Shared Genetic Determinants of Axial Length and Height in Children

The Guangzhou Twin Eye Study

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Objectives: To describe the association between axial length (AL) and height and to estimate the extent to which shared genetic or environmental factors influence this covariance.

Methods: Study participants were recruited from the Guangzhou Twin Registry. Axial length was measured using partial coherence laser interferometry. Height was measured with the participants standing without shoes. We computed twin pairwise correlations and cross-twin cross-trait correlations between AL and height for monozygotic and dizygotic twins and performed model-fitting analyses using a multivariate Cholesky model. The right eye was arbitrarily selected to represent AL of participants.

Results: Five hundred sixty-five twin pairs (359 monozygotic and 206 dizygotic) aged 7 to 15 years were available for analysis. Phenotypic correlation between AL and height was 0.46 but decreased to 0.19 after adjusting for age, sex, and age × sex interaction. Bivariate Cholesky model–fitting analyses revealed that 89% of phenotypic correlation was due to shared genetic factors and 11% was due to shared random environmental factors, which includes measurement error.

Conclusions: Covariance of AL and height is largely attributable to shared genes. Given that AL is a key determinant of myopia, further work is needed to confirm gene sharing between myopia and stature.

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Results of population-based studies1-9 have suggested that taller adults and children have greater axial length (AL), although the association with refraction was inconsistent. The eye globe is increased 0.25 mm per 0.1-mm increase in height among adults.10-12 The fact that cessation in growth of AL and height may occur at a similar age13 suggests that these 2 traits may share similar developmental pathways. Although no convincing explanation for these associations has been proposed to date, 2 previous studies13,14 found that correlations between height and refraction remained significant after data were corrected for socioeconomic status variables, such as education and income, suggesting that stature may be a risk factor for myopic development independent of socioeconomic status. Given that stature15 and myopia16,17 are significant genetically influenced traits, we speculate that shared genes or shared environmental factors may explain the association between height and refractive error.

Refraction is a complex phenotype that involves various biometric variables of the eye, including AL, corneal curvature, anterior chamber depth, lens thickness, vitreous chamber depth, and refractive power of the structure. Among these, AL has consistently been shown to be a genetically influenced trait that is closely related to myopia. Therefore, we chose AL in the present study to explore underlying genetic relationships between AL and stature. To the best of our knowledge, this issue has not been investigated before.

Monozygotic (MZ) twins are genetically identical, whereas dizygotic (DZ) twins have, on average, 50% of their genes in common. Quantitative genetic analysis of twins can be used to estimate genetic and environmental contributions to trait variations. In addition, biometrical models based on twin data have been used to estimate shared genetic determinants of
Axial length was measured using a noncontact partial coherence laser interferometry technique (IOLMaster; Carl Zeiss Meditec, Oberkochen, Germany) in a dark room (illumination, <5 lux) before pharmacologic dilation of pupils. The mean of 5 continuous measurements was used. Measurements with a ratio of signal to noise less than 2.0 (displayed as "Borderline SNR" or "Error") or with more than a 0.1-mm difference from the others (displayed as "Evaluation") were deleted and remeasured. The right eye was arbitrarily selected to represent phenotypic characteristics of participants in the data analysis. Height was measured with the participants standing without shoes following a standard protocol. The median values of 3 consecutive readings were then recorded to the nearest 0.1 cm.

DATA ANALYSIS AND GENETIC MODELING

To assess gene sharing between AL and height, we first examined twin pairwise correlations and cross-twin cross-trait correlations for MZ and DZ twins. We then performed model-fitting analyses using a multivariate Cholesky model.

In the classic twin design, the following 4 components comprise the total phenotype variance: additive genetic (A), dominance genetic (D), common environmental (C), and random environmental (E), which includes measurement error. Given the confounding effects of C and D, it is inappropriate to put these 2 factors in the same model. Therefore, we fit ADE and ACE models separately.

The bivariate Cholesky model is shown in Figure 1. Measured phenotypes for twin 1 and twin 2 are shown as rectangles, and latent additive genetic and random environmental factors are shown as circles. A indicates additive genetic factor; a, additive genetic determinants of AL and height; E, random environmental factor; e, additive environmental determinants of AL and height; and 1.0, additive genetic correlation in monozygotic twins; and 0.5, additive genetic correlation in dizygotic twins.

Figure 1. Cholesky model for axial length (AL) and height. Measured phenotypes for twin 1 and twin 2 are shown as rectangles, and latent additive genetic and random environmental factors are shown as circles. A indicates additive genetic factor; a, additive genetic determinants of AL and height; E, random environmental factor; e, additive environmental determinants of AL and height; and 1.0, additive genetic correlation in monozygotic twins; and 0.5, additive genetic correlation in dizygotic twins.

### METHODS

PARTICIPANTS

Study participants were recruited from the Guangzhou Twin Registry, which has been described in depth elsewhere. In brief, this registry was established in Guangzhou City, China, in 2005-2006. All twins born between January 1, 1987, and December 31, 2000, were identified using the official Household Registry of Guangzhou, followed by door-to-door verification. In July and August 2006, we invited twins aged 7 to 15 years (as of July 1, 2006) living in 2 districts for baseline data collection. Among 705 pairs invited, 565 pairs (359 MZ and 206 DZ twins) participated in the study, yielding a participation rate of approximately 80%. For all invited participants, written informed consent was obtained from parents or legal guardians of the twins following an in-depth explanation of the study. Ethical approval was obtained from the Sun Yat-sen University ethical review board and the Zhongshan Ophthalmic Center ethics committee, and the study was conducted in accord with the tenets of the World Medical Association’s Declaration of Helsinki.

In this twin cohort, zygosity of all same-sex twin pairs was determined by 16 multiplex short tandem repeats (PowerPlex 16; Promega, Madison, Wisconsin) at the Forensic Medicine Department of Sun Yat-sen University in 2006. Opposite-sex twin pairs were considered DZ without genotyping.

### EXAMINATION AND MEASUREMENT

Axial length was measured using a noncontact partial coherence laser interferometry technique (IOLMaster; Carl Zeiss Meditec, Oberkochen, Germany) in a dark room (illumination, <5 lux) before pharmacologic dilation of pupils. The mean of 5 continuous measurements was used. Measurements with a ratio of signal to noise less than 2.0 (displayed as "Borderline SNR" or "Error") or with more than a 0.1-mm difference from the others (displayed as "Evaluation") were deleted and remeasured. The right eye was arbitrarily selected to represent phenotypic characteristics of participants in the data analysis. Height was measured with the participants standing without shoes following a standard protocol. The median values of 3 consecutive readings were then recorded to the nearest 0.1 cm.
RESULTS

DESCRIPTIVE STATISTICS

The study included 565 twin pairs (359 MZ and 206 DZ), with AL and height data available for all. The mean (SD) age was 11.7 (2.5) years, and 50.6% were female. The mean (SD) AL and height in this cohort were 23.50 (1.10) mm (range, 20.27-27.11 mm) and 144.3 (14.6) cm (range, 106.5-183.4 cm), respectively. Estimated regression coefficients for AL and height with age, sex, birth order, and zygosity are given in Table 1. Multivariate linear regression models revealed that age and sex were statistically significant for AL ($R^2=0.24$) and height ($R^2=0.76$). However, age × sex interaction was significant for height but not for AL; therefore, correlation coefficients were adjusted for this interaction for AL and height. The regression coefficient for birth order was not significant for AL ($−0.03$, $P=0.22$) for random environmental factors. Bivariate heritability (ie, proportion of phenotypic correlation between AL and height [$r=0.19$]) attributable to shared genetic factors was 89% ($0.19 \times 0.92 \times 0.89/0.19$). Bivariate environmentality (ie, proportion of phenotypic correlation between AL and height attributable to shared random environmental factors) was 11% ($0.22 \times 0.08 \times 0.11/0.19$). These results suggested that phenotypic correlation between AL and height, although modest ($r=0.19$), was largely determined by genetic rather than environmental commonality.

CORRELATIONAL ANALYSES

Table 2 gives phenotypic correlations, twin correlations, and cross-twin cross-trait correlations between AL and height. Unadjusted phenotypic correlation was 0.46, which was highly statistically significant. This correlation remained significant when it decreased to 0.19 after adjusting for age, sex, and their interaction for AL and height. Monozygotic twin correlations exceeded DZ twin correlations for both phenotypes. Cross-twin cross-trait correlations for AL and height were similar in MZ and DZ twins.

MODEL-FITTING ANALYSES

Cholesky Model Fitting

Table 3 gives results of model-fitting analyses. Although ADE and ACE models fit the data well, we selected ADE as the Cholesky full model because the Akaike information criterion was lower in ADE than in ACE. Results suggested that the best-fitting model was model 3, in which additive genetic and random environmental factors exert significant influences on AL and height variations and covariance.

Maximum-Likelihood Variable Estimates

Figure 2 shows standardized Cholesky factor loadings and their 95% confidence intervals in the best-fitting model. Estimates of shared genetic factors computed from the best-fitting model were 89% for AL and 92% for height, confirming substantial genetic influences on these traits. Estimates of shared random environmental factors were 11% for AL and 8% for height. Correlations between AL and height were 0.19 for genetic factors and 0.22 for random environmental factors. Bivariate heri-

Table 1. Multivariate Linear Regression Models for Axial Length (AL) and Height

<table>
<thead>
<tr>
<th>Variable</th>
<th>Estimated Regression Coefficient (95% Confidence Interval)</th>
<th>SE</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.19 (0.16 to 0.22)</td>
<td>0.02</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Sex, female vs male</td>
<td>−0.70 (−1.16 to −0.21)</td>
<td>0.25</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Age × sex interaction</td>
<td>−0.01 (−0.06 to 0.03)</td>
<td>0.02</td>
<td>.62</td>
</tr>
<tr>
<td>Birth order, first vs second</td>
<td>−0.03 (−0.14 to 0.08)</td>
<td>0.06</td>
<td>.57</td>
</tr>
<tr>
<td>Zygosity, MZ vs DZ</td>
<td>−0.01 (−0.13 to 0.10)</td>
<td>0.06</td>
<td>.83</td>
</tr>
<tr>
<td>Height</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>4.39 (4.16 to 4.62)</td>
<td>0.12</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Sex, female vs male</td>
<td>8.42 (4.80 to 12.03)</td>
<td>1.84</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Age × sex interaction</td>
<td>1.05 (0.73 to 1.38)</td>
<td>0.17</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Birth order, first vs second</td>
<td>−0.05 (−0.88 to 0.77)</td>
<td>0.42</td>
<td>.90</td>
</tr>
<tr>
<td>Zygosity, MZ vs DZ</td>
<td>−0.13 (−0.99 to 0.73)</td>
<td>0.44</td>
<td>.77</td>
</tr>
</tbody>
</table>

Abbreviations: DZ, dizygotic; MZ, monozygotic.

Recently, associations between ocular variables and anthropometric measurements of height, weight, and body mass index have received considerable attention. These investigations were unable to quantify shared genetic or environmental contributions to associations among phenotypes (ie, AL, height, and refraction) because results were primarily based on unrelated singletons. To our knowledge, the present study is the first to explore shared genetic and environmental determinants of associations between AL and height in a population-based sample of young Chinese twins.

The association between stature and ocular biometry observed herein is consistent with some findings and inconsistent with others. In a Finnish study and a Danish study, men with myopia were taller than those without myopia, a difference that was not observed among the women. Significant associations between height and refraction were also found in children. Eye globe and body stature are in developmental phases in children, whereas they are stable in adults. Lens opacity may also alter refraction in adults. Although the age range of our twins is large, we conducted model-fitting analyses based on the total sample because such analyses require a large sample. However, when we divided our total sample into 2 age groups (<10 years and ≥10 years) and computed correlations between AL and height in each, no significant difference in correlation was found between the 2 groups, suggesting that the pattern of association be-
Table 2. Unadjusted and Adjusted Phenotypic Correlations and Cross-Twin Cross-Trait Correlations for Axial Length (AL) and Height for Monozygotic (MZ) and Dizygotic (DZ) Twins

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unadjusted</th>
<th>Adjusteda</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Phenotypic Correlations (n=1130)</td>
<td>Phenotypic Correlations (n=1130)</td>
</tr>
<tr>
<td>AL</td>
<td>1.00 [Reference]</td>
<td>1.00 [Reference]</td>
</tr>
<tr>
<td>Height</td>
<td>0.46 (0.42 to 0.51)b</td>
<td>0.19 (0.13 to 0.24)b</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Twin Correlations and Cross-Twin Cross-Trait Correlations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AL1 Height1 AL1 Height1 AL1 Height1</td>
</tr>
<tr>
<td>MZ twins (n=359 pairs)</td>
<td></td>
</tr>
<tr>
<td>AL2</td>
<td>0.92 (0.90 to 0.93)b</td>
</tr>
<tr>
<td>Height2</td>
<td>0.45 (0.33 to 0.53)b</td>
</tr>
<tr>
<td>DZ twins (n=206 pairs)</td>
<td></td>
</tr>
<tr>
<td>AL2</td>
<td>0.47 (0.36 to 0.57)b</td>
</tr>
<tr>
<td>Height2</td>
<td>0.44 (0.32 to 0.54)b</td>
</tr>
</tbody>
</table>

Abbreviation: Ellipsis, not applicable.
b Correlations are significantly different from zero at P<.01.
c Correlations are significantly different from zero at P<.05.

Table 3. Results of Model-Fitting Analyses Using a Multivariate Cholesky Modela

<table>
<thead>
<tr>
<th>Model</th>
<th>Description</th>
<th>df</th>
<th>P Value</th>
<th>Information Criterion</th>
<th>∆χ²</th>
<th>∆df</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Full ADE Cholesky model</td>
<td>11</td>
<td>.80</td>
<td>-14.97</td>
<td>. . .</td>
<td>.80</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Full ACE Cholesky model</td>
<td>11</td>
<td>.71</td>
<td>-13.98</td>
<td>. . .</td>
<td>.71</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Same as model 1 but drop dominant genetic variances and covariances between AL and height</td>
<td>14</td>
<td>.85</td>
<td>-19.27</td>
<td>1.71</td>
<td>3</td>
<td>.64</td>
</tr>
<tr>
<td>4</td>
<td>Same as model 1 but drop additive genetic variances and covariances between AL and height</td>
<td>14</td>
<td>&lt;.001</td>
<td>6.94</td>
<td>27.92</td>
<td>3</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>5</td>
<td>Same as model 3 but drop additive genetic variance unique to AL</td>
<td>15</td>
<td>&lt;.001</td>
<td>569.29</td>
<td>592.26</td>
<td>4</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>6</td>
<td>Same as model 3 but drop additive genetic covariance between AL and height</td>
<td>15</td>
<td>.01</td>
<td>1.99</td>
<td>24.96</td>
<td>4</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>7</td>
<td>Same as model 3 but drop random environmental covariance between AL and height</td>
<td>15</td>
<td>.04</td>
<td>-3.88</td>
<td>19.10</td>
<td>4</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Abbreviations: ACE, additive genetic, common environmental, and random environmental; ADE, additive genetic, dominance genetic, and random environmental; AL, axial length; ellipses, not applicable.
a The best-fitting model is boldfaced.

tween AL and height is similar in younger and older samples in our study. Nevertheless, it will be important to replicate our findings in adults and in large population samples of children with a smaller age range.

In our study, we found a significant association between AL and height (r=0.45). When we adjusted data for age and sex, the correlation decreased (r=0.19) but remained significant. Further modeling results suggest that 89% of adjusted correlation between AL and height (r=0.19) was due to shared genetic factors, and the remaining 11% was due to shared environmental factors. In contrast, analyses of genetic variance of AL suggest that only about 3% was in common with height, and the remaining genetic variance was unique to AL. Axial length and height are likely determined by many genes with small effect sizes. Our findings suggest that pleiotropic effects of these genes may influence the relationship between eye size and stature.

The present study is limited because our conclusions were derived from model-fitting analyses rather than from gene identification studies. Model-fitting analyses test hypotheses indirectly; therefore, only inferences of a genetic association can be made by comparing alternative models. However, the Online Mendelian Inheritance in Man database shows overlap of chromosome regions between loci identified for myopia and stature, supporting our results of shared genetic associations between AL and height. Among loci identified for myopia (MYP1 through MYP14), MYP6 and MYP14 were identified by genome-wide linkage in common myopia among Jewish families. MYP7 through MYP10 were identified by genome-wide linkage in common myopia among DZ twins. The remaining loci were mainly identified by linkage analysis in familial high-myopia cases. Based on a twin cohort, a recent genome-wide linkage study identified the quantitative trait locus for AL on chromosome 3. There have been many reports of quantitative trait loci for stature. Notably, STQTL6 (Xq24-q25) and MYP13 (Xq23-q25) overlapped, whereas STQTL10 (3q23) and MYP8 (3q26), STQTL7 (7q31.3) and MYP4 (7q36), and STQTL12...
Figure 2. Standardized variable estimates (95% confidence intervals) in the best-fitting Cholesky model for axial length (AL) and height. Measured phenotypes are shown as rectangles, and latent additive genetic and random environmental factors are shown as circles. A indicates additive genetic factor; E, random environmental factor.

(4q28-q32) and MPY11 (4q22-q27) were close to each other. Given that GPR126,29 HMGA2,30 ZBTB38,31 CDK6,31 LCORL,31 UQCC,32 and GDF532 genes have been recently identified within quantitative trait loci for stature, the finding of significant shared genes for AL and height in the present study suggests that identified genes for stature may be considered candidate genes for myopia as well.

Axial length may be considered a possible endophenotype for myopia. However, myopia is a complex phenotype involving various biometric variables, and AL is only one of these components. It is possible that genetic and environmental factors related to other myopia-related variables such as corneal refraction and lens refraction differ for AL. Therefore, the genetic covariance identified herein may be applicable only to the association between AL and height, not between myopia and height. On the other hand, it is recognized that myopia may develop with reduction of corneal and lens refractive power in tandem with axial elongation during early development of emmetropia.33 Results of a population-based study34 among 12-year-old Australian children suggested that AL accounted for about half of the refraction variation. A 2008 twin study35 estimated that 50% of genetic covariance in refraction was due to genetic factors influencing AL. Therefore, AL represents one of the most important ocular dimensions related to development of refractive error.

In summary, we confirm that there is a significant association between AL and height in children and that most of this correlation is attributable to genetic covariance between the 2 traits. Given the existence of significant shared genetic factors, we may need to consider pleiotropic effects of myopia and height in future quantitative trait locus–based association studies and gene-searching efforts.

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REFERENCES


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