Distribution and Heritability of Peripheral Eye Length in Chinese Children and Adolescents: The Guangzhou Twin Eye Study

Xiaobu Ding, Decai Wang, Qunxiao Huang, Jian Zhang, Jessica Chang, and Mingguang He

Purpose. Peripheral eye length (PEL) provides a measure of overall eye shape, which may play a role in the development of myopia. The current study explores the distribution andheritability of PEL, relative PEL (RPEL, defined as PEL minus axial eye length) and relative ratio PEL (RRPEL, defined as PEL divided by axial eye length) in Chinese children and adolescents.

Methods. Subjects included both male and female youths participating in the Guangzhou Twin Eye Study. Eye length was measured by partial coherence laser interferometry axially, 40° temporally (PEL-T40) and 40° nasally (PEL-N40). Structural equation modeling (SEM) was used to estimate the relative contribution of genetic and environmental factors on PEL, RPEL, and RRPEL, adjusting for age and sex.

Results. We examined 104 monozygotic (MZ) and 54 dizygotic (DZ) twins aged 8 to 20 years old. The intraclass correlation coefficients were 0.89 for PEL-T40, 0.92 for PEL-N40, 0.80 for RPEL-T40, 0.73 for RPEL-N40, 0.77 for RRPEL-T40, and 0.73 for RRPEL-N40 in MZ pairs, and 0.52, 0.50, 0.39, 0.58, 0.37, and 0.58 in DZ pairs, respectively. The best fit adjusted models estimated that additive genetic effects accounted for approximately 86.2%, 89.8%, 79.9%, 75.5%, 77.1%, and 74.5% of the variance for the above mentioned traits, respectively, while dominant genetic effects and shared environmental factors were negligible.


Myopia is the most common cause of visual impairment worldwide, especially in East Asia, where approximately 70% to 80% of urban teenagers are affected. The pathogenesis of myopia is not fully understood, but axial eye length (AEL) is a key measure that correlates with the development and progression of myopia. Prior studies have shown significant correlation between AEL and axial refraction, and changes in AEL are highly correlated with progression of myopia.

Growing evidence suggests that not only AEL, but also peripheral eye length (PEL) and overall eye shape has a significant impact on the development of myopia. Specifically, the oblate eye shape has been shown to have a protective effect, while the prolate eye shape has been associated with increased risk for myopia. Furthermore, Mutti’s study demonstrated that the change of peripheral refraction (PR) was prior to AEL elongation during myopia onset, although the effect was found to be very small (~0.024 diopters [D] of myopic progression per diopter of relative peripheral hyperopia), or even not statistically significant in a study from Singapore.

Given that PEL may play an independent role in the development of myopia and, therefore, may be considered as another quantitative trait relevant to myopia, it is important to understand the genetic contribution to PEL. Prior research in adults has found that genetic variance explained approximately 90% of the total phenotypic variance in AEL. Consistent with these findings, our previous work on PR heritability found that additive genetic effects explained over 80% of the variation in our sample. However, given that PR involves various biometric parameters, it is unclear if a genetic contribution to PR reflects a significant genetic effect on PEL. The aim of this study was to estimate the influence of genetics on PEL using a sample of Chinese twins.

Materials and Methods

Participants

Subjects were drawn from the participants of the Guangzhou Twin Eye Study, which has been described elsewhere. Briefly, the study started in 2006 and so far has completed five consecutive annual follow up visits for a population of more than 1000 twin pairs. For the current study, we enrolled children 8 to 22 years of age who visited the Zhongshan Ophthalmic Center between August 6 and August 24, 2011. Those with manifest strabismus, amblyopia, nystagmus, or any ocular disease causing best corrected visual acuity worse than 20/20 were excluded. In addition, subjects were excluded if a cyclopegic examination revealed a pupil diameter less than 8 mm. The study was conducted in accordance with the tenets of the World Medical Association’s Declaration of Helsinki, and the ethical review board of the Zhongshan Ophthalmic Center approved all procedures. Written informed consent was obtained from subjects or from their parents or legal guardians. Zygosity of all same sex twin pairs was determined at the Forensic Medicine Department of Sun Yat-sen University using a 16 multiplex short-tandem repeat (STR) DNA typing system (Gene Print PowerPlex; Promega Corporation, Madison, WI). Opposite sex twin pairs were assumed to be dizygotic (DZ).

Axial Eye Length Measurement

AEL was measured by optical biometry using the Zeiss IOLMaster (Meditec, Jena, Germany). Five measurements were taken, and if the range of values was greater than 0.10 mm, the outliers were deleted by...
the operator, and the measurements were repeated. Once the variation of five measurements was within 0.10 mm, the measurements were averaged by the IOLMaster to produce a final reading.

**Peripheral Eye Length Measurement**

Before PEL measurements, cycloplegia was induced by two drops of cyclopentolate 1% solution administered 5 minutes apart, followed by a third drop given 20 minutes later. The pupil diameter was measured by an ophthalmologist with a ruler and handheld light after an additional 15 minutes.

PEL was measured with the IOLMaster using a novel approach that has been described in detail elsewhere.\(^{21}\) In brief, two paper strips were placed on the lateral apertures at 50 mm from the central aperture to provide fixation markers for 40° temporal and nasal. The exam was performed first on the right eye after setting the IOLMaster to overview mode. The left eye was covered in order to avoid the binocular vision biasing the fixating angle. The subjects were asked to fixate on the paper strip marker located to their right to provide a temporal field measurement at the 40° angle (PEL-T\(_{40}\)). Five serial measurements of PEL-T\(_{40}\) were made in quick succession without repositioning the subject. Measurements where the signal to noise ratio (SNR) was less than 2.0 were excluded and the subject was remeasured. The PEL-T\(_{40}\) eye length was estimated by taking the average of the five serial measurements. An analogous procedure was followed to collect nasal field measurements at the 40° angle to calculate the PEL-N\(_{40}\) measurements.

**Statistical Analysis**

**Variable Definitions.** The right eye was arbitrarily selected to represent the phenotypic characteristics of each subject. In order to de-emphasize the association between peripheral and axial eye length, we created a composite measure: relative peripheral eye length (RPEL), which was defined as the PEL minus the AEL. Specifically, RPEL-T\(_{40}\) was computed as the PEL-T\(_{40}\) minus the AEL, and RPEL-N\(_{40}\) was defined as the PEL-N\(_{40}\) minus the AEL. In addition, The T\(_{40}\)N\(_{40}\) asymmetry was defined as the PEL-T\(_{40}\) minus the PEL-N\(_{40}\). Furthermore, considering the relative peripheral eye length can also be defined as PEL divided by AEL, we calculated the relative ratio PEL at temporal 40° (RRPEL-T\(_{40}\)), which defined as PEL-T\(_{40}\) divided by AEL, and relative peripheral eye length at nasal 40° (RRPEL-N\(_{40}\)), which defined as PEL-N\(_{40}\) divided by AEL. Myopia was defined as spherical equivalent refractive error of less than or equal to –0.50 D and hyperopia as greater than +2.00 D.

**Classic Twin Analysis.** Twins have been widely used to investigate the relative importance of genetic and environmental factors on the development of complex diseases.\(^{22}\) Twin pairs are either monozygotic (MZ), sharing 100% of their genes, or DZ, sharing on average only 50% of their segregating genes, similar to regular siblings. The basic assumption underlying the classic twin approach used in this study is that the amount of variance attributable to common environmental effects is similar for both MZ and DZ twin pairs, and, therefore, when a trait is influenced by genetic factors, the with-pair resemblance for that trait will be higher in MZ than in DZ twins. To assess the contributions of genetic and environmental effects, the phenotypic variation observed in twin pairs is divided into: additive genetic (A), dominant genetic (D), common environmental (C), and unique environmental (which includes measurement error) effects (E).

**Correlations and Genetic Models.** Intraclass twin correlations were first calculated for MZ and DZ twins. A higher correlation between MZ as compared with DZ twins suggests a genetic influence on the trait. Moreover, a potentially significant dominant genetic effect is suggested when the DZ pair-wise correlation is less than half of the correlation in MZ pairs. Structural equation modeling (SEM)\(^{23}\) was then used to determine the importance of A, D, C, and E effects on eye length measures while accounting for the potential effects of sex and age, two factors that have been found to be significantly associated with AEL in prior studies.\(^{24,25}\) As dominant genetic and common environmental effects cannot be studied simultaneously in twins raised together, these effects were modeled separately. ACE and ADE models were made and the significance of each effect was assessed by comparing the fit of nested models. The most parsimonious model was selected based on a minus twice log likelihood (−2LL) value and \(\chi^2\) test. A significant change in \(\chi^2\) values between the full and reduced model indicates that the parameter removed from the full model was significant and, therefore, should be retained in the model. Conversely, a nonsignificant change in \(\chi^2\) suggests that the parameter eliminated from the full model was not significant and, therefore, should be dropped to achieve parsimony.

Descriptive statistics and intraclass correlations were estimated using Stata10.0 (Stata Corporation, College Station, TX). SEM was conducted using the Mx program (Statistical Modeling, Richmond, VA). The level of statistical significance was set at \(P < 0.05\).

**Results**

One hundred and ninety twin pairs were assessed in the current study (120 MZ and 70 DZ pairs). Of these twins, 32 pairs were excluded: 12 had pupil diameter smaller than 8 mm and 20 pairs had best corrected visual acuity worse than 20/20. Among the twins that met the inclusion criteria (\(N = 158\) pairs, 104 MZ and 54 DZ), 62 pairs were MZ male, 42 were MZ female, 9 were DZ male, 12 were DZ female, and 33 pairs were of mixed sex. The mean (±SD) ages of MZ (14.6 ± 2.8 years) and DZ (14.7 ± 2.8 years) twins were not significantly different (\(t\)test, \(P = 0.912\)). The spherical equivalent (SE) of MZ (−1.64 ± 2.43 D) and DZ (−1.84 ± 2.58 D) first born twins were not significantly different (\(P = 0.572\), \(t\)test). Among the 104 MZ pairs included in this analysis, 27 were emmetropic, 61 were myopic, and 16 pairs demonstrated a difference in refractive status: in 12 pairs, one twin had myopia while the other was emmetropic, and in 4 pairs, one twin was hyperopic while the other was emmetropic. Among the 54 DZ pairs, 10 were emmetropic, 27 were myopic, and 17 pairs had a difference in refractive status in which one twin was myopic while the other was emmetropic.

**Table 1.** Peripheral Eye Length Measurements (Mean ± SD; mm) by Zygosity

<table>
<thead>
<tr>
<th></th>
<th>PEL-(_{40})</th>
<th>PEL-(_{N40})</th>
<th>RPEL-(_{40})</th>
<th>RPEL-(_{N40})</th>
<th>T(<em>{40})(</em>{-N40}) Asymmetry</th>
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</thead>
<tbody>
<tr>
<td>Monozygosity, (n = 104)</td>
<td></td>
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<tr>
<td>The first born</td>
<td>22.96 ± 0.95</td>
<td>23.01 ± 1.04</td>
<td>−1.30 ± 0.58</td>
<td>−1.25 ± 0.53</td>
<td>−0.05 ± 0.32</td>
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<tr>
<td>The second born</td>
<td>22.98 ± 0.95</td>
<td>23.06 ± 1.04</td>
<td>−1.33 ± 0.56</td>
<td>−1.25 ± 0.53</td>
<td>−0.08 ± 0.35</td>
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<tr>
<td>Dizygosity, (n = 54)</td>
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<tr>
<td>The first born</td>
<td>22.97 ± 0.86</td>
<td>23.05 ± 0.91</td>
<td>−1.28 ± 0.58</td>
<td>−1.20 ± 0.66</td>
<td>−0.08 ± 0.37</td>
</tr>
<tr>
<td>The second born</td>
<td>22.84 ± 0.96</td>
<td>22.83 ± 0.95</td>
<td>−1.30 ± 0.55</td>
<td>−1.29 ± 0.61</td>
<td>−0.01 ± 0.32</td>
</tr>
<tr>
<td>Total, (n = 158)</td>
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<tr>
<td>The first born</td>
<td>22.97 ± 0.92</td>
<td>23.02 ± 1.00</td>
<td>−1.29 ± 0.61</td>
<td>−1.24 ± 0.58</td>
<td>−0.06 ± 0.33</td>
</tr>
<tr>
<td>The second born</td>
<td>22.93 ± 0.95</td>
<td>22.98 ± 1.01</td>
<td>−1.32 ± 0.56</td>
<td>−1.26 ± 0.55</td>
<td>−0.06 ± 0.34</td>
</tr>
</tbody>
</table>
PEL-T40, PEL-N40, RPEL-T40, and RPEL-N40 measurements of first born MZ as compared with first born DZ twins (Table 1) were not significantly different: PEL-T40 (22.96 ± 0.95 mm versus 22.97 ± 0.86 mm, \( P = 0.951 \)), PEL-N40 (23.01 ± 1.04 mm versus 23.05 ± 0.91 mm, \( P = 0.476 \)), RPEL-T40 (–1.30 ± 0.58 mm versus –1.28 ± 0.58 mm, \( P = 0.832 \)), and RPEL-N40 (–1.25 ± 0.53 mm versus –1.20 ± 0.66 mm, \( P = 0.608 \)). The distribution of axial, temporal, and nasal PEL are shown in Figure 1. In addition, the asymmetry between PEL-T40 and PEL-N40 within each eye was not significantly different (\( P > 0.05 \)) for both MZ and DZ twin pairs.

Scatter plots of the pair-wise correlation for PEL-T40, PEL-N40, RPEL-T40, and RPEL-N40 between twin pairs by zygosity are shown in Figure 2. Intraclass correlation coefficients (ICCs, equivalent to a pair-wise correlation coefficient) between twin pairs were found to be 0.89 for PEL-T40, 0.92 for PEL-N40, 0.80 for RPEL-T40, 0.75 for RPEL-N40, 0.77 for RRPEL-T40, and 0.75 for RRPEL-N40 in MZ pairs, and 0.52, 0.50, 0.39, 0.58, 0.37, and 0.58 in DZ pairs, respectively (Table 2). All correlations were significant (\( P < 0.05 \)) for both MZ and DZ twins, although correlations were consistently greater in MZ compared with DZ twins. For RPEL-T40 specifically, the DZ correlation was less than half the MZ correlation (Table 2). Several reports have shown an asymmetry between PEL-T40, PEL-N40, RPEL-T40, and RPEL-N40 data. Because the correlation analysis suggested a potentially significant dominant genetic effect for RPEL-T40, an ADE model was initially fit (Table 3). The variation in all PEL measures (PEL-T40, PEL-N40, RPEL-T40, and RPEL-N40) was best explained by AE models. Additive genetic effects (A) explained 86.2% (95% confidence interval [CI]: 81.0%-90.0%) of the phenotypic variance for PEL-T40 and 89.8% (95% CI: 85.9%-92.6%) for PEL-N40. The genetic component of variation was somewhat smaller for RPEL-T40, RPEL-N40, RRPEL-T40, and RRPEL-N40, 79.9% (95% CI: 72.2%-85.4%), 75.5% (95% CI: 66.6%-82.0%), 77.1% (95% CI: 68.40%-83.3%), and 74.5% (95% CI: 65.4%-74.5%), respectively (Table 3).

**DISCUSSION**

This study is the first to investigate the heritability of PEL at 40° using a novel measurement method in 158 Chinese twin pairs. In this sample, our analysis suggests that additive genetic effects are the most important contributor to phenotypic variation in all PEL variables. The estimated proportion of total variation explained by genetic effects was smallest for RRPEL-N40 (74.5%) and greatest for PEL-N40 (89.8%).

Several reports have shown an asymmetry between temporal and nasal refraction, which suggests that the temporal and nasal posterior eye shape may also show asymmetry, but the distribution of this asymmetry remains unclear. In a three-dimensional eye shape reconstruction study of five myopic and two emmetropic patients using MRI, temporal and nasal asymmetry was only found in one myopic subject. Another eye shape reconstruction study using MRI examined 88 eyes of 44 patients with high myopia and 80 eyes of 40 emmetropic patients as controls. They did not find significant asymmetry among emmetropic controls, and while the high myopia group demonstrated asymmetry; it consisted of either nasal or temporal protrusion, whereas previous reports of refraction showed that the nasal field refraction hypermetropic shift was consistently greater than the temporal field refraction. In our present study, we did not find any significant asymmetry between temporal and nasal PEL among 316 subjects, which included 4 hyperopic, 107 emmetropic, and 205 myopic patients. Given these conflicting reports, it remains unclear whether the nasal–temporal refraction asymmetry in moderate myopia can be attributed to eye shape profile.

The relative heritability of ocular biometric traits is commonly adjusted by AEL, which may be used as a fundamental measure to account for overall eye size. For example, in our previous study the relative heritability of anterior chamber depth and lens thickness decreased when adjusted by AEL, but remained significant. Similarly, the relative heritability of PEL decreased slightly after adjusting for AEL but also remained significant, which suggests that the genetic determination of PEL may be independent of AEL. In addition, we further calculated the relative PEL as the ratio of PEL toward AEL and found that the heritability was very similar.

We previously found some shared genetic effects between AEL and stature, however, in a linear correlation model, we did not find statistically significant phenotypic correlation between PEL and height or weight (\( P > 0.05 \)) for all PEL parameters except \( P = 0.037 \) for height in RPEL-T40; therefore, we did not further explore the heritability model for when the effects of height and weight were adjusted.

PR is a complex phenotype involving various biometric variables, including not only PEL but also factors such as corneal refraction and lens refraction. Of these many measures, AEL and PEL are most directly related to eye shape. In the PR study, the temporal–nasal PR asymmetry was also found to be most likely genetically determined, though heritability was only 55%. In the current PEL study, however, we did not find any difference between temporal and nasal PEL. This supports our previous conclusion that the PR asymmetry is not due to PEL, but instead may be due to corneal or lens features.

**Table 2.** Intraclass Twin Correlation Coefficients (95% CI) for All Eye Length Measurements

<table>
<thead>
<tr>
<th></th>
<th>PEL-T40</th>
<th>PEL-N40</th>
<th>RPEL-T40</th>
<th>RPEL-N40</th>
<th>RRPEL-T40</th>
<th>RRPEL-N40</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monozygosity</td>
<td>0.89 (0.82, 0.95)</td>
<td>0.92 (0.85, 0.97)</td>
<td>0.80 (0.71, 0.87)</td>
<td>0.73 (0.63, 0.81)</td>
<td>0.77 (0.70, 0.83)</td>
<td>0.73 (0.65, 0.80)</td>
</tr>
<tr>
<td>Dizygosity</td>
<td>0.52 (0.38, 0.66)</td>
<td>0.50 (0.36, 0.64)</td>
<td>0.39 (0.26, 0.53)</td>
<td>0.58 (0.43, 0.71)</td>
<td>0.37 (0.23, 0.50)</td>
<td>0.58 (0.47, 0.67)</td>
</tr>
<tr>
<td>Total</td>
<td>0.77 (0.70, 0.84)</td>
<td>0.79 (0.72, 0.85)</td>
<td>0.65 (0.57, 0.73)</td>
<td>0.67 (0.59, 0.74)</td>
<td>0.62 (0.51, 0.71)</td>
<td>0.66 (0.56, 0.74)</td>
</tr>
</tbody>
</table>
FIGURE 2. Intrapair correlation for peripheral eye length and relative peripheral eye length in MZ and DZ twin pairs in the Guangzhou Twin Eye Study.
Our study is among the first to evaluate the distribution and heritability of PEL. Measuring PEL in combination with AEL may provide a useful description of eye shape. Given the high heritability of PEL and relative PEL, we hypothesize that genetics play a key role in posterior retinal contour shape. However, when considering our results, it is important to keep in mind that we only examined PEL at 40°, and did not measure PEL at other angles. Although 40° has typically been used in other clinical studies of PR, it is possible that findings may differ when other angle sizes are assessed. In addition, in part due to the fact that most of young participants were myopic, the oblate eyes (PEL > axial length) were uncommon. Therefore, the results may be mainly relevant to myopic eyes.

In conclusion, this study of adolescent Chinese twins found additional genetic effects had a substantial influence on phenotypic variation in PEL and relative PEL. Our findings contribute to the evidence for a genetic as opposed to environmental basis for the development of eye shape.

References


