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

Myung Hun Kim,[1] Di Zhao,[2] Woori Kim,[3] Dong-Hui Lim,[1] Yun-Mi Song,[4] Eliseo Guallar,[2] Juhee Cho,[2,5] Joohon Sung,[3] Eui-Sang Chung,[1] and Tae-Young Chung[1]

[1]Department of Ophthalmology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea
[2]Department of Epidemiology and Welch Center for Prevention, Epidemiology and Clinical Research, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland
[3]Department of Epidemiology, School of Public Health and Institute of Health and Environment, Seoul National University, Seoul, Korea
[4]Department of Family Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea
[5]Department of Health Sciences and Technology, Samsung Advanced Institute for Health Sciences and Technology, Sungkyunkwan University, Seoul, Korea

Correspondence: Eui-Sang Chung, Department of Ophthalmology, Samsung Medical Center, Sungkyunkwan University School of Medicine, 50 Ilwon-dong, Gangnam-gu, Seoul, Korea 135-710; eschung@skku.edu.

Tae-Young Chung, Department of Ophthalmology, Samsung Medical Center, Sungkyunkwan University School of Medicine, 50 Ilwon-dong, Gangnam-gu, Seoul, Korea 135-710; tychung@skku.edu.

Submitted: November 5, 2012
Accepted: April 17, 2013

Citation: Kim MH, Zhao D, Kim W, et al. Heritability of myopia and ocular biometrics in Koreans: the healthy twin study. *Invest Ophthalmol Vis Sci*. 2013;54:54:3644–3649. DOI:10.1167/iovs.12-11254

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.[1–3] 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.[4,5] 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%.[6] In 2008, Dirani et al.[7] 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.[8] 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[9,10] or by adding extended family relationships.[9,11] 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.[12] 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), 982 individuals for axial length, and 1333 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 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

TABLE 1. Refractive Phenotypes of the Study Participants by Age Group and Sex

Age Group, y	SE, D*			AL, mm*			ACD, mm*			CA, D*		
	Male, $n = 612$	Female, $n = 896$	*P* Value	Male, $n = 612$	Female, $n = 896$	*P* Value	Male, $n = 612$	Female, $n = 896$	*P* Value	Male, $n = 612$	Female, $n = 896$	*P* Value
~29	−2.49 ± 2.07	−3.13 ± 2.43	0.06	25.03 ± 1.27	24.41 ± 1.23†	<0.01	3.20 ± 0.33	3.14 ± 0.25	0.22	1.15 ± 0.69	1.35 ± 0.73	0.07
30~39	−1.79 ± 2.04	−1.99 ± 2.43	0.32	24.52 ± 1.11	24.03 ± 1.30	<0.001	3.03 ± 0.32	2.88 ± 0.35	<0.001	0.97 ± 0.64	0.99 ± 0.63	0.70
40~49	−0.88 ± 1.51	−1.37 ± 2.10†	0.01	24.14 ± 1.06	23.46 ± 1.32	<0.001	2.81 ± 0.29	2.74 ± 0.33	0.06	0.74 ± 0.45	0.85 ± 0.57†	0.04
50~59	−0.16 ± 1.43	−0.42 ± 2.25	0.26	23.83 ± 0.97	23.38 ± 1.24†	<0.01	2.70 ± 0.30	2.52 ± 0.35	<0.001	0.72 ± 0.43	0.80 ± 0.45	0.18
60~	0.54 ± 1.63	0.41 ± 1.55	0.57	23.66 ± 0.70	23.29 ± 0.91†	<0.01	2.63 ± 0.36	2.43 ± 0.36	<0.001	0.72 ± 0.37	0.90 ± 0.54†	<0.01
Total	−1.04 ± 2.03	−1.38 ± 2.44†	<0.01	24.26 ± 1.13	23.75 ± 1.30	<0.001	2.89 ± 0.38	2.76 ± 0.40	<0.001	0.86 ± 0.56	0.96 ± 0.61†	<0.01
Twins	−1.27 ± 2.20			23.68 ± 1.31			2.87 ± 0.35			0.89 ± 0.59		
Singletons	−1.35 ± 2.33			24.11 ± 1.22			2.85 ± 0.42			0.95 ± 0.59		

SE, Spherical Equivalent; AL, Axial Length; ACD, Anterior Chamber Depth; CA, Corneal Astigmatism.

* Mean ± SD.

† $P < 0.0001$; significantly different within age groups.

Table 2. Intraclass Correlation Coefficient (ICC) for SE and Ocular Biometric Parameters

			First-Degree Relatives							
	MZ*		DZ*		SB*		DZ + SB*		Spouse*	
Trait	*N*	ICC	*N*	ICC	*N*	ICC	*N*	ICC	*N*	ICC
SE, D	239	0.83	45	0.46	352	0.40	507	0.34	142	0.20
AL, mm	161	0.87	28	0.56	180	0.47	261	0.40	100	0.24
ACD, mm	206	0.90	35	0.71	331	0.47	447	0.49	121	0.09
CA, D	206	0.72	35	0.28	331	0.25	447	0.30	121	0.00

SB, sibling; MZ, Monozygotic twins; DZ, Dizygotic twins.
* Adjusted for age and sex, *N* (pairs).

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 value 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 value 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, 239 MZ twin pairs, 45 DZ twin pairs, 352 sibling pairs, and 142 spouse pairs were included. For axial length, 161 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, 35 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 3). 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.[9,10] Yeh et al.[9] investigated 33 monozygotic 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 0.33 and 0.67,

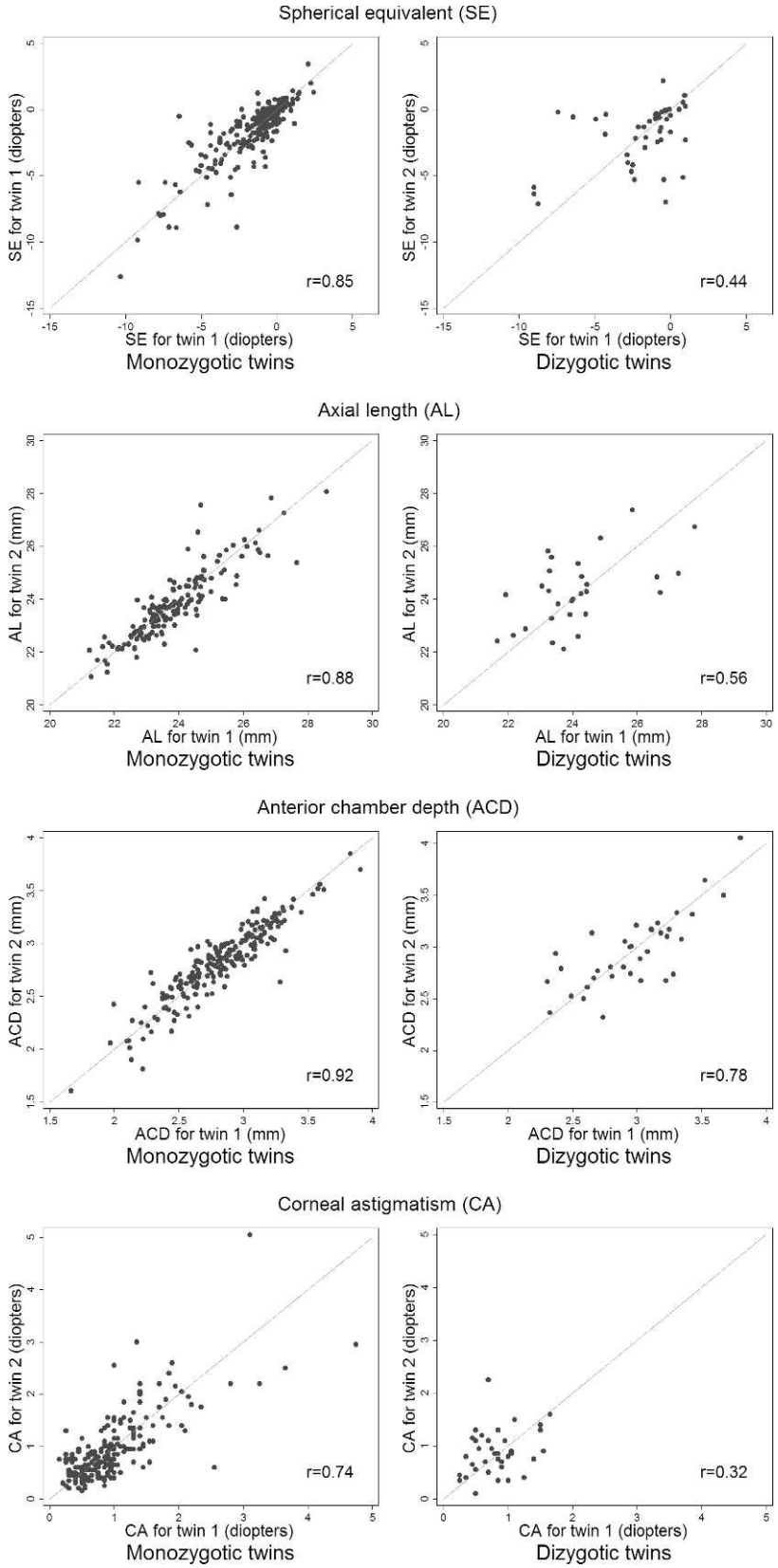

Figure. Scatterplots for SE and ocular biometric parameters in "MZ twin pairs" and "DZ twin pairs and sibling pairs."

Investigative Ophthalmology & Visual Science

Table 3. Variance Components and Heritability Estimates for SE and Ocular Biometric Parameters

Trait	Variance Component A	C	E	Best-Fitting Model	Narrow Sense Heritability*, $h^2 \pm SE$
SE, D	0.78†		0.22	AE	0.78 ± 0.03
AL, mm	0.86†		0.14	AE	0.86 ± 0.02
ACD, mm	0.83†	0.11†	0.05	ACE	0.83 ± 0.04
CA, D	0.70†		0.30	AE	0.70 ± 0.04

A, additive genetic effects; C, shared environment effects; E, unique environment effects.

* After adjusted for age, sex, age,^{2} age × sex, and age^2 × sex.

† $P < 0.0001$.

respectively, from a study with 58 twin pairs and 13 siblings. These studies may have been limited by small sample sizes. Further research is necessary to understand the differences in the prevalence and heritability of refractive errors across Asian populations.

In our study, the estimated narrow sense heritability for SE, AL, ACD, and CA was similar to those found in Western countries. A Danish study of 114 twin pairs reported heritabilities of 89% to 94% for refraction, total refraction, and axial length.[17] An Australian study of 612 twin pairs reported heritabilities of 75% to 88% for 1224 men and women.[18] In addition, there was a large-scale, twin family study with over 2000 twins in the UK that reported similar heritability (up to 77%).[19] However, these studies did not demonstrate any significant shared environmental effects, even though both studies included a relatively large numbers of twins and used structural equation genetic modeling techniques. They presented only a modest shared environmental effect of 2% to 7%. In other words, while the heritability was similar to those in Western populations, we found a larger environmental effect across ocular biometrics. This might be due to more shared environmental risk factors among Asians. The Singapore Cohort Study of the Risk Factors for Myopia found significant correlations between myopia and socioeconomic status such as housing type, family income, and education of parents.[20] Tsai et al. also found a significant association between education and myopia in the Taiwan twin study.[10] Along with the heritability, environmental risk factors might play a more important role in myopia among Asian populations compared with Western populations.

Moreover, there may be a greater tendency of myopia to aggregate within Asian families possibly due to the shared family environments such as family culture or lifestyles. The clustering of myopia within a family may be attributed to a culture of shared risk factors such as reading (or protective factors such as outdoor activity) or shared susceptibility genes for myopia in the family.

There were several limitations of our data. Most of the twins in this study were women, and we may not have enough power to identify interactions by sex. However, twins have been shown, on average, to have similar morbidity rates to singletons. Any ascertainment bias was reduced as study participants were unaware of any specific myopia studies: phenotyping was performed as part of a larger Healthy Twin Study, of which the ocular exam was a small part. Regardless of these limitations, our study included a sufficient number of adult twins to detect certain shared environmental effects for spherical equivalence among Koreans. Moreover, because of age matching, our study would be better placed to detect latent genetic effects for myopia, whereas other family studies—by including children and parents with age and potential generational differences—have more power to detect environmental effects that are known to influence the complex age-related trait, myopia.[21]

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.

Acknowledgments

Supported in part by the National Research Foundation of Korea, Ministry of Education, Science, and Technology Grants 2011-220-E00006, 2010-0029113, and 2010-0025814.

Disclosure: **M.H. Kim**, None; **D. Zhao**, None; **W. Kim**, None; **D.-H. Lim**, None; **Y.-M. Song**, None; **E. Guallar**, None; **J. Cho**, None; **J. Sung**, None; **E.-S. Chung**, None; **T.-Y. Chung**, None

References

1. Lin LL, Chen CJ, Hung PT, Ko LS. Nation-wide survey of myopia among schoolchildren in Taiwan, 1986. *Acta Ophthalmol Suppl*. 1988;185:29–33.
2. Morgan I, Rose K. How genetic is school myopia? *Prog Retin Eye Res*. 2005;24:1–38.
3. Wu HM, Seet B, Yap EP, Saw SM, Lim TH, Chia KS. Does education explain ethnic differences in myopia prevalence? A population-based study of young adult males in Singapore. *Optom Vis Sci*. 2001;78:234–239.
4. Dirani M, Chamberlain M, Garoufalis P, Chen C, Guymer RH, Baird PN. Refractive errors in twin studies. *Twin Res Hum Genet*. 2006;9:566–572.
5. Goss DA, Hampton MJ, Wickham MG. Selected review on genetic factors in myopia. *J Am Optom Assoc*. 1988;59:875–884.
6. Sanfilippo PG, Hewitt AW, Hammond CJ, Mackey DA. The heritability of ocular traits. *Surv Ophthalmol*. 2010;55:561–583.
7. Dirani M, Shekar SN, Baird PN. Adult-onset myopia: the Genes in Myopia (GEM) twin study. *Invest Ophthalmol Vis Sci*. 2008;49:3324–3327.
8. He M, Hur YM, Zhang J, Ding X, Huang W, Wang D. Shared genetic determinant of axial length, anterior chamber depth, and angle opening distance: the Guangzhou Twin Eye Study. *Invest Ophthalmol Vis Sci*. 2008;49:4790–4794.
9. Yeh LK, Chiu CJ, Fong CF, et al. The genetic effect on refractive error and anterior corneal aberration: twin eye study. *J Refract Surg*. 2007;23:257–265.
10. Tsai MY, Lin LL, Lee V, Chen CJ, Shih YF. Estimation of heritability in myopic twin studies. *Jpn J Ophthalmol*. 2009;53:615–622.
11. Lin LL, Chen CJ. Twin study on myopia. *Acta Genet Med Gemellol (Roma)*. 1987;36:535–540.
12. Spector TD, Snieder H, MacGregor AJ, eds. *Advances in Twin and Sib-Pair Analysis*. Oxford: Oxford University Press; 2000;151–165.
13. Sung J, Cho SI, Lee K, et al. Healthy Twin: a twin-family study of Korea–protocols and current status. *Twin Res Hum Genet*. 2006;9:844–848.
14. Sung J, Cho SI, Song YM, et al. Do we need more twin studies? The Healthy Twin Study, Korea. *Int J Epidemiol*. 2006;35:488–490.
15. Song YM, Lee D, Lee MK, et al. Validity of the zygosity questionnaire and characteristics of zygosity-misdiagnosed twin pairs in the Healthy Twin Study of Korea. *Twin Res Hum Genet*. 2010;13:223–230.

16. Keller MC, Medland SE, Duncan LE, et al. Modeling extended twin family data I: description of the Cascade model. *Twin Res Hum Genet*. 2009;12:8–18.
17. Lyhne N, Sjolie AK, Kyvik KO, Green A. The importance of genes and environment for ocular refraction and its determiners: a population based study among 20-45 year old twins. *Br J Ophthalmol*. 2001;85:1470–1476.
18. Dirani M, Chamberlain M, Shekar SN, et al. Heritability of refractive error and ocular biometrics: the Genes in Myopia (GEM) twin study. *Invest Ophthalmol Vis Sci*. 2006;47:4756–4761.
19. Lopes MC, Andrew T, Carbonaro F, Spector TD, Hammond CJ. Estimating heritability and shared environmental effects for refractive error in twin and family studies. *Invest Ophthalmol Vis Sci*. 2009;50:126–131.
20. Saw SM, Carkeet A, Chia KS, Stone RA, Tan DT. Component dependent risk factors for ocular parameters in Singapore Chinese children. *Ophthalmology*. 2002;109:2065–2071.
21. Keller MC, Medland SE, Duncan LE. Are extended twin family designs worth the trouble? A comparison of the bias, precision, and accuracy of parameters estimated in four twin family models. *Behav Genet*. 2010;40:377–393.