Heritability of Central Corneal Thickness in Nuclear Families

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PURPOSE. Many ocular parameters show strong heritable tendencies. The significance of central corneal thickness (CCT) in the context of glaucoma has been the subject of much debate recently, but its heritability has not been extensively explored. This study was designed to investigate the parent–child heritability of CCT among groups who have CCT considered to be at the extreme ends of the normal range.

METHODS. Index cases were recruited through a tertiary referral center if their CCT was greater than 578 μm (thick) or less than 510 μm (thin), representing ±1 SD from a previously published meta-analysis mean of 544 μm (±0.3 μm SD). Subsequently, CCT was measured in all available family members of the index cases. Family units were then analyzed to estimate the degree of heritability of CCT from parent to child.

RESULTS. Thirty-three index cases were included in the analysis (10 >1 SD and 23 <1 SD from the meta-analysis mean CCT). The mean CCT of the children of index cases with a CCT more than 1 SD from the mean (n = 15) and less than 1 SD from the mean (n = 40) was 568 μm (±0.3 μm SD) and 521 μm (±0.2 μm SD), respectively (t = 6.14; P < 0.0001). The parent–child heritability estimate for CCT was h^2 = 0.68 (95% CI, 0.64–0.75).

CONCLUSIONS. These results indicate that CCT shows strong parent–child heritability, with offspring likely to demonstrate CCT similar to the parental index case. (Invest Ophthalmol Vis Sci. 2009;50:4087–4090) DOI:10.1167/iovs.08-3271

Many ocular parameters, including corneal curvature, anterior chamber depth, and axial length, show strong heritable tendencies.1, 2 Risk factors for ocular diseases such as open-angle glaucoma may also demonstrate heritability,3 as can various ocular disorders.1, 4–8 The significance of central corneal thickness (CCT) has been the subject of much debate in the literature recently. CCT varies widely between healthy persons and those with various ocular and systemic conditions.9–15 Normal CCT has a mean value of 544 μm and has 95% confidence intervals (CIs) that range from approximately 577 μm to 610 μm.6 However, glaucoma and glaucoma-suspect patients may have CCT that differs from this mean. The mean CCT among patients with ocular hypertension has been reported to be thicker than normal (563 μm),7 whereas patients with normal tension glaucoma have thinner than normal CCT (504 μm).9 By comparison, those with primary open-angle glaucoma have CCT that does not differ significantly from normal (542 μm).9 There is a relationship between CCT and the risk for glaucoma14, 15 and progression in glaucoma severity.16–18 In the Ocular Hypertension Treatment Study (OHTS), the mean CCT was 575 μm; however, patients with ocular hypertension and CCT values in the lowest one-third of the participants (<555 μm) were more likely to develop glaucoma.14 Surprisingly, in the OHTS, a self-reported positive family history of glaucoma was not found to be associated with the development of glaucoma. Because patients with ocular hypertension have significantly increased CCT,2 we speculated that if CCT shows high heritability in nuclear families, then perhaps some cases of self-reported family history of glaucoma in the OHTS were actually family members with ocular hypertension and thick CCT receiving treatment. A familial pattern of CCT might therefore have led to a lack of association between having a self-reported family history of glaucoma and the development of glaucoma.

Two recent twin studies reported the heritability of CCT to be greater than 90%.19, 20 In addition, in a study using optical pachymetry, a CCT heritability of 60% to 70% was reported in nuclear families of Greenland Eskimos.21 In the present study, we used ultrasound pachymetry to investigate the heritability of CCT in nuclear families of index Australian cases at the extreme ends of the normal distribution of CCT.

METHODS

The recruitment of study subjects conformed to the tenets of the Declaration of Helsinki. We recruited 33 index cases through a glaucoma clinic in a tertiary referral center. Inclusion criteria included CCT less than or greater than 1 SD from the meta-analysis mean defined by Doughty6 (544 μm ± 0.3 μm SD). Cases with CCT less than 510 μm were classified as “thin” (Fig. 1), and those with CCT more than 578 μm were classified as “thick” (Fig. 2). All participants were Caucasian of Western European descent. Those with corneal dystrophies, scarring, trauma, edema, ectasias, or evidence of anterior segment inflammation were excluded. We enrolled first-degree relatives of the index cases, consisting of 55 offspring and 10 siblings, who were documented in pedigree diagrams. After each family member received written information regarding the purpose of the study and signed written consent in accordance with the Flinders Clinical Research Ethics Committee, corneal pachymetry was performed with a pachymeter (Tomey AL1000 Bio/Pachymetry unit; Tomey Corporation, Nagoya, Japan). This unit uses a transducer frequency of 20 MHz (±10%) and is accurate to ±5 μm with a resolution of 1 μm. The pachymeter records CCT in 10 sequential measurements, and displays yielded a mean ± SD CCT measurement. Recordings were accepted if the SD from the 10 readings was less than or equal to 3 μm.
Statistical analysis was performed (Statistical Analysis System 6.12; SAS Institute Inc, Cary, NC) and included descriptive statistics, Student’s t-test, Shapiro-Wilk test, and heritability estimate. The heritability estimate ($h^2$) was taken as twice the simple linear regression correlation coefficient of the index parent value against the mid-child value, and 95% confidence intervals for the correlation coefficient were taken as 1.96 times the coefficient SD. In addition, the heritability of CCT was estimated using variance components modeling as implemented in SOLAR version 4.2. The covariate sex was not significant.

The CCT of a subject used in the analysis was considered to be the mean of the two eyes. Test statistics, 95% confidence intervals, and P values are presented. $P < 0.05$ was considered statistically significant.

RESULTS

Thirty-three index cases were entered into the analysis. Twenty-three subjects (14 females, 9 males) had CCT less than 1 SD.
below the meta-analysis mean (thin CCT, <510 μm), and 10 subjects (8 females, 2 males) had CCT more than 1 SD above the meta-analysis mean (thick CCT, >578 μm) (Figs. 1, 2). Among the nuclear family units of thick CCT index cases, the mean CCT of the children \((n = 15)\) was 568 μm (32 μm SD), and among family units of thin CCT index cases, the mean CCT of the children \((n = 40)\) was 521 μm (22 μm SD; Fig. 3). This difference was statistically significant \((t = 6.14; P < 0.0001)\). When the correlation between index parent CCT and the mid-child CCT was examined, it yielded a parent–child heritability estimate for CCT of \(h^2 = 0.68\) (95% CI, 0.64–0.73). Similarly, the calculation undertaken in SOLAR gave \(b^2 = 0.66\), which was highly significant \((P < 0.0001)\). Variance components modeling took into account all pedigree relationships. Furthermore, siblings of thick CCT index cases \((n = 4)\) had a mean CCT of 590 μm (17 μm SD), and siblings of thin CCT index cases \((n = 6)\) had a mean CCT of 507 μm (26 μm SD; \(t = 5.61; P < 0.001)\). However, CCT did not differ significantly between spouses of thick CCT index cases (535 μm; 27 μm SD) and spouses of thin CCT index cases (538 μm; 31 μm SD; \(t = 0.27; P = 0.79)\). Distributions of CCT in all first-degree relatives (offspring and siblings) in each index case category were not significantly different from a normal distribution (Shapiro-Wilk test; \(P = 0.452\) and \(P = 0.553\) for thin and thick index families, respectively).

Among our sample, 50% (3 of 6) of siblings had thin CCT when the index case was thin, with 75% (3 of 4) of siblings had thick CCT when the index case was thick. Among family units with one parent who had a thin CCT, 28% (8 of 29) of offspring demonstrated thin CCT. However, if a family unit had two parents with thin CCT, then 72% (8 of 11) of offspring were similarly thin. A comparable proportion of offspring demonstrated thick CCT when one parent had a thick CCT (3 of 15; 20%). Our sample did not contain family units that had two parents with thick CCT. There were no offspring who exhibited thick CCT when either parent had a thin CCT and vice versa. There was no association between sex and thick CCT \((\chi^2 = 0.42; P = 0.52)\) or thin CCT \((\chi^2 = 0.57; P = 0.46)\) among the offspring. Sex was not significant as a covariate in the variance components modeling \((P = 0.72)\).

**DISCUSSION**

Many aspects of ocular health show elements of genetic and environmental influence in their development. The degree to which a parameter is heritable may indicate how this parameter is associated with disease and may provide insight into the pathophysiology of the associated disease.

We found that CCT showed a significant heritable tendency from parent to child. This could be seen not only in the significant heritability estimate of 0.68 but also in the statistically significant difference in mean CCT between offspring from thick and thin CCT index cases. The excellent correlation between heritability estimates by two different methods provides additional confidence in the results. The highly significant \(P\) value of the variance components modeling highlights
the major effects of genes in determining CCT and validates future attempts to map genes for this potentially complex trait. Environmental factors may have an impact on a family unit, elevating heritability estimates. However, given that CCT changes little throughout adult life and that our data suggest no significant difference between spouses of thin or thick index cases, there does not seem to be a major effect of environment on this trait. Furthermore, our previous twin studies suggested a low environmental component for CCT.19,20

Our sample showed a significant tendency for offspring to have CCT similar to that of index case parents. Because our groups of index cases with thick and thin CCT were based on measurements greater than or less than 1 SD from the population mean, respectively, the chance of anyone being in either of these groups was approximately 16%. However, at least half the siblings of index cases in the thick or thin groups had CCT that was similarly outside the 1 SD cut-off. Furthermore, the number of parents in each family unit who were in either of these groups affected the proportion of offspring who were also within that group. We can conclude from these results that CCT is a heritable ocular parameter, passed down from parent to child. This suggests that it may contribute to the heritable component of complex ocular disease and could be particularly important in primary open-angle glaucoma in which CCT is thought to be an independent risk factor.14 Persons with spurious ocular hypertension caused by markedly increased CCT may be at low risk for glaucoma despite their apparent increase in intraocular pressure (IOP).14 Our findings suggest that persons with thick CCT and ocular hypertension without glaucoma are more likely to have first-degree relatives with similar findings. Some of these may be receiving prescribed topical therapy to treat the apparent ocular hypertension, but may be under the mistaken belief that they have glaucoma (despite the lack of any glaucomatous disc or field changes). Given that this would constitute a self-reported family history of glaucoma, we speculate that this mechanism could account for the lack of family history of glaucoma appearing as a risk factor for conversion of ocular hypertension to glaucoma in the OHTS. Conversely, there is a documented association of thin CCT with more advanced glaucoma. Our results suggest that the siblings and offspring of such persons are likely to have similarly thin CCT and, hence, may be at increased risk, particularly when elevated IOP is used as a criterion for referral to ophthalmologists. An understanding of CCT heritability could flag first-degree relatives of those with severe glaucoma and thin CCT as warranting clinical assessment and more careful surveillance.

The limitations of this study include the fact that the subjects were drawn from an ophthalmic clinic; therefore, this study may not reflect the heritability of CCT in the general population. The reason for this strategy was to provide data of relevance to ophthalmologists assessing patients in the context of ocular hypertension and glaucoma so that valid interpretations could be drawn in the clinical setting. Index cases were only recruited if they had CCT greater than or less than 1 SD from the population mean, without any regard for the CCT of their family members. Family members were measured at a separate time and without investigator knowledge of the CCT of the index case. Therefore, selection and measurement bias should have been minimized.

In conclusion, our results indicate that CCT shows strong parent–child heritability, with siblings and offspring more likely to demonstrate CCT similar to that of their index case sibling or parent. This knowledge has potential implications for screening of family members of patients with glaucoma and ocular hypertension. Clearly, the CCT values of both parents are relevant to the offspring. Further understanding of modes of inheritance and segregation will follow once the genes determining CCT variation in healthy persons are identified.

References