

Dominant Genetic Effects on Corneal Astigmatism: The Genes in Myopia (GEM) Twin Study

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PURPOSE. This study was conducted to assess the relative influence of genetics and environment on corneal astigmatism and corneal curvature in a large sample of twins.

METHODS. A total of 612 twin pairs (345 monozygotic [MZ] and 267 dizygotic [DZ]) aged between 18 and 86 years (mean age, 52.11 ± 15.85 years) were recruited from the Australian Twin Registry (ATR). Each subject completed a general questionnaire, undertook a dilated eye examination, including ocular biometric measurements, and contributed a blood sample. Corneal astigmatism was defined as the absolute difference between the K1 and K2 meridians and corneal curvature as the average of K1 and K2.

RESULTS. Intrapair correlations were significantly higher ($P < 0.001$) in MZ twin pairs compared with those in DZ twin pairs for both corneal astigmatism (CA; $r_{mz} = 0.48$ vs. $r_{dz} = 0.13$) and corneal curvature (CC; $r_{mz} = 0.84$ vs. $r_{dz} = 0.41$). A sex-limited model with parameters estimating additive genetic, nonadditive genetic, and unique environmental influences (denoted ADE) was the most parsimonious model explaining both measures. Heritability estimates were as high as 60% and 71% for CA and CC, respectively.

CONCLUSIONS. This study provides evidence that genetic factors explain interindividual variation in CA and CC, with nonadditive genetic factors explaining most of the variance due to those genetic factors. Heritability estimates were sex specific and indicate the need for future linkage studies for the identification of genes involved in the etiology of CA and CC. (*Invest Ophthalmol Vis Sci.* 2008;49:1339–1344) DOI:10.1167/iops.07-1011

Astigmatism is a refractive error in which incoming light rays focus at different points, rather than at a single point, on the retina, typically resulting from irregularities in the curvature of the cornea (corneal astigmatism; CA).¹ The prevalence of astigmatism (+0.50 D or worse) has been reported to vary with ethnicity,^{2–5} age,^{4–6} and sex.^{2,7} In the Sydney Myopia Study,⁸ 4.8% of 6-year-old children had refractive astigmatism (worse than or equal to +1.00 D). This prevalence is

comparable to those reported in Finland (3.8%),⁹ southern urban and rural India (3.8%),^{10,11} and Poland (4%).⁷ However, the prevalence of refractive astigmatism in Australian children is much lower than in Chinese (38.6%),¹² Taiwanese (14.6%),³ and Singaporean children (19.2%).¹³ This variation in prevalence of refractive astigmatism with ethnicity is also found in adult populations, with the overall prevalence being higher than that in younger cohorts.^{6,14–16}

Family studies have supported a major role for genetics in astigmatism, with children with astigmatic parents being at a significantly higher risk (approximately two times) of the development of astigmatism than those with nonastigmatic parents.⁶ The first twin study of the genetics of astigmatism, conducted in the early 1950s, showed a high concordance of astigmatism between monozygotic (MZ) twin pairs.^{17,18} This conclusion was challenged by subsequent twin studies.^{19–21} For instance, Teikari et al.²² reported a similar concordance for astigmatism in both MZ and dizygotic (DZ) twin pairs, which implies a stronger role of environmental risk factors. However, there are drawbacks to some methods used to study astigmatism—for instance, postal surveys, sample sizes, and selective age ranges.²¹

A larger twin study (506 female twin pairs) based in the United Kingdom²³ reported findings contrary to those in previous reports and showed a correlation for astigmatism almost four times larger in MZ than in DZ twin pairs, thus suggesting a major role of nonadditive genetics in this phenotype. Further support for nonadditive genetic effects on astigmatism came from a study by Grijbovski et al.,²⁴ who surveyed 3334 twin pairs and found a heritability of 63%, with dominant genetic effects explaining the majority (54%) of the variance in astigmatism.²⁴

The present twin study was conducted to determine the heritability of CA, as well as corneal curvature (CC), in a large sample of MZ and DZ twin pairs of both sexes over a broad age range. In the GEM twin study direct clinical examination was used to address the effects of sex and age in CA and CC.

MATERIALS AND METHODS

Recruitment

Both MZ and DZ twins of either sex, aged 18 years or older were invited to participate in the GEM twin study through the Australian Twin Registry (ATR) located at the University of Melbourne, Victoria, Australia. The ATR is a national registry of more than 31,000 twin pairs, which accounts for approximately 10% of the Australian twin population. Individuals with ocular disorders that may lead to changes in astigmatism, such as corneal dystrophy or keratoconus, were excluded from the main analysis. Twenty-seven individuals were excluded from the main analysis: 20 had visually significant lens opacifications (grade 4 on the Wilmer Grading Scale),²⁵ 4 had strabismus (congenital esotropia), and 3 had glaucoma (managed with medications).

Ethics approval for the GEM twin study²⁶ was provided by the Royal Victorian Eye and Ear Hospital (RVEEH) Human Research and Ethics Committee the ATR. Written informed consent was obtained from each twin before any testing. The protocol adhered to the tenets of the Declaration of Helsinki, and all privacy requirements were met.

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Study Protocol

Each individual completed a general questionnaire and underwent a comprehensive ophthalmic assessment, and individual blood samples for DNA analysis were collected via venepuncture. The protocol of the Genes in Myopia (GEM) study has been reported elsewhere.²⁷ In brief, the general questionnaire consisted of questions on demographics, ethnicity, educational background, and medical and ocular history and a series of questions to determine or confirm the zygosity of the twins.

Zygosity. In the GEM twin study, the twins were asked a series of simple questions in an attempt to determine zygosity. Participants were asked if they were identical twins and if people (besides family and long-term friends) could easily tell them apart. The majority (>95%) of twins were aware of their zygosity, either due to their upbringing, physical and psychological similarities, or previous DNA testing that was performed by other research teams. In cases in which zygosity was uncertain, standardized genotyping with a panel of 12 polymorphic markers (parentage panel; Linkage Mapping Set, ver. 2; Applied Biosystems, Foster City, CA) was performed by the Australian Genome Research Facility.²⁸

Ophthalmic Assessment. A visual acuity assessment, subjective refraction, and dilated objective refraction measurements were obtained in the GEM twin study. The methodology used for these measures is outlined in Garoufalidis et al.²⁷ In brief, an optical biometer (IOL Master; Carl Zeiss Meditec, Oberkochen, Germany) was used in dilated eyes (tropicamide 1%) to obtain CA (the absolute difference between the K1 and K2 meridians) and CC (average of K1 and K2). Dilated autorefractometry was measured with 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 the spherical equivalent (SE; sphere + half the cylinder). To ensure maximum dilation, objective refraction and ocular biometric measurements were performed at least 25 minutes after instillation of tropicamide.

Statistical Analysis

Values for CC fitted a normal distribution. However, the distribution of CA was positively skewed (skewness = 1.452 ± 0.077 , kurtosis = 4.112 ± 0.154), although a symmetrical distribution was achieved when the data were log transformed (Fig. 1). According to the requirements for maximum likelihood estimation in the computer program Mx,²⁹ the transformed data were used in further genetic analysis.

In the classic twin design, common environmental influences are confounded with nonadditive genetic influences. In both CA and CC, the twin pair correlation between identical twins was more than double the twin pair correlation between nonidentical twins. As such, nonadditive genetic influences are expected to contribute a greater proportion of variation than environmental influences common between twins. In addition, the total variance in CA and CC was greater in males/females than it was in females/males. Considering these preliminary results, a model was fitted that allowed for quantitative differences in the proportions of additive genetic (sum of allelic effects), nonadditive genetic (dominance and epistasis), and environmental influences unique to each twin. Age, sex, education, height, weight, and refraction (SE) were included as covariates. Starting with a model in which all possible parameters were free to vary, we reduced the number of parameters in a stepwise manner to determine the most parsimonious model. The difference in log likelihood between the full and submodels was distributed by χ^2 analysis, with the degrees of freedom equal to the difference in degrees of freedom between the full and submodels (likelihood ratio test).³⁰ Moreover, to compare the two correlation coefficients, the test statistic $t = z_1 - z_2 / SE(z_1 - z_2)$; equivalent to z for large n was used where z was calculated by using the Fisher z -score transformation of Pearson's r . The formula for z is $\ln[(r + 1)/(r - 1)]/2$ and the SE of $z_1 - z_2$ is $\sqrt{(1/(n_1 - 3) + (1/(n_2 - 3)))}$ where n_1 and n_2 are the sample size of two populations. The results were considered statistically significant at $P \leq 0.05$ (two-tailed).

RESULTS

Baseline Measures between MZ and DZ Twins

A total of 612 twin pairs (345 MZ and 267 DZ twin pairs) aged between 18 and 86 years (mean age = 52.11 ± 15.85 years) were recruited and examined in the GEM twin study. Of these twins, 67% (824/1224) were female and 33% were male, with this being statistically significant ($P < 0.05$). There were no significant differences in age, CA, and CC between MZ and DZ twin pairs (Table 1).

In the GEM twin cohort, the mean values for CA and CC were not statistically significantly different between the right and left eyes ($P > 0.05$; Table 1). The mean CA was 0.76 D in the right eye and 0.80 D in the left eye ($P > 0.05$) and the mean CC was 44.12 and 44.18 D in the right and left eyes, respec-

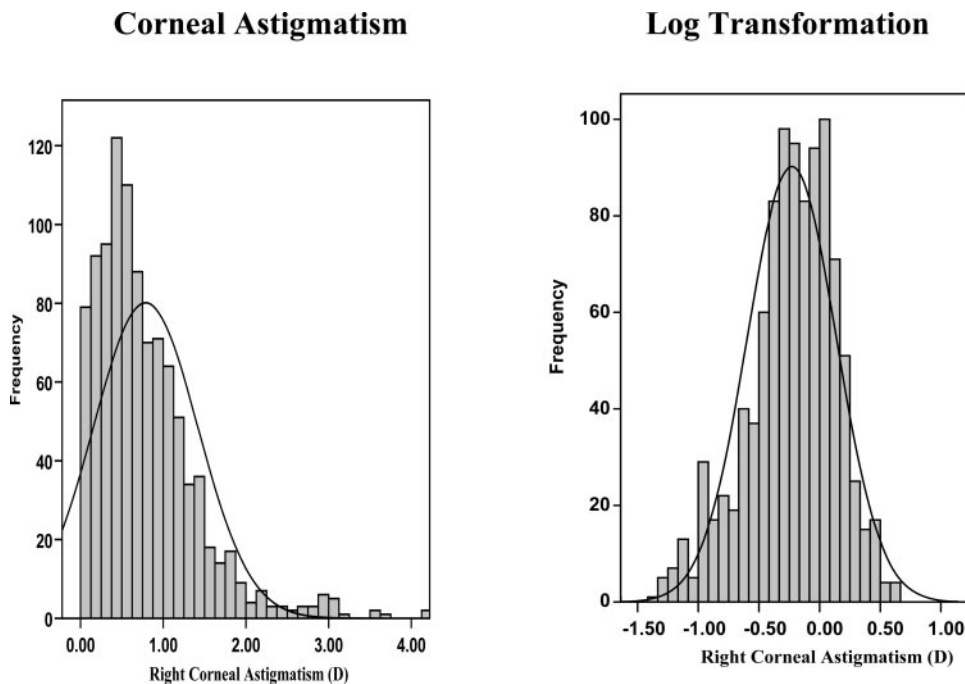


FIGURE 1. Normal distribution of CA.

TABLE 1. Baseline Measures for All Twins by Zygosity

	MZ Twins	DZ Twins	<i>P</i>
Twin Pairs (<i>n</i>)	345 (56%)	267 (44%)	—
Age (years)	52.11 ± 15.85	52.63 ± 14.96	0.56
Right corneal astigmatism (D)	0.745 ± 0.738	0.819 ± 0.792	0.13
Right corneal curvature (D)	43.57 ± 1.35	43.32 ± 1.29	0.11

MZ, monozygotic; DZ, dizygotic; DS, diopters sphere.
 **P* < 0.05, two-tailed *t*-test.

tively (*P* > 0.05). Therefore, statistical analysis was undertaken only for the right eye, unless comparisons were made. Mean CA was significantly different between the males (0.70 D) and

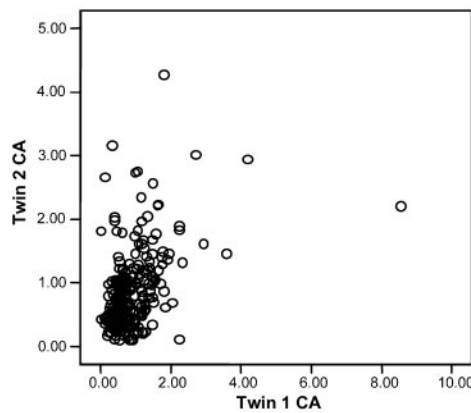
females (0.78 D; *P* < 0.001). Similarly, mean values for CC were significantly steeper in the females (44.29 D) compared with that in the males (43.76 D; *P* < 0.001).

Intrapair Correlations for CA and CC in All Twin Pairs

Intrapair correlations for CA were almost four times higher in MZ twin pairs (*r* = 0.48) than in their DZ same-sex counterparts (*r* = 0.13; *P* < 0.001; Fig. 2a). This finding supports a major role for dominant genetic effects in CA. Similarly, the intrapair correlations for CC significantly higher in MZ (*r* = 0.84) than in DZ (*r* = 0.41) twin pairs (*P* < 0.001; Fig. 2b).

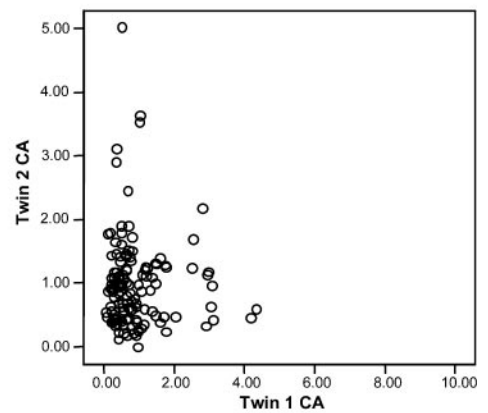
A Corneal Astigmatism

Monozygotic Twin Pairs



r = 0.48

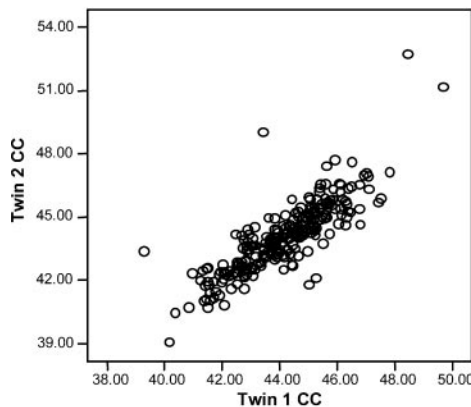
Dizygotic Twin Pairs



r = 0.13

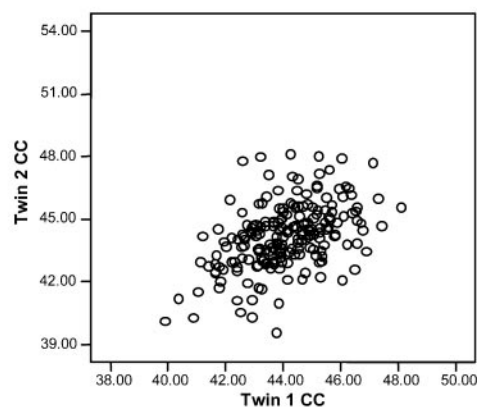
B Corneal Curvature

Monozygotic Twin Pairs



r = 0.84

Dizygotic Twin Pairs



r = 0.41

FIGURE 2. Intrapair correlations of CA and CC in twin pairs.

TABLE 2. Intrapair Correlations by Zygosity

	MZ (n = 345) <i>r</i>	All DZ (n = 267) <i>r</i>	DZ (SS) (n = 181) <i>r</i>	DZ (OS) (n = 86) <i>r</i>	<i>P</i>
CA	0.48	0.13	0.13	0.11	0.94
CC	0.84	0.41	0.59	0.40	0.37

n, number of twin pairs; MZ, monozygotic; DZ, dizygotic; SS, same sex; OS, opposite sex; CA, corneal astigmatism; CC, corneal curvature; *P*, significance value for the difference between same-sex and opposite-sex DZ intrapair correlations.

Intrapair Correlations for All Measures in All Twin Pairs by Zygosity

Intrapair correlations for CA and CC were significantly higher in MZ than in same-sex DZ ($P < 0.01$) twin pairs. Exclusion of opposite-sex DZ twin pairs had no effect on any of the intrapair correlations for both measures. In addition, there was no significant difference in the intrapair correlations of CA and CC between same-sex DZ and opposite-sex DZ twin pairs ($P > 0.05$; Table 2).

Intrapair Correlations for CA and CC by Age

Intrapair correlations of CA and CC were significantly higher ($P < 0.05$) in MZ than in DZ twin pairs in all age groups (Table 3).

Heritability Estimates

In the GEM twin cohort, MZ intrapair correlations for CA and CC were more than double DZ intrapair correlations, suggesting that nonadditive genetic effects are a greater source of variation than are the environmental effects common between twins. The variances in CA and CC were significantly different between the males and the females. Therefore, a sex-limited ADE model was fitted to the data for CA and CC (Table 4). However, it should be noted that the effect of common environmental influences marginally outweighed the effect of non-additive genetic influences on CC in females, and an ADE model was fitted to determine the effect of genetic influences.

The heritability estimates for CA (males, 50%; females, 60%) and CC (males, 70%; females, 41%) provided evidence to support a genetic component in both of these ocular measures (Table 5). Moreover, for CA, nonadditive genetic effects had a greater percentage of variation (males, 28%; females, 47%) compared with additive genetic effects (males, 22%; females,

TABLE 3. Intrapair Correlations for Corneal Astigmatism and Corneal Curvature by Age

	MZ (<i>r</i>)	DZ (<i>r</i>)
18–30 years (n = 41 MZ, 26 DZ TP)		
CA	0.53	0.10
CC	0.93	0.42
31–45 years (n = 48 MZ, 41 DZ TP)		
CA	0.41	0.15
CC	0.72	0.28
46–60 years (n = 135 MZ, 104 DZ TP)		
CA	0.52	0.20
CC	0.88	0.44
61–75 years (n = 82 MZ and 37 DZ TP)		
CA	0.66	0.07
CC	0.86	0.61
76–86 years (n = 16 MZ, 5 DZ TP)		
CA	0.81	0.06
CC	0.98	0.45

MZ, monozygotic; DZ, dizygotic; TP, twin pairs.

TABLE 4. Results of Sex Limitation ADE Model Fitting

Variable	Model	Log-Likelihood	df	ch.fit	cd.df	<i>P</i>
Corneal astigmatism	Sex lim.	1361.11	635			
	ADE*					
	ADE	1390.86	638	29.75	3	<0.001
	AE	1417.89	639	27.03	1	<0.001
Corneal curvature	E	1417.89	640			
	Sex lim.	5242.04	877			
	ADE*					
	ADE	5352.54	880	110.494	3	<0.001
	AE	5361.99	881	9.45	1	0.002
	E	5474.27	882	121.73	1	<0.001

A, additive genetics, D, dominant genetics, E, Unique environment; df, degrees of freedom; ch.fit, chi square; cd.df, difference in degrees of freedom; sex lim., sex limited.

*Best-fit model, $P < 0.05$.

13%), with the remaining variance being explained by unique environmental effects (males, 50%; females, 40%; Table 5). In contrast, additive genetic effects accounted for most of the variance in CC, explaining 61% and 41% of the genetic variance in the males and the females, respectively (Table 3) with dominant genetic effects accounting for only 10% of the variance in the males (Table 5). Environmental effects unique between twins in a pair were found to explain 29% and 59% of the variance for CC in the males and the females, respectively (Table 5). Moreover, considering the smaller differences between MZ and DZ intrapair correlations for CC, we undertook heritability analysis with an ACE model and found that the AE model provided the best-fit genetic model, with additive genetic effects explaining 57% of the variance and the remaining 43% being attributable to unique environmental effects. The overall heritability estimate for CC was 0.57 (CI: 0.49–0.58) in the ACE model. In summary, genetic factors influence the development of both CA and CC, with unique environmental factors having a role in explaining the overall variance in these corneal measures.

DISCUSSION

The findings in the GEM twin study have provided evidence to support a strong genetic component in astigmatism, in that MZ intrapair correlations were significantly higher than those in DZ twin pairs. As a part of the GEM twin study, we have shown that nonadditive genetic effects explain 50% of the variance in CA which is in agreement with previous studies that have reported estimates of 63%²³ and 42% to 61%.²⁴ In the present study, we found differences in variance in CA between the males and the females. The GEM twin study found that the ADE model was the best-fit model to explain the variance in astigmatism, which agrees with previous reports.^{23,24} However, in the GEM twin study, heritability estimates were sex specific, with heritability estimated at 50% for the males and 60% for the females.

TABLE 5. Heritability Estimates

Variable	Sex	A	D	E	h ² (CI)
Corneal astigmatism	M	0.22	0.28	0.50	0.50 ± 0.08
	F	0.13	0.47	0.40	0.60 ± 0.07
Corneal curvature	M	0.61	0.10	0.29	0.70 ± 0.09
	F	0.41	0.00	0.59	0.41 ± 0.08

A, additive genetic; D, dominant (nonadditive) genetic; E, unique environment; h², heritability.

The twin study by Grijbovski et al.²⁴ was based on self-reported (postal survey) astigmatism, and therefore obvious limitations in the study must be considered, including the analysis of dichotomous data being restricted to univariate modeling and the generalizability of their data (65% response rate). Unfortunately, in their study, Hammond et al.²³ assessed only females, and therefore sex effects could not be explored. The effects of sex in the heritability of astigmatism need further clarification; however, it can be assumed that sex plays some role in the genetic etiology of astigmatism.

The findings in the GEM twin study contradict findings in other twin studies in which a stronger role for environmental factors was reported in the development of astigmatism, and no significant differences were shown in intrapair correlations between MZ and DZ twin pairs.^{20,31} The latter twin study,³¹ with approximately 72 twin pairs, had a very narrow age range (30–31 years). Therefore, their results may be explained by a lack of statistical power. The postal surveys by Teikari et al.³¹ may have been inaccurate. In addition, twins with uncorrected astigmatic errors, those who failed to report their prescriptions, and individuals with low amounts of astigmatism not requiring spectacle correction were not represented in their study.

We found a strong genetic component to CC, with additive genetic effects explaining most of the genetic variance. There were quantitative differences in the sources of genetic and environmental effects between sexes. The high heritability estimate for CC found in the GEM twin study (males, 70%, females, 41%) supports earlier findings reported by Lyhne et al.³² where a heritability estimate as high as 92%. However, they found that an AE model was the most parsimonious one to explain CC (mean radius of CC). The findings in the GEM twin study are in agreement with those in earlier twin studies by Lin and Chen,³³ Valluri et al.,²⁰ and Biino et al.,³⁴ in which strong genetic components to CC were described.

The study by Biino et al.³⁴ of 789 subjects in a Sardinian population suggests that genetic influences responsible for the development of CC may not be population specific. Moreover, similar to previous studies, unique environmental factors are seen to explain a large part of the variance in CC (up to 60% in the females in the GEM twin study). This phenomenon may be explained by the cornea's forming the anterior surface of the eye and thus being more exposed to the environment. CC is only one measure of the cornea; therefore, it may be of benefit to explore other measures, such as the corneal surface and power to understand better the etiology of corneal development and its association with refractive error. It is important not to overlook the measurement error component, which may explain a large part of the unique environmental effect seen in disease; however, in most cases the error is not quantifiable. As it is clear that there is growing evidence to support a genetic component to CC, this ocular measure may be genetically associated with the development of astigmatism or may be under its own genetic control.

Common to most large twin studies are ascertainment and volunteer biases that may have some effect on the generalizability of the data presented in twin studies. One method of controlling these effects would be to recruit twin pairs outside the ATR, which was outside the scope of this study. However, the ATR holds approximately 10% of the twins in the general population, and the GEM twin study was able to recruit more than 15% of the twin pairs aged 18 years or older registered with the ATR.

It would be of great benefit for future research to undertake linkage analysis on these measures, to identify gene(s) associated with the development of CA and CC and provide better treatment options and diagnostic kits.

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