Central Corneal Thickness Is Highly Heritable: The Twin Eye Studies

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PURPOSE. A classic twin study was performed to determine the heritability of central corneal thickness (CCT), an important parameter in glaucoma assessment.

METHODS. The concordance of CCT between monozygotic (MZ) and dizygotic (DZ) twins was compared. A total of 256 twin pairs (131 MZ and 125 DZ) were recruited from three centers: the Twin Eye Study in Tasmania, the Brisbane Adolescent Twin Study, and the Twins U.K. Adult Registry held at St. Thomas’ Hospital in London. As part of an extensive ophthalmic evaluation, CCT was measured by ultrasound pachymetry. Structural equation modeling with the Mx program (Department of Psychiatry, Medical College of Virginia, Richmond, VA) was used to determine the heritability of CCT.

RESULTS. The mean age of subjects was 38 years (range, 8–81). The mean CCT of all eyes examined was 544.5 ± 37.3 μm (SD). The CCT measurements correlated more highly in MZ twins than in DZ twins, with intraclass correlation coefficients of 0.95 and 0.52, respectively, suggesting a strong genetic influence. A model of additive genetic and unique environmental effects provided the best fit, yielding a heritability of 0.95 (95% confidence interval [CI], 0.93–0.96) with the remaining effects provided the best fit, yielding a heritability of 0.95. (Invest Ophthal Vis Sci. 2005;46:3718–3722) DOI:10.1167/iovs.04-1497

Central corneal thickness (CCT) has been proposed recently as an important factor in glaucoma diagnosis and management, and as such the analysis of determinants of CCT is of interest. Given the hereditary nature of primary open angle glaucoma (POAG), future mutation screening may identify susceptible individuals, who could be closely reviewed clinically, allowing intervention before disease progression. At present, mutations in only three genes (myocilin, optineurin, and WDR36) have been shown to cause POAG, and each accounts for only a small proportion of cases.1–3 For a complex heterogeneous disease such as POAG, the study of an intermediate phenotype or significant confounder such as CCT may facilitate identification of further glaucoma-related genes.

Elevated intraocular pressure (IOP) is an important risk factor for POAG. Reducing IOP is associated with a significant reduction in the rate of visual field progression.4 Goldmann applanation tonometry (GAT) is accepted as the gold standard for IOP measurements. Although GAT assumes a CCT of 500 μm, it has been shown to reflect most accurately the true IOP when the CCT is 520 μm.5 However, CCT varies greatly in the normal population.6 Consequently, CCT is a confounder when performing GAT, with underestimation of IOP in eyes with thin corneas and overestimation in eyes with thick corneas.7 The Ocular Hypertension Treatment Study (OHTS) demonstrated that CCT significantly influences the likelihood of conversion from ocular hypertension to glaucoma.8 Thinner CCT has been associated with advanced glaucoma, although the mechanism has not yet been determined.9 CCT has been reported to be associated with glaucoma progression, although there is still debate about the issue.9

A hereditary basis for CCT was suggested in 1978 through a population-based familial aggregation study of Greenland Eskimos, which estimated CCT heritability to be between 0.6 and 0.7.10 Reduced CCT has been associated with some genetic diseases such as congenital glaucoma,11 osteogenesis imperfecta,12 Down syndrome,13 X-linked megalocornea,14 keratoconus,15 Marfan syndrome,16 and Ehlers-Danlos syndrome,17 whereas increased CCT has been found in patients with congenital aniridia.18

Twin studies are an excellent method of studying the relative importance of genetic and environmental influences on a phenotype.19 Such investigations are based on the assumption that siblings share the same environmental influences, yet monozygotic (MZ) twins have identical genes and dizygotic (DZ) twins have, on average, only half of their segregating genes in common. Thus, a greater concordance in MZ twins than in DZ twins may be attributable to genetic factors.

We conducted a classic twin study to determine the heritability of CCT in a general population. Using modern genetic modeling techniques, we compared the covariance of CCT between MZ and DZ twins.
TABLE 1. Summary of Intraclass Correlations between MZ and DZ Twin Pairs from the Two Study Populations

<table>
<thead>
<tr>
<th></th>
<th>Total MZ</th>
<th>DZ</th>
<th>U.K. Twins MZ</th>
<th>DZ</th>
<th>Australian Twins MZ</th>
<th>DZ</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number</strong></td>
<td>262</td>
<td>250</td>
<td>128</td>
<td>114</td>
<td>154</td>
<td>136</td>
</tr>
<tr>
<td><strong>Mean age (SD) (y)</strong></td>
<td>40.6 (15.2)</td>
<td>35.4 (13.3)</td>
<td>43 (10.6)</td>
<td>41.5 (9)</td>
<td>38 (18.3)</td>
<td>30.3 (14.2)</td>
</tr>
<tr>
<td><strong>Mean CCT (SD) (μm)</strong></td>
<td>542 (39)</td>
<td>547 (37)</td>
<td>538 (32)</td>
<td>549 (33)</td>
<td>545 (44)</td>
<td>546 (38)</td>
</tr>
<tr>
<td><strong>Intraclass correlation of mean CCT</strong></td>
<td>0.95</td>
<td>0.52</td>
<td>0.94</td>
<td>0.53</td>
<td>0.96</td>
<td>0.52</td>
</tr>
</tbody>
</table>
RESULTS

Two hundred fifty-six unselected twin pairs (131 MZ, 125 DZ) were recruited from Australia and the United Kingdom. All were white. One hundred eighty-eight pairs were same-sex female twins (117 U.K., 71 Australian), 32 pairs were same-sex male twins (3 U.K., 29 Australian), and 36 pairs were mixed-sex twins (1 U.K., 35 Australian). The mean age of all subjects was 38 ± 15 years (range, 8–81). The Australian twins were on average younger than the U.K. twins (mean age, 34 ± 17 and 43 ± 11 years, respectively). Demographic information is provided in Table 1.

The CCTs in all subjects studied were normally distributed (Fig. 1). The CCT for each subject’s right and left eyes correlated highly (intraclass correlation coefficient: 0.97). Further analysis was performed using the mean CCT of both eyes for each subject. Analysis for each eye separately was similar (results not shown).

The mean CCT of all subjects was 544.5 ± 37.3 μm. A weak negative correlation between CCT and age was identified (r = -0.09, P = 0.048). Given that this effect was small, age was not included in further analysis. There was no significant correlation of CCT with refractive error (r = 0.048).

Overall, there was no significant difference (P = 0.5, unpaired t-test) in CCT between U.K. twin pairs (543.1 ± 32.6 μm) and Australian twin pairs (545.6 ± 40.9 μm). However, the CCT of U.K. MZ twins was significantly thinner than U.K. DZ twins (mean, 538 ± 32 for MZ and 549 ± 35 for DZ, P = 0.02). In the Australian group there was no significant difference between the CCT of MZ and DZ twins (P = 0.78).

Male twins were found to have a mean CCT of 550 ± 36.6 μm and female twins had a mean CCT of 542 ± 36.8 μm (Table 2), which was not significantly different (P = 0.12, unpaired t-test).

CCT correlated highly within MZ twin pairs (product moment correlation coefficient, 0.95; r² = 0.9, P < 0.001), whereas the correlation of CCTs in DZ twin pairs was lower (correlation coefficient, 0.52; r² = 0.27, P < 0.001; Fig. 2). When the U.K. and Australian groups were analyzed separately, the MZ and DZ correlations were very similar to that of the whole group, with MZ correlations of 0.94 and 0.96 and DZ correlations of 0.53 and 0.52, respectively (Table 1). The MZ and DZ correlations for the average CCT were also similar if the twins of different gender were analyzed separately (Table 2). The higher correlation of CCT in MZ twins implied a strong genetic influence on CCT.

RESULTS OF MAXIMUM-LIKELIHOOD MODELING FOR ALL SUBJECTS ARE SUMMARIZED IN Table 3. An AE model, combining both additive genetic effects and unique environment effects, provided the best-fitting model (with the lowest AIC). The heritability of CCT in this study was calculated to be 0.95 (95% confidence interval [CI], 0.93–0.96), with the remaining variance (0.05, 95% CI, 0.4–0.7) being attributable to environmental effects. These results did not significantly differ for the U.K. twins alone (b² = 0.94, 95% CI 0.91–0.96) or the Australian twins group (b² = 0.95, 95% CI, 0.93–0.97). Dominant genetic effects and shared environmental effects were found not to be significant in this study.

DISCUSSION

This study revealed CCT to be a highly heritable trait. With a heritability of 0.95, genetic factors were the primary influence in the determination of CCT. Unique environmental effect (which included measurement error) contributed only 5% of the variance. The measured heritability of CCT was substantially greater in our study than that calculated in the Greenland Eskimos study (0.6–0.7). Factors that could contribute to this difference include differences in study design and/or greater measurement error in the Greenland Eskimos study, as it relied on optical determination of CCT. Alternatively, fundamental population differences may exist between the white twins in this study and the Greenland Eskimo population.

Given that our results demonstrated no significant difference in CCT between male and female subjects, or between the U.K. and Australian groups, combined analysis of the sample populations was justified. The mean CCT in the total study group (mean, 544.5 μm; 95% CI, 472–617) was similar to that generated by a recent meta-analysis of normal white adult CCT, which found a mean of 535 μm (95% CI, 474–596). Twins have been found to be very similar to singletons for many complex traits, and the equal-environment assumption of twin studies is now widely accepted. The similarity of results between the U.K. and Australian twins, in conjunction with the

Table 2. Intraclass Correlations between MZ and DZ Twins of Different Gender

<table>
<thead>
<tr>
<th></th>
<th>F/F</th>
<th>M/M</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>MZ</td>
<td>DZ</td>
</tr>
<tr>
<td>Number (U.K./Australian)</td>
<td>228 (126/102)</td>
<td>148 (108/40)</td>
</tr>
<tr>
<td>Mean age in years (SD)</td>
<td>40.8 (15)</td>
<td>39.4 (11)</td>
</tr>
<tr>
<td>Mean CCT (μm) (SD)</td>
<td>540.9 (39)</td>
<td>545.2 (34)</td>
</tr>
<tr>
<td>Intraclass correlation of mean CCT</td>
<td>0.95</td>
<td>0.54</td>
</tr>
</tbody>
</table>

F/F, same-sex female twin pairs; M/M, same-sex male twin pairs; Mixed, mixed-sex twin pairs.
wide age range and open sampling method (population-based volunteer recruitment unselected for eye disease), may make our results generalizable to other white populations. However, racial differences in CCT have recently been highlighted through several population studies. Nemesure et al.\(^\text{29}\) reported that CCT was thinner among the black Barbados population compared with the white Barbados population (mean \(529.8 \pm 37.7 \mu \text{m}\) vs. \(545 \pm 45.7 \mu \text{m}\)). Mean CCT measurements among Hispanic patients were found to lie between those of African-Americans and a white population.\(^\text{29,30}\) However, Cho and Lam\(^\text{34}\) suggested that the Chinese population has the highest mean CCT (574.5 \(\mu \text{m}\)). Given the difference in CCT between racial groups, our results may not be entirely applicable to those in other populations.

Our data showed a negative association of CCT with age, of marginal significance (correlation coefficient, \(-0.09\); \(P = 0.048\)). Some studies examining the impact of age on CCT have reported no significant association, especially among white populations.\(^\text{30,32–34}\) whereas others have found a definite inverse association for nonwhites.\(^\text{29,35–37}\) There was no correlation of CCT with refractive error in this study (\(P = 0.47\)). Other studies examining this relationship have reported mixed results. In a prospective multicenter study of 896 eyes, Price et al.\(^\text{34}\) found no correlation of CCT with refraction or axial length. Other investigators found CCT to be thinner in myopes.\(^\text{34,38}\)

Although the genes determining CCT in the normal population have not been identified, there are many potential candidate genes including those that are associated with diseases having thick or thin CCT phenotypes.\(^\text{11–18}\) Using a combination of genome-wide scan and multipoint linkage analysis, a sibling pair study of the DZ twins from this sample population have met with limited success as a result of candidate genes including those that are associated with diseases having thick or thin CCT phenotypes.\(^\text{11–18}\) Searching for POAG genes other than myocilin, optineurin, and WDR36 has been difficult. Linkage studies, even of large families, have met with limited success as a result of genetic heterogeneity and the age-dependent phenotype. Sib-pair studies have yielded a large number of genetic regions of interest but with uncertain significance. Determining the most heritable ocular structures or physiological processes will allow recategorization of the glaucoma population and the potential for regression-based linkage approaches to help dissect this complex phenotype, as has been performed for other complex traits.\(^\text{39}\) Our preliminary data suggest that CCT is more heritable than optic disc cup area (0.86) (Poulsen JL et al.\(^\text{JOVS 2005;46:ARVO E-Abstract 1092}\), refraction (0.85),\(^\text{30}\) and IOP (0.7) (MacKinnon J et al.\(^\text{JOVS 2004;45:ARVO E-Abstract 4390}\)). We have demonstrated that genetic effects play an important role in CCT, with an estimated heritability of 0.95. These results may lead to the discovery of further glaucoma-related genes.

### Acknowledgments

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