Clinical and Epidemiologic Research

High Heritability of Posterior Corneal Tomography, as Measured by Scheimpflug Imaging, in a Twin Study

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Purpose. Anterior corneal curvature shows significant heritability. Scheimpflug imaging also permits assessment of posterior tomography. We estimated heritability of posterior and anterior tomographic parameters.

Methods. Oculus Pentacam images were obtained in twins from the TwinsUK cohort. Mean anterior and posterior radii of curvature (right cornea) were compared within twin pairs, and heritability calculated (maximum likelihood structural equation modeling, using OpenMx package). Heritability estimates also were calculated for other parameters (anterior and posterior elevation at apex and thinnest point; pachymetry at apex and thinnest point; average pachymetry progression index).

Results. Images from 138 twins were included (32 monozygotic [MZ] and 37 dizygotic [DZ] twin pairs). Mean (SD) age was 61 (11) years; 91% were female. Coefficients for intrapair correlation for MZ and DZ twins were, respectively, 0.89 and 0.42 for anterior curvature, and 0.93 and 0.46 for posterior curvature ($P \leq 0.0001$ for differences between MZ and DZ correlations; Fisher *r*-to-*z* transformation). Heritability estimates (95% confidence interval [CI]) for anterior and posterior curvature were 89% (79%–93%) and 90% (83%–94%), respectively. Estimates for all other parameters were 75% or higher, except anterior apical elevation (61%). Point estimates for posterior parameters were consistently higher than anterior parameters, although CIs overlapped. Age-matching yielded similar estimates. Intereye correlations were high; correlations with age were weak ($r < 0.30$).

Conclusions. This is the first study to explore heritability of a number of different parameters of corneal tomography, including posterior curvature. Almost all parameters appeared highly heritable, with a trend toward higher heritability estimates for posterior (versus anterior) parameters.

Keywords: corneal curvature, posterior, heritability

The cornea provides the major component of the eye's refractive power. A number of methods are available for quantifying parameters of corneal tomography, and most studies have shown that genetic factors contribute significantly to corneal curvature. Estimates of the heritability of corneal curvature have ranged from 16% to 95% (most of these estimates were in excess of 40%).[1–11] From a meta-analysis of five previous studies,[5–8,10] a figure of 55% has been derived.[12] The highest estimate so far has come from the Beaver Dam Eye Study, which suggested that corneal curvature was 95% heritable, after adjusting for height.[11] Interestingly, the Australian Genes in Myopia Twin Study found sex specificity, with heritability estimated at 70% in males and 41% in females.[10]

Recently the genome-wide complex trait analysis approach,[13] which can provide a lower bound estimate of the heritability of a trait,[14] has been used for the first time to derive heritability estimates of corneal curvature and axial length in unrelated subjects.[15] Lower bounds of heritability for corneal curvature were estimated at 42% and 35% for subjects from the Avon Longitudinal Study of Parents and Children and Singapore Chinese Eye Study cohorts, respectively.[15]

These previous studies have all explored curvature of the anterior cornea, which is more readily amenable to measurement. However, posterior corneal tomography is of great relevance, and can be affected earlier in corneal ectatic diseases.[16] Technology incorporating a rotating Scheimpfug camera (the Oculus Pentacam [Oculus, Wetzlar, Germany]) has been developed to provide imaging of both the anterior and posterior corneal surfaces; measurements of posterior corneal tomography have been shown to be accurate and reproducible.[17] In this study, we obtained such measurements in monozygotic (MZ) and dizygotic (DZ) twin pairs, to explore the relative contribution of genetic and environmental factors to variation in tomographic parameters. Our primary novel aim was to quantify heritability of radius of posterior corneal curvature. We also generated heritability estimates for the following parameters: mean anterior radius of curvature, anterior and posterior corneal elevation (both at the apex and

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Table 1. Mean (SD) Parameter Values and Correlation Coefficients (for Intrapair Correlation) for MZ and DZ Twins

Parameter	Mean (SD) Value		P, Shapiro-Wilks	Correlation Coefficients		
	MZ Twins	DZ Twins		MZ Pairs	DZ Pairs	P for Difference
Radius of curvature, mm						
Anterior	7.68 (0.24)	7.64 (0.26)	0.79	0.89	0.42	0.0001
Posterior	6.31 (0.27)	6.28 (0.25)	0.33	0.93	0.46	<0.0001
Corneal thickness, µm						
Apex	532 (34)	538 (34)	0.84	0.93	0.53	<0.0001
Thinnest	527 (34)	534 (34)	0.81	0.93	0.53	<0.0001
Progression index	0.99 (0.13)	0.99 (0.13)	0.31	0.78	0.25	0.002
Elevation at apex, µm						
Anterior	1.75 (1.15)	1.42 (1.22)	<0.001	0.60	0.29	0.119
Posterior	5.06 (2.39)	4.12 (2.65)	0.002	0.76	0.45	0.043
Elevation at thinnest point, µm						
Anterior	1.95 (1.95)	1.70 (1.78)	<0.001	0.75	0.13	0.001
Posterior	9.77 (4.52)	8.28 (4.1)	0.046	0.79	0.42	0.016

P value for difference in correlations is given in the right-hand column. The table also shows the results of a test for normality (Shapiro-Wilks) in the middle column: $P < 0.05$ indicates significant deviation from a normal distribution; in these cases Spearman correlation coefficients were calculated.

thinnest point), corneal thickness (at apex and thinnest point), and average progression index. The elevation gives the distance in micrometers of a particular point above the best-fit sphere. The progression index quantifies the change in corneal thickness with eccentricity. Both the posterior corneal elevation and the pachymetry progression index are clinically relevant, as they can be early markers of ectatic disease.[16,18] In addition, we quantified intereye correlation within the same subject, and explored potential correlations with age.

Methods

Healthy twin volunteers were recruited from the TwinsUK registry based at St. Thomas' Hospital in London as part of a wider study, which involved an eye examination, pupil dilatation, recording of ERG responses with a conductive fiber electrode, and noninvasive ocular imaging. The study had local research ethics committee approval and was conducted in accordance with the tenets of the Declaration of Helsinki.

Corneal Imaging

Scheimpflug corneal imaging was performed using the Oculus HR (High-Resolution) Pentacam (Oculus). Images were taken from both members of a twin pair at the same time of day, usually within 10 minutes of each other. Members of one twin pair came on different days, but images were acquired at the same time of day.

Exclusion Criteria

Images were excluded if participants had worn contact lenses in the previous week or if they had undergone any corneal surgery or cataract surgery. Only images of acceptable quality were included (as defined by the "Quality Score" generated by the Pentacam, which takes into account alignment, corneal coverage, blinking, and ocular motion).

For assessing correlations within twin pairs and heritability, images were excluded if corresponding measurements were not available for the fellow twin.

Calculating Correlations

Coefficients for intrapair correlation were calculated for MZ and DZ twins. A test for normality (Shapiro-Wilks) was performed for each parameter. Where the distribution was found to differ significantly from normal, Spearman correlation coefficients were used; otherwise, Pearson coefficients were calculated. Correlations were compared (using the Fisher *r*-to-*z* transformation), and two-tailed *P* values less than 0.05 for difference between MZ and DZ correlations were taken as significant.

Also, correlation coefficients were calculated for intereye correlation (both for anterior and posterior curvature) for subjects in whom measurements in both eyes were available, and for correlation between anterior and posterior curvature in the same eye.

Calculating Heritability

Heritability calculations were performed with maximum likelihood structural equation twin modeling. This was performed using the OpenMx package (http://openmx.psyc.virginia.edu) in the R statistical computing environment (http://www.r-project.org). In this technique, the variance of a trait is estimated by the contributions of three factors: the additive genetic component (A), the shared environment (C), or the nonadditive genetic component (D), and the unique environment (E). Univariant ACE/ADE models were executed with standardized path coefficients and expected variance and covariance matrices. The goodness of fit of the full and reduced ACE/ADE models were compared with the observed data. The most parsimonious model to explain the observed variance was selected; this was identified as the AE model for all traits. Heritability was calculated as the proportion of total variance of the trait (V) due to the additive genetic effect (A) in the best-fitting model (AE in all traits studied).

Results

Demographics of Participants

Images from 138 twin subjects (32 MZ pairs and 37 DZ pairs) were analyzed. All participants were Caucasian with the

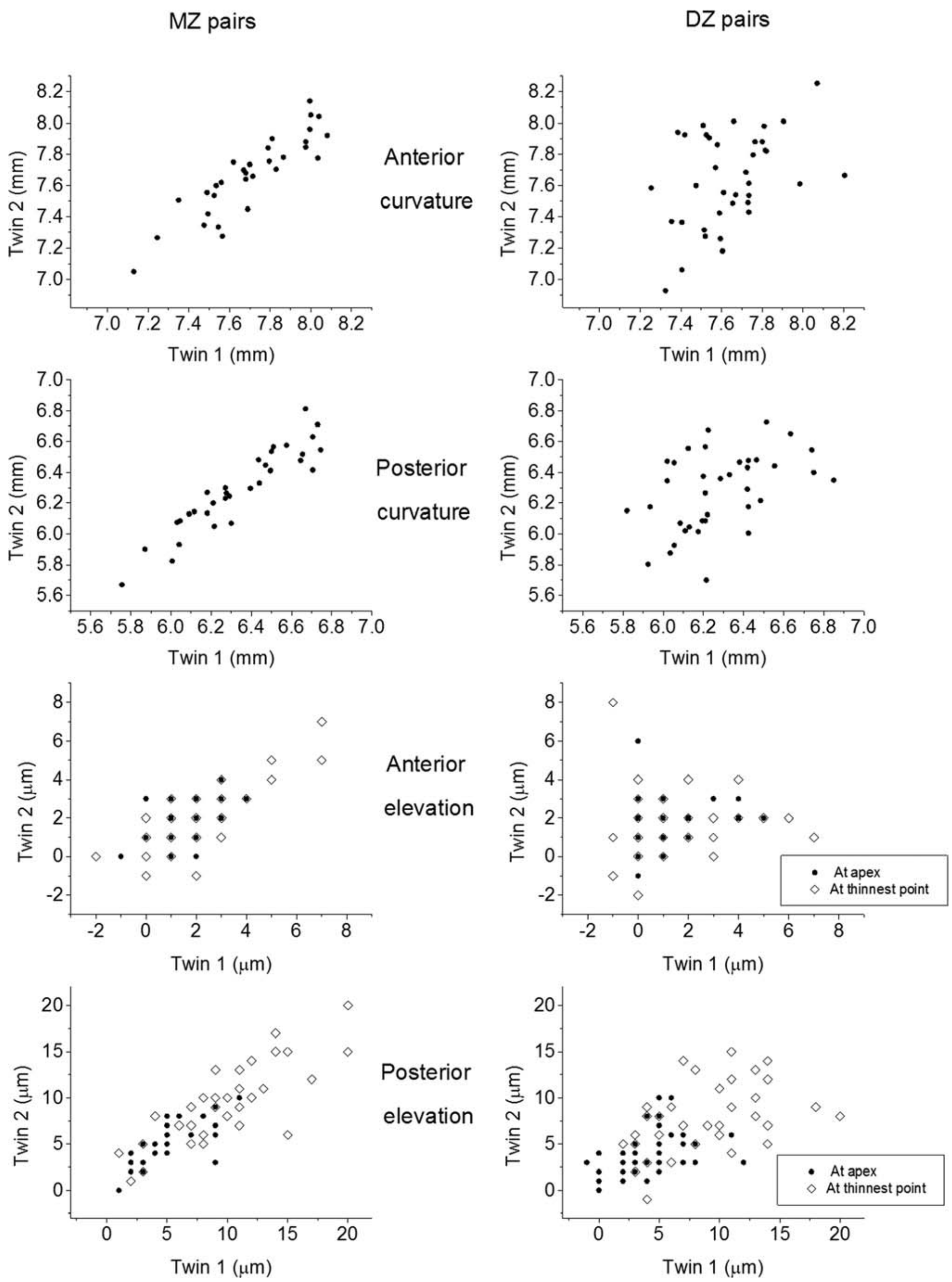

FIGURE 1. Measurements in twin pairs (twin 2, the second twin to be imaged, is plotted against twin 1) for radii of anterior and posterior curvature (*top*), and anterior and posterior elevation (*bottom*). Monozygotic pairs are on the *left* and DZ on the *right*.

exception of one MZ twin pair of mixed (Caucasian/Asian) ethnicity. Mean (SD) age of the participants was 61 (11) years. Most (91%) were female, with only 12 males (3 DZ and 3 MZ pairs). Mean (SD) ages were 58 (11) years and 64 (9.1) years for MZ and DZ twins, respectively, with MZ pairs significantly younger ($P = 0.03$). Median ages (range) were 59 (34–76) and 64 (36–81) years, respectively. Proportions of male twin pairs were not significantly different between the MZ and DZ groups ($P = 0.79$).

No subjects had a previous diagnosis of corneal ectatic disease. Six subjects had a diagnosis of dry eye or were using artificial tear substitutes; the proportions were not significantly different for MZ and DZ subjects (3.1% and 5.4%, respectively, $P = 0.51$).

Mean Parameter Values and Correlations

Table 1 shows the mean values for each recorded parameter for MZ and DZ twins, and also the results of testing for normality. The elevation measurements were found to deviate significantly from a normal distribution, and so for these data, Spearman correlation coefficients were derived. The table also shows the correlation coefficients, which were higher for MZ twins for all parameters. The difference between MZ and DZ correlations was significant for all parameters (suggesting a substantial genetic contribution), with the exception of the anterior apical elevation. The data are shown graphically in Figure 1, and the tighter correlations in MZ pairs can be appreciated visually.

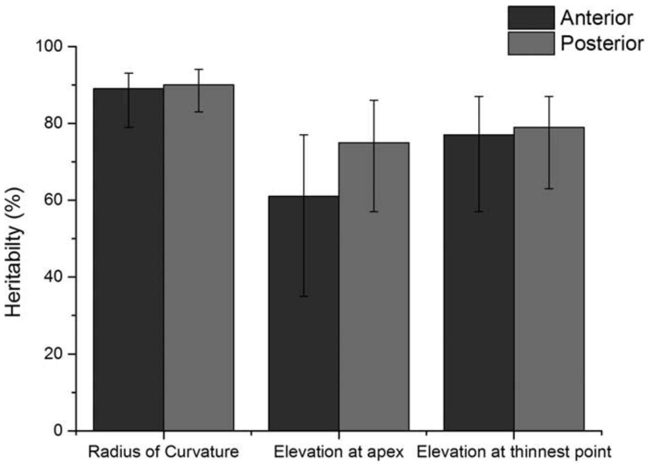

Figure 2. Point estimates of heritability (with 95% CIs) of anterior and posterior parameters.

Heritability

Derived estimates for heritability (using the AE model, see Methods section) of anterior and posterior parameters are shown graphically in Figure 2. Estimates appear to be consistently higher for posterior parameters, suggesting that variation in posterior corneal tomography may show stronger genetic contribution (although confidence intervals [CIs] overlap). Table 2 gives the point estimates and CIs for all parameters.

The mean age of the DZ twins was significantly higher than that of the MZ twins, and theoretically this could affect the estimate of heritability. Therefore, we chose an age-matched subset, consisting of 27 MZ and 27 DZ pairs. The age-matching was performed by taking each decade and ensuring the same numbers of MZ and DZ twin pairs were represented (excluding any surplus MZ or DZ pairs as appropriate), while maintaining the same sex distributions. The mean ages of the resulting samples were similar ($P = 0.93$): mean (SD) age was 61.7 (8.5) years for MZ twins, and 61.4 (8.9) years for DZ twins. Heritability estimates were then calculated using this age-matched subset, and these are shown in the right-hand column of Table 2. The estimates in most cases are very similar to those derived from the total sample.

Correlations With Age

Correlations with age were explored for each parameter. Table 3 shows correlation coefficients for all twins (middle columns) with *P* values. Although some correlations were statistically significant, the magnitude of the correlation coefficient was below 0.25 for all parameters. However, as intrapair twin correlation could potentially confound these estimates, the calculation was repeated using only one twin from each pair (right-hand columns). Correlations were similarly weak, with none reaching significance, although this may be due to the reduction in power with the reduced sample size.

Intereye and Within-Eye Correlation

Suitable quality images were available for both eyes for 124 subjects. Coefficients for intereye (right and left eyes) correlation were 0.97 and 0.96 for mean anterior and posterior curvature, respectively, and 0.97 for corneal thickness (both when measured at the apex and at the thinnest point). Coefficients for within-eye correlation (i.e., between anterior and posterior curvature) were 0.90 and 0.89 for right and left eyes, respectively.

Table 2. Point Estimates of Heritability (With 95% CIs) for all Parameters, With Estimates for Age-Matched Data Also Shown

Parameter	Heritability Estimate, % (95% CI) Full Sample	Age-Matched
Radius of curvature, mm		
Anterior	89 (79–93)	88 (78–94)
Posterior	90 (83–94)	91 (83–95)
Corneal thickness, μm		
Apex	92 (87–96)	92 (85–95)
Thinnest	92 (86–95)	92 (85–95)
Progression index	76 (58–86)	75 (54–86)
Elevation at apex, μm		
Anterior	61 (35–77)	55 (23–75)
Posterior	75 (57–86)	74 (53–85)
Elevation at thinnest point, μm		
Anterior	77 (57–87)	74 (47–87)
Posterior	79 (63–87)	77 (58–87

Discussion

The present study used the classic twin approach to quantify relative genetic and environmental contributions to the variance in corneal tomographic parameters, as obtained by Scheimpflug imaging (using a device that has been shown to have good precision for the parameters explored[19]). Correlations for MZ twins were significantly higher than those for DZ twins for most parameters. This is, to our knowledge, the first study to explore heritability of posterior corneal curvature: this was found to be highly heritable; we estimated that 90% of the variation in posterior corneal curvature could be explained by genetic factors (95% CI 83%–94%). All other parameters also appeared to be significantly heritable (with most estimates above 70%). Heritability estimates for anterior corneal curvature and corneal thickness also were high, and in keeping with those of previous studies.[1–12,15]

Previous studies have shown central corneal thickness to be heritable, with a meta-analysis yielding an estimate of 0.85.[12] We were able to separately quantify corneal thickness both at the apex and at the thinnest point, and found both to have similarly high heritability (estimated in this study at 92%), as well as the average pachymetry progression index (76%). Anterior and posterior elevation measurements also were explored for the first time in a twin study, and these also suggested an important genetic contribution. Interestingly, posterior parameters gave consistently higher point estimates of heritability, although CIs showed significant overlap, and hence we cannot confidently assert that posterior tomography is more heritable.

Posterior corneal tomography, as assessed by Scheimpflug imaging, is of great clinical interest, as in ectatic corneal conditions the posterior corneal surface is often a subtle indicator of early pathological changes,[16,20] which are not seen on the anterior surface, as the corneal epithelium can mask such alterations. It is also of great importance in calculating intraocular lens requirements in cataract patients who have had previous refractive surgery.[21] If the posterior cornea is affected earlier in ectatic disorders, one might speculate that, were this to reflect a greater vulnerability to environmental factors, this might be reflected in a lower heritability estimate.

TABLE 3. Correlations of Tomography Parameters With Age in the Present Study

Parameter	Correlation With Age (All Twins)		Correlation (One Twin Per Pair)	
	r	*P* Value	*r*	*P* Value
Radius of curvature, mm				
Anterior	−0.21	0.01	−0.19	0.11
Posterior	−0.08	0.37	−0.06	0.63
Corneal thickness, μm				
Apex	−0.20	0.02	−0.16	0.18
Thinnest	−0.20	0.02	−0.16	0.20
Progression index	−0.02	0.85	−0.06	0.62
Elevation at apex, μm				
Anterior	−0.03	0.68	−0.10	0.39
Posterior	0.23	0.006	0.17	0.15
Elevation at thinnest point, μm				
Anterior	−0.11	0.22	−0.11	0.38
Posterior	0.13	0.12	0.06	0.65

Spearman coefficients are given for non-normally distributed variables. See Table 1.

The finding of potentially higher heritability, compared with the anterior surface, could suggest that genetic factors play a more significant role. The posterior corneal surface is clearly less exposed to the external environment, so in this respect, the finding of a high heritability might not be unexpected

Genome-wide association studies have identified multiple loci associated with both keratoconus and corneal thickness.[22] Future studies could investigate whether loci exist with associations both for corneal curvature and ectatic disease. A recent Australian study explored some of the identified loci, finding associations between two of the single nucleotide polymorphisms and keratoconus in their independent cohort, but none were significantly associated with corneal curvature.[23]

The strong intereye correlation (between right and left eyes) both for anterior and posterior curvature also is of interest. Significant asymmetry in either parameter between the two eyes could be suggestive of disease. Between-eye asymmetry of a number of corneal parameters has been shown to be greater in patients with bilateral keratoconus in comparison with subjects with normal corneas.[24]

Limitations of the present study include a relatively small sample size, and ethnic and sex homogeneity: the vast majority of participants were Caucasian females, which could limit generalizability to wider populations. Also, the question arises as to how representative data from twins are of the general population. Although some ocular parameters appear to differ between twins and their siblings, corneal curvature and thickness have not been shown to differ,[25] suggesting the present findings could be representative in this respect. The higher mean age for DZ twins in this study might also lead to an overestimate of heritability (as environmental factors may be less shared for the DZ than the MZ cohort). However, as the study explored heritability of anterior and posterior parameters in the same cohort, it might be expected that such a limitation would affect both estimates similarly, and so not rendering the comparison invalid. Diurnal variation has been shown in corneal curvature,[26] and so this could potentially contribute to variability in measurements. However, members of each twin pair were imaged at the same time of day, so correlation within pairs would not be expected to be affected.

Our sample size also was not large enough for us to adequately distinguish between the goodness of fit of the ADE and ACE models (which would allow quantification of the contribution of dominant genetic or common environmental factors), and so the AE model was selected as the most parsimonious. A larger sample would provide additional power in this regard. We did not find strong correlations with age. However, ages were not evenly distributed, with 90% of subjects being older than 48. A study population with a wider age-distribution may have yielded stronger correlations.

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