EXTENDED REPORT

Correlations in refractive errors between siblings in the Singapore Cohort Study of Risk factors for Myopia

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Background: The prevalence of myopia in parts of South East Asia has risen dramatically over the past 1–2 generations, suggesting that environmental factors may be particularly important determinants of refractive development in these populations.
Aim: To assess the contribution of familial factors (shared genes and/or shared family environment) to refractive error and ocular component dimensions of school-aged children in Singapore.
Methods: Data were available for 315 children who had one or more siblings also participating in the Singapore Cohort Study of the Risk factors for Myopia (SCORM). Refractive error and ocular biometric parameters were measured under cycloplegia at baseline when children were 7–9 years, and at yearly follow-up sessions for the next 3 years, using consistent clinical procedures. The time children spent performing a variety of nearwork-related tasks was obtained from questionnaires. Familial influences were assessed by calculating between-sibling correlations.
Results: After adjusting for age and sex, the between-sibling correlation in refractive error was 0.447 (95% CI 0.314 to 0.564), suggesting that familial factors account for 63–100% of the variation in the cohort. The between-sibling correlation for 1-year change in refractive error was similarly high, at 0.420 (95% CI 0.282 to 0.543). All ocular component dimensions were correlated significantly between siblings, especially for corneal curvature and vitreous chamber depth—the major structural determinants of refraction. The amount of time siblings spent engaged in nearwork tasks (reading, watching TV, playing video games, computing) and in outdoor activities was also highly correlated between siblings ($p<0.001$).
Conclusion: Shared genes and/or shared environment are important factors in the refractive development of children in Singapore. Because the time spent in nearwork tasks is highly correlated between siblings, epidemiological studies will benefit from precise, quantitative measures of refractive error in parents and more distant relatives in order to begin to dissociate genetic and environmental sources of variation.

There is compelling evidence for both genetic and environmental influences on refractive development.[1–10] However, the specific genetic polymorphisms or environmental risk factors responsible remain largely unknown. Because myopia is associated with a range of ocular pathologies,[11] greater knowledge of the aetiology of refractive errors could have significant public health benefits by leading to new treatments for slowing the progression of myopia.

Dissociating the effects of genetic and environmental risk factors in multifactorial (complex) diseases is notoriously difficult. However, there may be modest gains in the power to detect environmental risk factors for myopia if genetic sources of variation can be uncovered and accounted for, and vice versa.[12]

Longitudinal studies offer a powerful approach to examine risk factors for myopia. One such longitudinal study, the Singapore Cohort Study of the Risk factors for Myopia (SCORM) is following the refractive development of a large sample of children attending three schools in Singapore.[13–15] We assessed the familial contribution to (1) refractive error; (2) the change in refractive error during a 1-year period; (3) ocular component dimensions; and (4) 1-year change in ocular component dimensions, for pairs of siblings participating in the SCORM. We also investigated the extent to which children's nearwork and outdoor activity habits were correlated, in order to explore whether these environmental factors were likely to have contributed to the resemblance between siblings.

METHODS

Study population and clinical procedures

All children aged 7–9 years at baseline attending three schools in Singapore were invited to participate in the SCORM. Children with syndromic myopia, congenital cataract, serious systemic diseases or who refused instillation of eyedrops were excluded. Written informed consent was obtained after the nature of the study had been explained to parents. The study received approval from the Singapore Eye Research Institute Ethics Committee, and followed the tenets of the Declaration of Helsinki for research involving human subjects. Details of the study have been reported previously.[14 16] Of the 2819 eligible children, 1979 (70.2%) participated at baseline. Follow-up data were collected at yearly visits using the same clinical procedures as at baseline.

Thirty min after the instillation of the last of three drops of 1% cyclopentolate, which were given at 5 min intervals, five consecutive refraction and keratometry readings were obtained (Canon RK5 autokeratorefract-ometer; Canon, Tochigiken, Japan). Residual accommodation was not measured prior to refraction. The mean spherical equivalent (MSE) refractive error was calculated as the sphere power and half the cylinder power in the right eye. Ocular component dimensions were obtained after instillation of one drop of 0.5% proparacaine, using a 10 MHz ultrasound biometer (Nidek Echoscan US-800; Nidek, Tokyo, Japan). The average of six measurements was taken if the SD of the readings was <0.12 mm. If the SD was ≥ 0.12 mm, the six measurements were repeated until the SD was <0.12 mm.

The parents completed a questionnaire at baseline that included questions on the number of books that their children finished reading per week in the past year, the number of hours per day

Abbreviations: MSE, mean spherical equivalent; SCORM, Singapore Cohort Study of the Risk factors for Myopia

spent watching TV, playing video games, using a computer, reading and the number of hours per week playing outdoors.

Three hundred and fifteen children had one or more siblings also participating in the study. We removed the two known pairs of twins, as well as three siblings from a sibship in which two siblings shared the same age (potential twins). This left 306 subjects for analysis, including 4 families each with 3 participating siblings. These 3-sibling families each permitted 3 sets of pairwise sibling comparisons, giving a total of 159 possible pairwise comparisons for the final dataset. The ethnic distribution of the 159 pairs of siblings was Chinese, 98 pairs (62%); Malay, 53 pairs (33%); and Indian, 8 pairs (5%). In the experience of SMS, it is very unlikely that siblings in Singapore live in different households. The mean (SD) age difference between siblings was 1.4 (0.6) years.

Trait magnitude data analysis

We analysed data for each subject's most recent visit, under the assumption that this would represent the best available indicator of the subject's refractive error and eye size in adulthood. The subject's age at the latest visit was coded separately for each trait being considered. All ocular component dimensions had a normal frequency distribution, whereas the distribution of MSE was leptokurtotic and skewed towards myopia (Kolmogorov–Smirnov test; $p<0.001$). Since arithmetic transformations did not remove the non-normality, a ranking-based method of transformation was used.[17] Linear regression and correlation analyses were carried out using SPSS V.12. As Pearson and Spearman correlations were similar (for these and subsequent analyses), only the Spearman correlations are reported in the Results section.

Odds ratios (ORs) were calculated in the 147 sibships containing 2 siblings. For these calculations, myopia, moderate myopia and high myopia were classified as untransformed refractive errors (MSE) in the right eye at the latest visit of $\leqslant -0.50$, $\leqslant -3.00$ and $\leqslant -6.00$, respectively.

Change in trait magnitude data analysis

Each subject's 1-year change in trait value was averaged across all available years and then adjusted for the effects of age and sex using linear regression. Statistical outliers were detected and removed before averaging. The frequency distributions of the 1-year changes were all non-normal, except for axial length. However, unlike with MSE, simple log or power functions were sufficient to transform the data to normality (not shown). Between-sibling correlations were calculated as described above.

RESULTS

Refractive error and ocular component dimensions

There were 159 sibling pairs in the SCORM cohort available for analysis after the removal of twins, and using all 3 potential pairwise comparisons for sibships comprising 3 siblings. After adjusting for age and sex using linear regression, there were significant between-sibling correlations in the magnitude of all the traits investigated (table 1). Refractive error, corneal curvature and vitreous chamber depth were the most highly correlated traits, suggesting that familial factors are important determinants for these traits. Anterior chamber depth seemed to be the least familial trait.

Table 1 Correlations in trait magnitudes between siblings

	Correlation	95% CI	Significance (p value)
MSE (transformed)*	0.447	0.314 to 0.564	<0.001
MSE (non-transformed)	0.458	0.327 to 0.574	<0.001
Corneal curvature	0.442	0.309 to 0.560	<0.001
Anterior chamber depth	0.182	0.028 to 0.329	0.023
Lens thickness	0.293	0.145 to 0.430	<0.001
Vitreous chamber depth	0.407	0.270 to 0.530	<0.001
Axial length	0.364	0.222 to 0.493	<0.001

MSE, mean spherical equivalent.
All measures are for the right eye only, and are adjusted for the effects of age and sex.
*MSE was transformed to normality using a rank-based strategy (see Methods section).

In the 147 sibships containing 2 siblings, the OR for myopia was 3.24 (95% CI 1.61 to 6.52; $p<0.001$), and the OR was 2.90 (95% CI 1.31 to 6.44; $p<0.01$) for moderate myopia. Too few children were highly myopic to provide a reliable estimate of the OR for high myopia (OR 11.50, 95% CI 0.91 to 145.20).

One-year changes in refractive error and ocular component dimensions

The average yearly changes in refractive error and ocular component dimensions were calculated for each sibling in the SCORM cohort, and then adjusted for the effects of age and sex. Table 2 shows sibling correlations for these 1-year changes in trait magnitude. There was strong evidence for a familial contribution to the changes in refractive error and vitreous chamber depth.

Exposure to environmental risk factors

As table 3 shows, the time spent engaging in each of the nearwork-related activities examined was significantly correlated between siblings. This was also true of the time children spent playing outdoors.

DISCUSSION

Familial factors gave rise to a highly significant similarity between siblings for refractive error: the correlation in MSE suggests that familial factors account for 63–100% of the variation of refractive error in this population (as estimated from twice the 95% CI for transformed MSE). Interestingly,

Table 2 Correlations between siblings for one-year changes in trait magnitudes

	Correlation	95% CI	Significance (p value)
MSE*	0.420	0.282 to 0.543	<0.001
MSE (non-transformed)	0.433	0.297 to 0.554	<0.001
Corneal curvature*	−0.036	−0.194 to 0.123	0.661
Anterior chamber depth*	0.071	−0.093 to 0.232	0.392
Lens thickness*	0.190	0.031 to 0.341	0.018
Vitreous chamber depth*	0.348	0.201 to 0.481	<0.001
Axial length	0.214	0.056 to 0.362	0.010

MSE, mean spherical equivalent.
All measures are for the right eye only, and are adjusted for the effects of age and sex.
*Values were transformed to normality prior to regression and correlation calculations, as described in the Methods section.

Table 3 Correlations between siblings for engagement in nearwork tasks

	Correlation	95% CI	Significance (p value)
Reading (h)	0.603	0.494 to 0.695	<0.001
Books per week	0.443	0.310 to 0.561	<0.001
Outdoor activity (h)	0.517	0.387 to 0.629	<0.001
TV (h)	0.576	0.463 to 0.672	<0.001
Video games (h)	0.555	0.437 to 0.656	<0.001
Computing (h)	0.641	0.540 to 0.726	<0.001

rates of refractive progression were also highly correlated between siblings, consistent with the above conclusion. Again, this could be due to similar genetic susceptibility, similar lifestyle behaviours or a combination of the two.

If siblings do not share similar levels of exposure to environmental risk factors for myopia, then one can conclude that familial resemblance must be wholly genetic in origin. Under these circumstances, and if one further assumes that all genetic variation is the result of additive polygenes, then the heritability of refractive error can be calculated as twice the correlation between siblings (which would give a heritability of about 0.90 for children in the SCORM). However, our results show that the assumption that siblings do not share similar levels of exposure to risk factors for myopia is probably wrong. Exposure to all the putative risk factors studied here was highly correlated between siblings. Thus, for siblings participating in the SCORM, it is not possible to unravel the influence of shared genes and shared environment.

Few studies have reported sibling–sibling correlations for refractive error.[18–20] In the study by Young *et al*[19] the brother–brother correlation for refractive error (r = 0.32) was lower than the sister–sister correlation (r = 0.72), with the brother–sister correlation being intermediate (r = 0.45). A similar pattern was evident for the children in the SCORM cohort (table 4). However, the sex differences observed here were not statistically significant.

Conclusions

Precise distinctions between genetic and environmental sources of variation are inevitably artificial[21] and can be difficult to interpret.[22] Perhaps more important is that risk factors for myopia are discovered at all, rather than whether they are subsequently deemed to be genetic or environmental in origin, and genetic versus environment distinctions may be helpful to this end. Between 63% and 100% of the variance in refractive error of children in the SCORM can be explained by familial factors. However, our results suggest that epidemiological data collected from siblings alone do not permit the partitioning of the observed variation in refractive error into genetic and environmental sources. Thus, the collection of quantitative measures of refractive error in parents and more distant relatives, or detailed molecular genetic analysis of children in the study cohort, may be valuable strategies in the future.

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Table 4 Correlations between same-sex and brother–sister sibling pairs

	Correlation	95% CI	Significance (p value)	n†
MSE*				
Brother–brother	0.029	−0.317 to 0.369	0.873	33
Brother–sister	0.546	0.392 to 0.673	<0.001	98
Sister–sister	0.585	0.281 to 0.791	0.001	28
Corneal curvature				
Brother–brother	0.272	−0.074 to 0.566	0.120	33
Brother–sister	0.474	0.306 to 0.616	<0.001	98
Sister–sister	0.501	0.166 to 0.741	0.007	28
Vitreous chamber depth				
Brother–brother	0.144	−0.213 to 0.471	0.429	32
Brother–sister	0.412	0.234 to 0.566	<0.001	97
Sister–sister	0.666	0.400 to 0.836	<0.001	28
Change in MSE*				
Brother-brother	0.398	0.070 to 0.656	0.038	33
Brother–sister	0.41	0.229 to 0.566	<0.001	95
Sister–sister	0.542	0.214 to 0.769	0.003	27
Change in vitreous chamber depth*				
Brother–brother	0.247	−0.114 to 0.556	0.193	31
Brother–sister	0.269	0.072 to 0.448	0.010	94
Sister–sister	0.609	0.309 to 0.807	0.001	27

MSE, mean spherical equivalent.
All measures are for the right eye only, and are adjusted for the effects of age and sex.
*Values were transformed to normality before regression and correlation calculations.
†Number of sibling pairs.

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