The Role of Educational Attainment in Refraction: The Genes in Myopia (GEM) Twin Study

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Purpose. Educational attainment has been proposed as one of the most consistent environmental risk factors associated with myopia. The Genes in Myopia (GEM) twin study is the first myopia twin study to determine the relative genetic contribution in educational attainment as well as assessing the shared genetic and environmental factors between educational attainment and refraction through structural equation modeling.

Methods. All twins from Victoria aged 18 years or older were invited to participate in this study through the Australian Twin Registry (ATR). Each twin completed a general questionnaire, and a comprehensive eye examination was undertaken. Education level was categorized to provide a level of attainment.

Results. A total of 612 twin pairs with a mean age of 52.36 years were examined. Higher educational attainment was significantly associated with a more myopic refraction ($r = -0.21$, $P < 0.01$), with educational attainment explaining 4.41% of the total variance in refraction. Findings from the GEM twin study found that genes (additive genetic effects) explained 69% of the variance in educational attainment and common and unique environmental factors accounted for 20% and 11% of the variance, respectively. Of the genetic influences on refraction, 3.2% were common with those influencing educational attainment.

Conclusions. The GEM twin study has shown that educational attainment is strongly influenced by genes, and therefore this risk factor should not solely be considered as an environmental risk factor. The same genetic factors that influence an individual's educational attainment may also be involved in the development of refractive error. (*Invest Ophthalmol Vis Sci.* 2008;49:534–538) DOI:10.1167/iovs.07-1123

Approximately 20% to 25% of individuals in Western populations have myopia or near-sightedness,[1,2] with the prevalence being much higher (80%) in urbanized areas of Asia.[3–5] Myopia is a complex eye disease in which both environmental and genetic factors appear to play a role in its development; however, their relative contributions remain unclear.[6] Major evidence to support a genetic contribution to myopia has come from twin studies and family-based linkage studies. Several twin studies[7–10] have collectively provided evidence to support a major genetic component, with concordance for myopia between identical (monozygotic) twins ($r > 0.80$) approximately twice that for myopia in nonidentical (dizygotic) twins ($r < 0.4$). As such, heritability estimates from twin studies range from 60% to 90% for refraction[11] and ocular biometric measures.[8] More recently, family-based linkage studies have identified at least 14 myopia loci (MYP1 to -14) associated with all forms of myopia.[12] So far, no gene(s) have been significantly associated with myopia in these regions.

Several environmental risk factors have been implicated as playing a role in myopia including intelligence and, most frequently, near-work activity.[13] However, these risk factors explain only between 2% and 13% of the total variance found in myopia.[14–16] For instance, a recent study by Saw et al.[16] examined refraction in 1204 Chinese school children aged 10 to 12 years as part of the Singapore Cohort Study of the Risk Factors for Myopia (SCORM). They found that environmental risk factors (nonverbal intelligence quotient and books read per week) explained 11.6% of the variance in myopia.[16] Nonetheless, considering myopia is complex in nature, it is essential to understand whether such risk factors are purely environmental or whether they share a common genetic basis with myopia. First, the etiology of these risk factors must be elucidated. For instance, what combination of social, cultural, environmental or genetic influences constitutes an individual's educational attainment?

Considering the difficulty of obtaining accurate measures of near-work activity retrospectively, it is common for studies to use educational attainment as a surrogate measure for near work in studies of myopia.[17] Studies into educational attainment have reported heritability estimates reaching as high as 60%.[18,19] Baker et al.[20] reported that additive genetic factors explained approximately 60% of the variance in the number of years of education in Australian twin pairs with 20% of variation attributable to the environment shared between pairs. Silventoinen et al.[21] surveyed 1598 twin pairs from Minnesota and 5454 from Finland and found that the crude heritability estimates for educational attainment (twice the difference between MZ and DZ intrapair correlations) ranged from 30% to 50%. Although these findings suggest both environmental and genetic components to educational attainment, the ophthalmic literature generally considers educational attainment as an environmental risk factor for myopia. A previous twin study of 114 twin pairs investigating myopia reported a significantly lower median intrapair-wise difference in educational attainment in MZ (monozygotic) twin pairs (0.0 years, 0.0–5.5 years) compared to DZ (dizygotic) twin pairs (1.0 year, 0.0–8.0 years).[10]

The use of twin studies is an effective tool in exploring gene–environment interactions (the magnitude of the effect of a genetic variant caused by a change in the environment) by quantifying the genetic component in disease while accounting for environmental factors in the same individuals. Jinks and Fulker[22] introduced a test to detect gene–environment interactions in disease through the analysis of MZ twin pairs. A gene–environment interaction is indicated when absolute differences (MZ twin 1 − MZ twin 2 = environment effects) for any measure of interest in MZ twin pairs are significantly associated with the corresponding sums (MZ twin 1 + MZ twin

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2 = shared genetic effects) of that measure in the same MZ twin pairs. Chen et al.[23] provided some insight into the potential for interplay between genes and the environment by showing that twin pairs who were concordant for reading habits had a higher concordance for myopia compared with those who were discordant for reading habits. However, they assessed twin pairs aged 10 to 15 years, where myopia may still be developing and therefore their concordance levels may hold true only at the time the children were examined. However, a gene–environment interaction has been indicated by only one previous twin study by Lyhne et al.[10] Using the Jinks and Fulker test and they reported a significant relationship ($r = 0.32$, $P < 0.05$) between absolute differences and the corresponding sums for myopia between MZ twin pairs.

The GEM twin study will be the first twin eye study to quantify the genetic component in educational attainment, determine whether genetic factors are common between educational attainment and refraction, and provide some insight into potential for gene–environment interactions in refraction. Using measures of myopia and reports of educational attainment, we sought to determine whether, of the genetic influences on myopia, some are common with those that influence education. From these analyses, the GEM twin study will provide some direction for research into putative gene–environment interactions in myopia and provide a better understanding as to the role of educational attainment in myopia.

Materials and Methods

Subjects and Recruitment

Twins of either gender, aged 18 years or older, with or without known eye disease were invited to participate in the GEM twin study. They were recruited from the Australian Twin Registry (ATR) located at the University of Melbourne, Victoria, Australia, a national registry of twin pairs (>31,000 registered twin pairs) who are willing to consider participating in twin studies. Approximately one third of all twins registered at the ATR reside in the state of Victoria. All twins registered as residing in Victoria were sent a letter of invitation, an information sheet, and a consent form from the ATR. Where both twins wished to be included, they were contacted directly to arrange appointment times for examination.

Ethical approval for the GEM twin study was provided by the Royal Victorian Eye and Ear Hospital Human Research and Ethics Committee. In addition, the Australian Twin Registry approved the project. Written, informed consent was obtained from each twin before testing. The protocol adhered to the tenets of the Declaration of Helsinki, and all privacy requirements were met.

Study Protocol

In brief, each individual underwent a general questionnaire, consisting of a medical history, educational attainment scale, and zygosity. In addition, dilated (single drop of tropicamide 1% at least 15 minutes before auto-refraction) autorefraction was obtained from each individual using an autorefractor (model KR 8100; Device Technologies, Melbourne, Australia). Three readings were taken for each eye and the average value recorded. Results for each eye were converted to their spherical equivalent (SE; half the amount of cylinder plus the spherical component). Myopia was defined as SE of equal to or worse than −0.50 D. Please refer to Garoufalis et al.[24] for a more detailed description of the GEM testing protocol.

Educational Attainment

Each individual was given a grade score of 0 to 7, with a grade score of 0 being equivalent to having no formal education and a grade of 7 as at least one degree from a national or internationally recognized university (Table 1). The education grading system assumed that university students had completed both primary and secondary education. No extra scores were given to participants who had completed a trade/TAFE (Technical and Further Education), as well as a university degree, or when an individual had obtained an additional postgraduate qualification. All individuals who had completed or were attending TAFE were considered to have at least completed 3 years of secondary school.

Table 1. Educational Attainment Scale

Group	Educational Classification
0	No education
1	Primary education incomplete
2	Completed primary education
3	Completed primary education and some years of secondary education
4	Completed primary and secondary education
5	Completed/attended trade school or TAFE
6	University attendance
7	University degree completed

TAFE, technical and further education.

Zygosity

Twin zygosity was determined by a series of questions recommended by the ATR.[25] These questions were validated as having a 95% accuracy in determining correct zygosity.[26] In the GEM twin study, the most of the twins were themselves aware of their zygosity, either due to their upbringing, physical and psychological similarities, or prior zygosity testing in other twin studies. Moreover, in cases where zygosity was uncertain ($n = 20$ twins), standardized genotyping using a panel of 12 polymorphic markers (Linkage Mapping Set version 2; ABI)[27] was performed by the Australian Genome Research Facility, Melbourne. The results of this genotyping were in complete agreement with the zygosity as previously determined by the examiner based on the series of twin questions and the assessment of physical characteristics in all cases.

Statistical Analysis: Modeling of Variance Components

Genetic modeling is primarily used to quantify the proportion of phenotypic variance attributable to either genetic or environmental factors. The phenotypic variance is then separated into additive genetic effects (A), nonadditive genetic effects (dominance or epistatic interactions (D), environment influences shared between siblings reared together (C), and individual specific environmental effects (E). Additive genetic effects are the sum of allelic effects that influence the trait. Common environmental influences typically refer to shared environments, such as similar schooling, housing, and other commonly shared environments. E has two components: first, individual specific environmental effects, such as smoking, and second, measurement error. Fitting a model with all parameters specified, parameters were removed in a step-wise manner. Twice the difference in log likelihoods between the full and submodels is distributed as χ^2, with the degrees of freedom equal to the difference in degrees of freedom between the two models (likelihood ratio test).[28]

A model with additive genetic, common environmental and unique environmental parameters (ACE) was fitted to educational attainment since the intrapair correlation for MZ twins was less than double the intrapair correlation between DZ twin pairs. The formulas given to explain C is ($C = 2r_{DZ} - r_{MZ}$), where r_{MZ} is the intrapair correlation for MZ twins and r_{DZ} is the intrapair correlation for DZ twins. Therefore, when the MZ intrapair correlation is more than double that of the DZ intrapair correlation, C would be estimated at 0. Heritability was defined as the phenotypic variance that can be explained by additive and nonadditive genetic effects.

The bivariate Cholesky decomposition model[29] was fitted to educational attainment and refraction to determine the extent to which genetic and environmental effects influencing educational attainment also influence refraction. In brief, the Cholesky model allows decomposition of variation in myopia into that due to genetic and environmental influences common with education and those specific to myopia. The approach to modeling is such that, initially, a model is specified that has all possible parameters. Parameters are then removed in a stepwise manner, and the subsequent, nested model is compared to the full model to see whether there is a significant difference in fit. Although the correlation between DZ twins for refraction was lower than half the correlation between MZ twin pairs for myopia, an ACE model was fitted, to address the specific question of environmental influences. Quantitative genetic modeling was achieved by using the Mx statistical program,[30] and all descriptive statistics were obtained with commercial software (SPSS ver. 12.1; SPSS, Chicago, IL).

Results

Recruitment

A total of 612 twin pairs (1224 twins) were recruited and examined in the GEM twin study, with 345 (56.4%) being MZ twin pairs and 267 (43.6%) being DZ twin pairs. There was almost double the number of female twins (806 twins, 65.8%) as there were male twins ($n = 418$ twins, 34.2%; $P < 0.05$), this phenomenon being common in a number of twin studies.[31]

Prevalence of Myopia

Of the 1224 twins examined, a total of 54 twins (33 MZ twins and 21 DZ twins) had no objective refraction measurements, leaving 1170 twins to estimate the prevalence of myopia in the GEM twin sample. Myopia (≤ −0.50 D) was found in 347 of 1170 twins (29.66%). Of the twins with myopia ($n = 347$ twins), low myopia (between −0.50 DS and −2.99 D) accounted for 70.03% (243/347) of myopia, followed by moderate myopia (between −3.00 DS and −5.99 D; 80/347, 23.05%), and high myopia (24/347, 6.92%; ≤ −6.00 D, −6.00 to −14.50 D).

Distribution of Education Attainment for all Individuals

Educational attainment was obtained for 1184 individuals (664 MZ twins, 520 DZ twins). All individuals had completed at least 3 years of secondary school (group 3) with 6.50% (77/1184) having completed a TAFE course and 14.27% (169/1184) having only a secondary or high school completion. More than one-third of individuals had either commenced or completed a university degree (463/1184, 39.10%), with 475 (40.13%) individuals completing some years of secondary school.

Educational Attainment by Zygosity, Gender, and Age

There was no significant difference in educational attainment between MZ and DZ twins, with 40% of MZ twins and 38.5% of DZ twins attending or completing a university course, respectively ($P > 0.05$). A higher proportion of the men (187/383 = 48.83%) were found to have completed or were attending university compared with the women (276/801 = 34.46%); however, this did not reach statistical significance ($P > 0.05$). There was a significant difference in mean age of individuals who had completed at least secondary school (54.94 years), compared with those who were attending or completed a university course (47.19 years; $P < 0.01$) with approximately 60% of individuals with university attendance being 55 years of age or less.

The Relationship of Refraction and Educational Attainment

Spearman's Rho correlations showed that educational attainment was significantly associated with refraction ($r = -0.21$, $P < 0.001$); however, educational attainment only explained 4.41% ($r^2 = 0.04$) of the total variance in refraction. A one-way ANOVA showed that mean scores for refraction between education groups were significant ($F = 1439.35$, $P < 0.001$).

Genetic Component in Educational Level

Case-wise concordance for education showed that a co-twin of an MZ twin had an 89% chance of having or obtaining the same level of education compared with a 71% chance for a co-twin of a DZ twin ($P < 0.05$). Monozygotic and DZ intrapair correlations for education were not significantly different when they were compared in groups of differing levels of myopia (Table 2), but this finding may be due to the small sizes in each group.

Gene–Environment Interactions

An absolute difference in refraction in MZ twin pairs correlated significantly (Spearman's rank correlations, nonparametric) with the sum of refraction between MZ twin pairs (0.38, $P < 0.01$) and therefore supported a gene–environment interaction in refraction.

Heritability Estimates for Educational Level

The MZ intrapair correlation ($r = 0.79$) for education level (categorical data) was less than double that of the DZ intrapair correlation ($r = 0.50$), and therefore the ACE model was used to obtain the heritability estimate for educational attainment. There were no indications of gender-specific effects, as the variance for educational attainment was similar between males and females, and the twin pair correlations between opposite-sex twins were comparable to their same-sex DZ counterparts. Overall, the heritability estimates show that additive genetic effects explained 69% (62%–74%) of the variance with common and unique environmental factors explaining 20% and 11%, respectively. Common environmental influences could be removed as a source of variation without a significant difference in fit of the model (Table 3). However, this may be due to a lack of power in this study.

Bivariate Cholesky Decomposition Model for the Covariance between Educational Attainment and Refraction

A bivariate Cholesky decomposition found that the correlation between educational attainment and refraction is due to both environmental and genetic factors common to both measures. Of the genetic influences on myopia, 3.2% [$(-0.16^2/-0.16^2 \times 0.88^2) \times 100$)] were common with those influencing education and 1.7% of total variation in myopia was due to environmental factors common to both twins and influencing both

Table 2. Correlations for Education in MZ and DZ Twins for Refractive Error

		MZ 199	DZ 148	
	n	*r*	*r*	*P*
Low (−0.50 to −2.99 D)	243	0.71	0.48	0.26
Moderate (−3.00 to −5.99 D)	80	0.89	0.42	0.11
High (≤ −6.00 D)	24	0.80	0.79	0.91

P, significance value between MZ and DZ intrapair correlation coefficients. $P < 0.01$ (two-tailed *t*-test).

TABLE 3. ACE Model Fitting for Educational Attainment

Variable	Model	Log-Likelihood	*df*	Ch.fit	Cd.*df*	*P*
Education	ACE	2698.98	1126			
	AE*	2701.32	1127	2.32	1	0.13
	CE	2738.63	1128	37.32	1	<0.001
	E	2755.99	1129	54.68	2	<0.001

A, additive genetics; C, common environment; E, unique environment; *df,* degrees of freedom; ch.fit, χ^2; cd.*df,* difference in degrees of freedom.

* Best fit model, $P < 0.05$.

myopia and educational attainment (Fig. 1). However, it should be noted that although these paths approached significance, a larger study is needed to confirm this pattern of shared genetic and environmental effects.

DISCUSSION

Approximately one in four participants in this study had myopia, a ratio similar to the prevalence of myopia in the general population and comparable to that reported by twin studies in the United Kingdom and Denmark, where approximately one in four individuals 49 to 79 years of age[9,10] had myopia.

In our twin study, educational attainment explained 4.4% (coefficient of determination) of the variation in refraction. This confirmed the findings from a smaller twin study of 114 twin pairs by Lyhne et al.[10] in Denmark, that found that educational attainment was negatively associated with refraction ($r = -0.33$, $P < 0.01$), and explained approximately 10.9% of the variance in refraction. We also found that higher education levels are significantly associated with a more negative (myopic) refraction, as previously reported in epidemiologic studies.[32]

Additive genetic factors explained most of the variation (69%) in educational attainment, replicating several previous findings. For instance, in one large Australian twin study investigating educational attainment, it was found that additive genetic factors explained approximately 60% of variation.[20] Although common environmental factors were not a significant contributor to variation, this may be due to the reduced power to detect their effects.[31] From the results of previous studies,[20,21] we would expect that environmental influences common between twins to be a significant contributor to variation in education.

It is possible that monozygotic twins, by virtue of their physical similarity and parental upbringing, experience more similar environments than their nonidentical counterparts. Therefore, it is argued that the higher intrapair correlations in MZ twin pairs compared with that in DZ twin pairs reported in disease is explained by the greater environmental similarity between MZ twin pairs rather than their shared genotypes.[33] Here, intrapair correlations for education in MZ and DZ twin pairs were not significantly different in low, moderate, and high myopia. Furthermore, the GEM twin study attempted to apportion the shared environment component to educational attainment, rather than disregarding the environmental influence involved in educational attainment.

The point estimate from the model suggests that approximately 3.2% of the genetic influences in myopia are shared with those influencing educational attainment. In other words, the genetic factors that influence an individual's educational attainment may also in part be involved in the development of refractive error.

In the GEM twin study, gene–environment interactions were indicated where a genetic component for a known risk factor (educational level) in myopia was identified, which supported the findings from the study by Lyhne et al.[10] Overall, the GEM twin study along with previous twin studies have provided some insights into potential gene–environment interactions in the development of myopia; however, more rigorous and accurate measures on environmental risk factors are needed for a better assessment of this interaction. In addition, to quantify the extent to which environmental factors modify gene function, a polymorphism in the disease of interest (myopia) must be identified.[34]

In the GEM twin study, categorical educational status (group 0–7, with 0 being no education and 7 being tertiary education) was used as opposed to continuous (number of years) educational status. The use of categorical education data may be flawed in that it does not consider individuals with postgraduate tertiary studies and does not accurately reflect the exact number of years of education that individuals have completed. However, Lyhne et al.[10] used continuous educational status and found a modest and similar association between years of education and refractive error to the present study.

It would provide some insight if we could determine whether educational attainment differed in the twins who did not participate in the GEM twin study compared with that of the twins reported in the study. However, only the twins who consented to participate in the GEM twin study were examined, and therefore this analysis was not undertaken. In addition, the ATR does not provide baseline educational attainment measures for all registered twins.

The inclusion of educational attainment in the GEM twin study has provided invaluable insights into the genetic determinants of educational attainment and how this may influence our thinking into risk factors implicated in the development of myopia. Before any risk factor is defined as a product of our environment, it is important to consider the determinants of that risk factor. The GEM twin study, along with previous behavioral twin studies, has shown that educational attainment is strongly influenced by genes, and therefore this risk factor

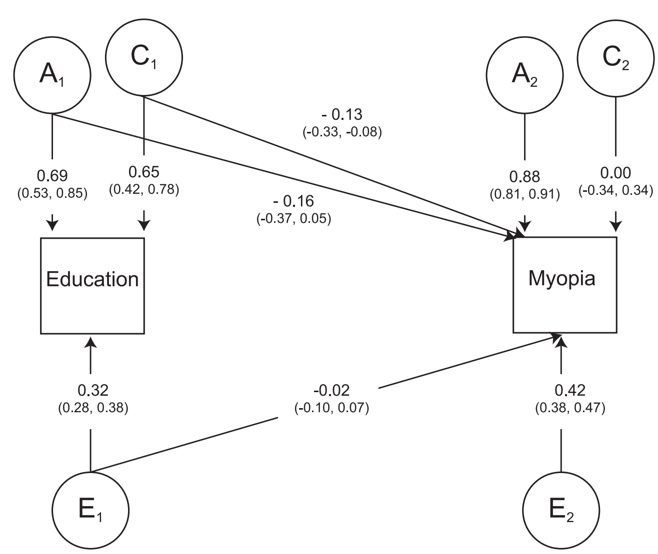

FIGURE 1. Bivariate Cholesky decomposition model for the covariance between educational attainment and refraction. A_1, additive genetics for educational attainment; C_1, common environmental factors for EA; E_1, unique environmental factors and measurement errors for EA; A_2, additive genetics for SE; C_2, common environmental factors for SE; E_2, unique environmental factors and measurement errors for SE.

should not solely be considered as an environmental risk factor. Indeed, other components of the environmental aspects of this risk factor should be considered, such as personality-related, social, cultural, and unique environmental risk factors. Establishing the determinants of each risk factor implicated in myopia will ultimately lead to a better understanding of how these risk factors influence the development of myopia at both the genetic and environmental level and to what extent there may be interactions between these determinants.

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