD, mm} & \textbf{CA, D} & \textbf{P Value} \\
\hline
\textbf{Male, n = 1624} & & & & & \\
\textbf{Female, n = 2042} & & & & & \\
\textbf{Total, n = 3666} & & & & & \\
\hline
\textbf{20–29} & -1.49 & 1.01 & 1.25 & 0.12 & 0.06 \\
\textbf{30–39} & -0.90 & 1.49 & 1.25 & 0.12 & 0.06 \\
\textbf{40–49} & -0.60 & 1.46 & 1.23 & 0.13 & 0.04 \\
\textbf{50–59} & -0.64 & 1.46 & 1.23 & 0.13 & 0.04 \\
\textbf{60+} & -1.04 & 2.05 & 1.38 & 2.14 & <0.01 \\
\hline
\textbf{Total Twins} & -1.27 & 2.20 & 1.38 & 2.14 & <0.01 \\
\textbf{Total Singletons} & -1.35 & 2.53 & 1.38 & 2.14 & <0.01 \\
\hline
\end{tabular}
\caption{Refractive Phenotypes of the Study Participants by Age Group and Sex.}
\end{table}
correlation coefficients (ICC) were calculated after adjusting for age and sex for nontwins. ICCs were estimated by the specific family type or as pooled estimates among those with the same genetic distance (e.g., pooled ICC of DZ and sibling pairs both of which are all first-degree relatives that share 50% of genetic information on average). After testing for normality, a mixed model was used to calculate ICCs where the ICC was calculated as a proportion of covariance within a particular family relationship over total variance, a sum of within-group variance, and residual variance. Descriptive statistics and ICC calculations were performed using statistical software (SAS, version 9.3; SAS Inc., Cary, NC).

Variance-component methods were applied to estimate the genetic contributions to eye phenotypes as heritability. We used extended families as well as twins, which can exclude dominance genetic effects and consider all types of family relationship,16 Narrow sense heritability was calculated as the proportion of the total phenotypic variance explained by additive genetic effects. Linear and nonlinear effects of age, sex, and interactions between age and sex were adjusted, such as age, sex, age 2, age-by-sex interaction, and age 2-by-sex interaction. After testing the genetic models including additive genetic effects, unmeasured shared environments, and unique environments, the best-fitting model was determined based on the maximum likelihood estimation. Heritability was estimated using a variance-components model implemented in a statistical genetic analysis software package (Sequential Oligogenic Linkage Analysis Routines, version 4.0.7; provided in the public domain by, http://solar.sfbrgenetics.org/).

**RESULTS**

The basic characteristics of refractive phenotypes of the study participants by age group and sex are shown in Table 1. There were significant differences of mean traits between males and females. By and large, females were more likely to be myopic and astigmatic than males. For SE in the group aged 40 to 49 years, females had significantly lower values than males ($P < 0.05$). For AL, females had shorter axial length than males with significance in all of the age groups. For ACD, females had shorter anterior chamber depth than males, with significance in the group aged 30 to 39 years and the group aged over 50 years. For CA, females had significantly higher values than males in the group aged 40 to 49 years and the group aged over 60 years. Within each mean trait by sex, there were significant differences by age groups ($P < 0.0001$). In our study between twins and singletons, age-specific standardized mean traits from the 2010 Korean standard population were considered. Singletons and twins did not show significant differences in any eye measurements.

ICCs adjusted for age and sex are shown in Table 2. For spherical equivalents, 259 MZ twin pairs, 45 DZ twin pairs, 352 sibling pairs, and 142 spouse pairs were included. For axial length, 106 MZ twin pairs, 28 DZ twin pairs, 180 sibling pairs, and 100 spouse pairs were included. For anterior chamber depth and corneal astigmatism, 206 MZ twin pairs, 55 DZ twin pairs, 331 sibling pairs, and 121 spouse pairs were included. For the pooled first-degree pairs, pairs were added as cases of one sibling with a DZ twin pair and singletons of a DZ twin pair with siblings were included.

ICCs from MZ twin pairs, pooled first-degree pairs, and spouse pairs were 0.83, 0.34, and 0.20, respectively, for spherical equivalent; 0.87, 0.40, and 0.24, respectively, for axial length; 0.90, 0.49, and 0.09, respectively, for anterior chamber depth; and 0.72, 0.30, and 0.00, respectively, for corneal astigmatism. The scatter plot of SE and biometric parameters are shown in the Figure.

In this study, variance component algorithm-based heritability was determined based on the maximum likelihood. The best-fitting models were an additive genetic and unique environment (AE) effects model for spherical equivalent, axial length, and corneal astigmatism and an additive genetic, shared environment, and unique environment (ACE) effects model for anterior chamber depth (Table 5). The estimated narrow sense heritability (95% confidence interval [CI]) was 0.78 (0.71-0.84) for spherical equivalent; 0.86 (0.82-0.90) for axial length; 0.83 (0.76-0.91) for anterior chamber depth; and 0.70 (0.63-0.77) for corneal astigmatism. For anterior chamber depth, two types of shared environment components, household effects and sibling effects, were analyzed. The ACE model with sibling effects as a shared environment component had the maximum likelihood. Thus, the best-fitting model of anterior chamber depth was the ACE model with sibling effects.

**DISCUSSION**

In the Healthy Twin study, we found that intraclass correlation coefficients for spherical equivalent and ocular biometrics were significantly higher in MZ twins compared with other relative pairs, with greater consistency and conformity. Specifically, pooled pairs with first-degree relatives had lower ICCs compared with MZ twin pairs. The estimated heritability of spherical equivalent and ocular biometrics in the Korean population add further evidence that all traits are highly heritable.

The prevalence of myopia in our study was lower than those reported in studies from Taiwan and Singapore.3-10 However, heritability of refractive errors and ocular biometrics in our study were higher than those reported in other studies in Asia.3,10 Yeh et al.5 investigated 33 monzygotic and 10 dizygotic twin pairs in Taiwan and found that the estimates of heritability for spherical aberration and corneal astigmatism were 0.56 and 0.46, respectively. Tsai et al.10 also found that the estimates of heritability for SE and AL were 0.35 and 0.67,
Figure. Scatterplots for SE and ocular biometric parameters in "MZ twin pairs" and "DZ twin pairs and sibling pairs."
In conclusion, genetic contributions to refractory phenotypes were very strong among Koreans. Yet, it is important to examine gene-environment interactions with a longitudinal twin study to identify risk factors and hence offer personalized improvements in preventive and treatment options for refractive errors.

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