Genes and Environment in Refractive Error: The Twin Eye Study

Christopher J. Hammond,[1,2] *Harold Snieder,*[1] *Clare E. Gilbert,*[2] *and Tim D. Spector*[1]

Purpose. A classical twin study was performed to examine the relative importance of genes and environment in refractive error.

Methods. Refractive error was examined in 226 monozygotic (MZ) and 280 dizygotic (DZ) twin pairs aged 49 to 79 years (mean age, 62.4 years). Using a Humphrey-670 automatic refractor, continuous measures of spherical equivalent, total astigmatism, and corneal astigmatism were recorded. Univariate and bivariate maximum likelihood model fitting was used to estimate genetic and environmental variance components using information from both eyes.

Results. For the continuous spectrum of myopia/hyperopia, a model specifying additive genetic and unique environmental factors showed the best fit to the data, yielding a heritability of 84% to 86% (95% confidence interval [CI], 81%–89%). If myopia and hyperopia (≤ -0.5 D and ≥ 0.5 D, respectively) were treated as binary traits, the heritability was 90% (95% CI, 81%–95%) for myopia and 89% (95% CI, 81%–94%) for hyperopia. For total and corneal astigmatism, modeling showed dominant genetic effects are important; dominant genetic effects accounted for 47% to 49% of the variance of total astigmatism (95% CI, 37%–55%) and 42% to 61% of corneal astigmatism variance (95% CI, 8%–71%), with additive genetic factors accounting for 1% to 4% and 4% to 18%, respectively (95% CIs, 0%–13% and 0%–60%, respectively).

Conclusions. Genetic effects are of major importance in myopia/hyperopia; astigmatism appears to be dominantly inherited. (*Invest Ophthalmol Vis Sci.* 2001;42:1232–1236)

Much has been written about the epidemiology of myopia, which is seen as an increasing public health problem. There has been less research on astigmatism and on hyperopia. There has been long-standing debate on the relative importance of "nature versus nurture" in refractive errors, particularly myopia.[1] Family studies of ocular refraction and its components have shown a high degree of concordance,[2] and postal questionnaire studies of twins in Finland have suggested genetic factors are important.[3] However, recent dramatic increases in the prevalence of myopia, particularly in the Far East,[4] have moved the focus of research toward environmental causes, particularly close work. The relative importance of genes and environment has not been quantified for refractive error.

The importance of genetic factors in myopia has been suggested by previous twin studies.[3,5–10] However, usually only myopes were selected in these studies, thereby ignoring the largest part of the continuous distribution of refractive error that covers the range from low negative (i.e., myopic) to high positive (i.e., hyperopic) values.

The previous twin study of hyperopia was limited by using only spectacle prescription data collected by postal survey.[11] Astigmatism has been variously described in twin and family studies as having a strong genetic basis,[5] no genetic basis,[12,13] or due to a potential single major autosomal dominant locus.[14] The genetics of astigmatism therefore remain uncertain.

Twin studies have been described as the "perfect natural experiment" to study the relative importance of genetic and environmental factors.[15] We describe a classical twin study to examine the heritability of refractive error. This is the first twin study to apply genetic modeling techniques and to use the continuous distribution of refractive error in a large population-based sample, all of whom have been systematically and objectively assessed using reproducible methods.

Methods

Subjects

The subjects were 506 female twin pairs ascertained from the general population through national media campaigns in the United Kingdom.[16] They were initially recruited to the St. Thomas' UK Adult Twin Registry and were unaware of any hypotheses and that they were going to undergo an eye examination. Research followed the tenets of the Declaration of Helsinki, and local ethics committee approval and informed consent was obtained. Twins between the ages of 50 and 79 years were invited to attend an eye examination and were examined between January 1998 and July 1999. Twelve pairs of twins refused or, more usually, were unable to attend for reasons of ill health. Zygosity was determined by standardized questionnaire[17] and confirmed by DNA short tandem repeat fingerprinting in approximately 40% of twin pairs where zygosity was uncertain. This occurred if the twins or the investigator was in any doubt about true zygosity or when the answers to the standardized questionnaire were not definitely MZ or DZ. The twins were asked about refractive correction and previous eye history using a standardized questionnaire. Of the 1012 eyes, refractive error data were not analyzed for 16 right eyes and 17 left eyes: the reasons were that 24 eyes were pseudophakic (postcataract surgery) and 9 were ungradeable because of corneal opacities, previous eye surgery, or injury which might have altered refraction. Individuals with strabismus or anisometropic amblyopia were included in the study. Modeling using data from which extreme values had been excluded was performed but produced virtually identical results, so the results of the full data set are reported here.

Measurements

All individuals underwent visual acuity testing using the ETDRS logmar chart and nondilated refraction using a Humphrey-670 automatic refractor. An automatic refractor measures refractive error by detection of infrared light aligned through the pupil and reflected back by the

From the [1]Twin Research and Genetic Epidemiology Unit, St. Thomas' Hospital; and [2]Department of Preventive Ophthalmology, Institute of Ophthalmology, London, United Kingdom.

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Corresponding author: Christopher J. Hammond, Twin Research and Genetic Epidemiology Unit, St. Thomas' Hospital, Lambeth Palace Road, London SE1 7EH, UK. ch@twin-research.ac.uk

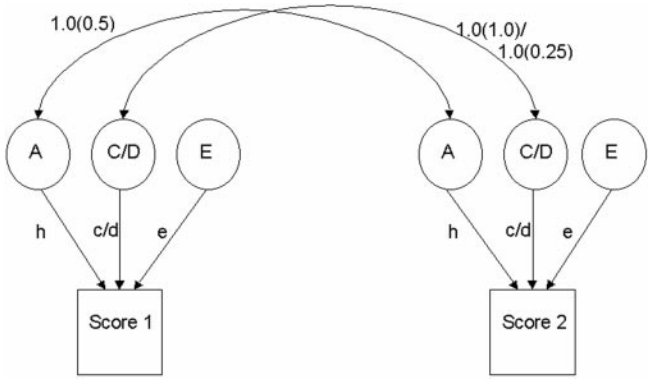

FIGURE 1. Path model for univariate analysis of a twin study. The observed phenotypes of twin 1 and twin 2 (score 1 and score 2) are represented in *squares.* Latent factors are represented in *circles*: A, C, D, and E are the additive genetic, dominant genetic, and common and individual environmental influences common to Score 1 and Score 2. A and D are correlated by a factor of 1.0 for MZ twins and 0.5 and 0.25, respectively, for DZ twins; C is correlated by a factor of 1.0 for both MZ and DZ twins (the equal environment assumption). Regression coefficients of the observed variables on the different latent factors are also shown in *lowercase*: for example, h is the regression coefficient of the additive genetic effect. C and D cannot be estimated simultaneously.

retina. Keratometry (corneal curvature) readings are obtained by capture of distortions of the reflections from nine source LEDs.

Three measures were recorded for each eye: spherical equivalent, total astigmatism, and corneal astigmatism, which is the difference between the two axes of the keratometry readings obtained by the autorefractor. All readings were recorded in diopters. Spherical equivalent and corneal astigmatism values approximated a normal distribution and so were analyzed using the raw data. Total astigmatism appeared left-skewed, and the square root values were used for subsequent analysis because they best approximated a normal distribution.

Astigmatism is a vector, consisting of magnitude and direction (angle). It has been attempted to reduce the magnitude and angle of astigmatism to one relative value,[18] which Naeser has termed the polar value of net astigmatism.[19] This was calculated from the total astigmatism data.

Thirty twins from this series were measured on two occasions to study the reproducibility of the measurements. Intraclass correlations obtained were 0.98 for spherical equivalent, 0.98 for keratometry readings, and 0.92 and 0.84 for total astigmatism of the right and left eyes, respectively.

Analytical Approach

Twin studies are based on the comparison of concordance (or correlation) between identical or MZ twin pairs and nonidentical or DZ twin pairs. MZ twins share the same genes, and DZ twins on average share only half their genes; any greater similarity between MZ twins can therefore be attributed to this additional gene sharing.

Quantitative genetic model fitting to twin data has been fully described elsewhere.[20,21] In short, the technique is based on the comparison of the covariances (or correlations) in MZ and DZ twin pairs and allows separation of the observed phenotypic variance into additive (A) or dominant (D) genetic components and common (C) or unique (E) environmental components. The latter also contains measurement error. Dividing each of these components by the total variance yields the different standardized components of variance, for example, the heritability (h^2), which can be defined as the ratio of additive genetic variance to total phenotypic variance. Figure 1 illustrates a path model used in twin studies.

Extension of univariate to multivariate models allows for information from both eyes to be included in the model. The main advantage of multivariate modeling is an increase in power.[22] A bivariate Cholesky decomposition[20,23] was used to analyze right and left eyes simultaneously for astigmatism and spherical equivalent measures. Myopia and hyperopia were also analyzed as bivariate data (yes/no), using standard methods.[20,24]

Model Fitting Procedure

The significance of variance components A, C, and D, was assessed by testing the deterioration in model fit after each component was removed sequentially from the full model, leading to a model in which the pattern of variances and covariances was explained by as few parameters as possible. Submodels were compared with the full model by hierarchic χ^2 tests. The difference in χ^2 values between submodel and full model is itself approximately distributed as χ^2, with degrees of freedom (df) equal to the difference in df of submodel and full model.

Statistical Software

Data handling and preliminary analyses were done with STATA.[25] All genetic modeling was carried out with Mx.[26]

RESULTS

There were 226 MZ twin pairs and 280 DZ twin pairs. The mean age of MZ twins was 62.4 years (SD, 5.7 years; range, 51–75 years), and the mean age of DZ twins was 62.1 years (SD, 5.7 years; range, 49–79 years). Table 1 shows mean values (±SD) and ranges for spherical equivalent, total astigmatism, and corneal astigmatism for right and left eyes in the two groups of twins. Values were similar for MZ and DZ twins and for right and left eyes. Only two thirds of twins had keratometry recorded, resulting in fewer twin pairs with values for corneal astigmatism.

The intraclass correlations for the measures are shown in Table 2. MZ twins were more highly correlated than DZ twins, as illustrated by the scatter plots in Figure 2. For spherical equivalent, the combination of a high correlation between MZ twins of >0.8 and DZ correlation approximately half that value suggests a strong additive genetic effect. The correlations for astigmatism are slightly lower for MZ twins than for spherical equivalent, suggesting more environmental (or measurement error) effects. For both measures of astigmatism, the DZ cor-

TABLE 1. Results of Autorefractor Readings for MZ and DZ Twin Pairs, after Exclusions

Measure	Eye	MZ	*n*	Range	DZ	*n*	Range
Spherical equivalent	Right	0.31 ± 2.45	215	−10.25 to +6.5	0.34 ± 2.51	266	−12.12 to +7.25
	Left	0.39 ± 2.44	217	−10.37 to +7.25	0.49 ± 2.37	263	−9.0 to +8.0
Total astigmatism	Right	0.75 ± 0.77	216	0 to 6.5	0.70 ± 0.77	264	0 to 6.75
	Left	0.75 ± 0.75	217	0 to 5.25	0.70 ± 0.71	262	0 to 5.5
Corneal astigmatism	Right	−0.40 ± 1.07	159	−4.0 to +5.5	−0.52 ± 1.0	168	−5.75 to +3.75
	Left	−0.43 ± 0.99	162	−3.0 to +3.75	−0.56 ± 0.96	166	−5.5 to +2.25

Values are means ± SD and range in dioptres. *n* = number of twin pairs included in analysis.

TABLE 2. Intraclass Correlations within MZ and DZ Twin Pairs for Measures of Refractive Error

	Eye	MZ	DZ
Spherical equivalent	Right	0.86	0.47
	Left	0.83	0.48
Total astigmatism	Right	0.52	0.20
	Left	0.52	0.10
Corneal astigmatism	Right	0.70	0.13
	Left	0.61	0.20

relations approximate a quarter of the MZ correlations, which suggests a role for dominant genes, because DZ twins share only a quarter of the dominant genetic effect compared with MZ twins.

These inferences were confirmed by the results of model fitting. Univariate modeling of spherical equivalent for each eye (data in Table 3) allowed the effects of common environment (C) and dominant genetic effect (D) to be dropped from the model with no significant change in fit. The AE model (one ascribing variance due to additive genes and individual environment only) therefore represented the best-fitting model.

Univariate analysis for astigmatism for each eye (also shown in Table 3) suggested the most likely model was one involving additive and dominant genes and individual environment: the ADE model. Multivariate analysis was used to increase power by using data from both eyes simultaneously.

Multivariate analysis confirmed the best-fitting models suggested by the univariate analysis reported above: the AE model for spherical equivalent and the ADE model for astigmatism (data not shown). The dominant genetic effects in astigmatism were significant for both total astigmatism ($P = 0.03$) and corneal astigmatism ($P = 0.03$).

Table 4 displays the parameter estimates and 95% confidence intervals (CIs) for the best-fitting models from the multivariate analysis. For spherical equivalent, the heritability was 84% to 86%, with the remaining 14% to 16% of the variance due to unique environmental variance. Dominant genes explained a significant proportion of the population variance for astigmatism: 47% to 49% for total astigmatism and 42% to 61% for corneal astigmatism (the wider 95% CI may reflect the smaller sample size of this measure). Additive genes explained a small proportion of the variance of astigmatism (1%–18%) and individual environment explained the rest of the variance (34%–50%).

Twenty-six percent of individuals were myopic (≤ -0.5 D), and 55% were hyperopic (≥ 0.5 D). Using these cutoffs and treating each of these traits as dichotomous (i.e., yes/no), modeling predicted that the heritability of myopia was 90% (95% CI, 81%–95%), and the heritability of hyperopia was 89% (95% CI, 81%–94%).

The effects of age were considered, because of possible loss of myopia with age[27] and also the potential myopic effect of early nuclear cataract. In fact the correlation between age and spherical equivalent was weak, with a correlation coefficient of 0.1. When age was incorporated into the model for spherical equivalent, it only accounted for a modest 1.4% (95% CI, 0.2%–3.9%) of the population variance. Similarly astigmatism was weakly correlated with age, with a coefficient of 0.15 for both total and corneal astigmatism. Modeling again predicted that age accounted for a small proportion of the population variance of astigmatism of <3%.

DISCUSSION

This study set out to determine the heritability of refractive error and has shown that additive genetic effect is responsible for up to 86% of the variance of spherical equivalent (myopia/hyperopia) in this population. Recent genomewide scans have identified loci for familial high myopia,[28,29] raising the possibility of future identification of gene defects in refractive error. Dominant genes appear important in the inheritance of astigmatism, with a slightly lower overall genetic component of ~50% for total astigmatism and up to 60% for corneal astigmatism.

Ours is the first twin study to objectively examine a population both wearing and not wearing spectacles and to use the continuous population distribution of refractive error to estimate the relative importance of heritability and environment using modern model fitting techniques.

The high heritability of spherical equivalent compares with previous twin studies: Finnish postal studies, using only spectacle prescription data sent by a sample of twins via postal questionnaire, reported a heritability for myopia for women of 0.61[8] and 0.75 for hyperopia,[11] treating the traits as dichotomous variables. However, these results only included twins who were both wearing spectacles and who sent in their prescription and will have excluded low levels of refractive error in either or both twins not requiring spectacle correction.

Other twin studies of myopia (such as the Chinese study of myopia that estimated a heritability of 0.61[7]) selected twins at least one of which was myopic and so might not be generalizable to the whole population. They also used subjective

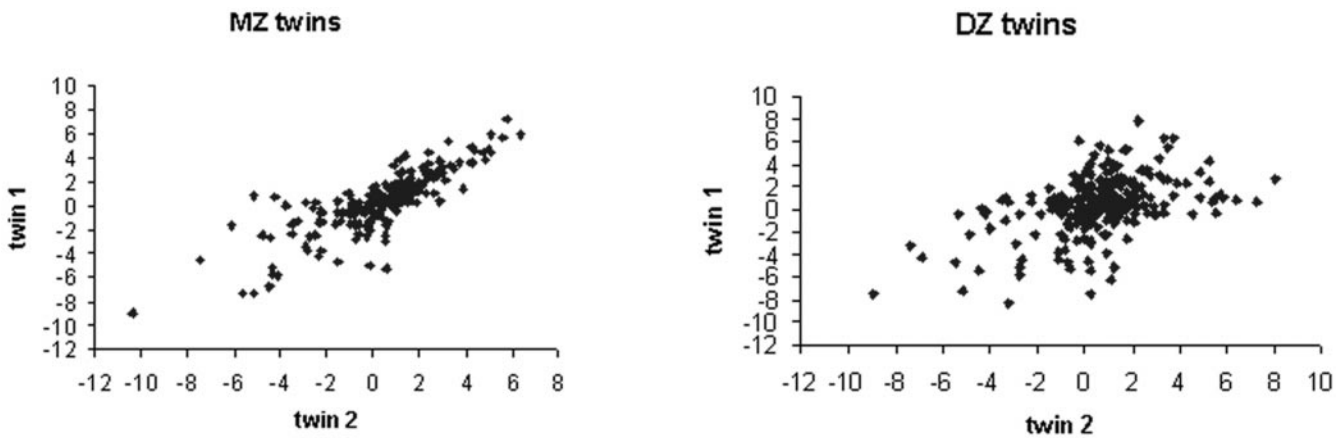

FIGURE 2. Values of spherical equivalent of the left eye (in diopters) for twin 1 plotted against twin 2 for monozygotic (MZ) and dizygotic (DZ) twin pairs. *Minus values* represent myopic subjects; *plus values* represent hyperopic ones.

TABLE 3. Model-Fitting Results for Univariate Analysis of Spherical Equivalent, (Square Root of) Total Astigmatism, and Corneal Astigmatism

Measure	Eye	Model	χ^2	$\Delta\chi^2$	df	*P*
Spherical equivalent	Right	ACE	18.392			
		ADE	18.547	0.155		
		AE	18.547	0.155	1	0.69
		CE	120.778	102.386	1	<0.001
	Left	ACE	3.924			
		ADE	5.788	1.864		
		AE	5.788	1.864	1	0.17
		CE	70.385	66.461	1	<0.001
Total astigmatism	Right	ADE	4.556			
		ACE	5.801	1.232		
		AE	5.801	1.232	1	0.26
		CE	24.21	18.409	1	<0.001
	Left	ADE	0.510			
		ACE	6.281	5.771		
		AE	6.281	5.771	1	0.016
		CE	27.784	21.503	1	<0.001
Corneal astigmatism	Right	ADE	14.388			
		ACE	21.506	7.118		
		AE	21.506	7.118	1	0.007
		CE	59.139	37.633	1	<0.001
	Left	ADE	13.656			
		ACE	15.996	2.34		
		AE	15.996	2.34	1	0.136
		CE	38.201	22.205	1	<0.001

χ^2, Chi-square goodness of fit statistic; $\Delta\chi^2$, change in χ^2 comparing submodel with full model; df, change in degrees of freedom between submodel and full model; *P*, probability that $\Delta\chi^2$ is zero.

refraction (as did Sorsby's less selective study of 118 twin pairs[5]), resulting in potential bias due to the zygosity of twins being obvious. Autorefraction was used in our study rather than retinoscopy and subjective refraction to avoid this bias.

Our heritability of 85% for spherical equivalent, similar to the 87% heritability found in a recent recalculation[30] of data from the United Kingdom in the early 1960s,[5] is remarkable given the focus of many studies on environment risk factors such as the "use-abuse" theory that close work produces myopia.[31] The Baltimore Eye Study showed the odds ratio for years of education was 1.36 in myopia and 0.67 in hyperopia.[32] This suggests that myopia and hyperopia may be subject to the same spectrum of genetic and environmental influences, justifying our use of unbiased continuous measurement of refractive error in a population. Even if myopia and hyperopia are treated separately with thresholds of ≤ -0.5 D and ≥ 0.5 D, the heritabilities were 90% and 89%, respectively, confirming the importance of the genetic effect.

This study shows that genetic effects have the greatest contribution to the overall population variance of spherical equivalent, but it does not invalidate the very real findings of a dramatically increasing prevalence of myopia, especially in the Far East.[4] The inherited factors may include a susceptibility to adaptive myopia when the predominant visual tasks move from far to near as society becomes more economically developed (e.g., myopia was only seen in Eskimos coincident with introduction of formal education).[33] Genes may be involved in behavior as well as the ocular mechanisms of myopia.

Heritability is population specific; our figure applies to this population of British women and could be different for other populations with different gene pools or environmental circumstances. Another potential limitation of this study could be possible recruitment bias as the twins are volunteers; this has been minimized by recruitment of twins initially unaware of the eye test or of its reason when asked to attend for the eye examination. Twin studies make the "equal environment assumption" that MZ and DZ twins share the same common family environment. In addition some have argued that twin data might not be generalizable to the singleton population. However, the equal environment assumption holds up to analysis and in general twins show similar morbidity and mortality to the rest of the population.[34] The prevalence of refractive error in the twins was similar to that of other population studies.[35]

Our study is the second study to suggest that astigmatism may be dominantly inherited, which was raised recently in an

TABLE 4. Standardized Parameter Estimates and 95% CIs of the Best Fitting Models of Multivariate Analysis of Spherical Equivalent, (Square Root of) Total Astigmatism, and Corneal Astigmatism

	Eye	a^2	95% CI	d^2	95% CI	e^2	95% CI
Spherical equivalent	Right	0.86	0.83–0.89			0.14	0.11–0.17
	Left	0.84	0.81–0.87			0.16	0.13–0.19
Total astigmatism	Right	0.05	0.006–0.13	0.47	0.37–0.53	0.48	0.42–0.56
	Left	0.01	0.0–0.07	0.49	0.42–0.55	0.50	0.43–0.58
Corneal astigmatism	Right	0.04	0.0–0.54	0.61	0.12–0.71	0.34	0.29–0.42
	Left	0.18	0.0–0.60	0.42	0.08–0.66	0.40	0.33–0.48

a^2, proportion of variance due to additive genes; d^2, proportion of variance due to dominant genes; e^2, proportion due to individual environmental effects; 95% CI, 95% confidence interval.

Italian family study using complex segregation analysis.[14] Our results are exciting because twin studies generally have low power to detect dominance due to the low DZ correlation, especially in univariate models.[36] We used information from both eyes in a multivariate model, optimizing power to detect dominant genetic effect.[20,22] The failure of a Finnish twin study to find a difference between MZ and DZ astigmatism correlations is unsurprising: they studied only 72 pairs of twins selected because both wore glasses and had sent in their prescriptions from a postal questionnaire.[12] This could underrepresent discordant twins one of whom, for example, did not require spectacles and those with low levels of astigmatism not requiring correction.

So far, we have only reported the analysis of the magnitude of the astigmatism, as have other studies.[14] Modeling of the polar value, which includes both magnitude and angle of the vector of astigmatism, resulted in the same ADE model as best-fitting (data not shown). However, application of the formula resulted in lower correlations because of relative values of oblique astigmatism being reduced, which impaired the fit of the model.

Age is a potential bias in a study such as ours, which looked at refractive error in a population with mean age of 62 years. The weak positive correlation of spherical equivalent with age ($r = 0.1$) suggests, like other population studies, that our younger twins are slightly more myopic than the older ones. However, because age only explained 1.4% (95% CI, 0.2%–3.9%) of the variance, it did not appear to be a significant factor in our population. We therefore felt justified in excluding age from the final modeling results. Recent population data support this, suggesting that there is little change in refractive error over 5 years.[37]

Conclusions

We have demonstrated that genetic effects are important in the development of refractive error, with heritability of 84% to 86% for myopia/hyperopia. The heritability of astigmatism is 50% to 65% and predominantly involves dominant genetic effects. These results offer exciting prospects in the search for susceptibility genes, which may further the understanding of the mechanisms and gene–environment interactions in the development of refractive error.

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