Heritability of Refractive Astigmatism: A Population-Based Twin Study Among 63- to 75-Year-Old Female Twins

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Purpose. To examine the heritability of refractive astigmatism in older women.

Methods. Astigmatism was measured with an autorefractor in 88 monozygotic and 82 dizygotic female twin pairs aged 63 to 75 years. The prevalence and distribution of astigmatism and polar values J0 and J45 were estimated by standard statistical methods. Bivariate maximum likelihood model fitting was used to estimate genetic and environmental variance components using information from both eyes.

Results. Mean astigmatism of the more astigmatic eye was 0.93 diopters (D; SD ±0.58). Astigmatism of at least 0.25 D, 0.5 D, 0.75 D, or 1.0 D in either eye was present in 99.7%, 88.5%, 66.5%, and 46.2% of cases, respectively. The main direction of astigmatism was against the rule. The age-adjusted quantitative genetic modeling revealed that additive genetic effects accounted for 33.3% (95% confidence interval [CI], 21.9%–43.8%) of the total variance of astigmatism and for 18% (95% CI, 4%–31%) of the total variance of polar value J45 of both eyes (bivariate model), with the remaining variances due to nongenetic effects. There were no significant correlations between the twin pairs for polar value J0.

Conclusions. In elderly female twins, additive genetic effects accounted for one-third of the variance of the amount of astigmatism and only a small fraction of the total variance of polar value J45.

Keywords: astigmatism, heredity, polar value, elderly, female

Refractive astigmatism (astigmatism) is the sum of the asphericities of different optical elements of the eye: the anterior and posterior cornea and lens and their relative positions with regard to the visual axis of the eye. Corneal astigmatism (CA) is the most significant determinant of total astigmatism. Different theories have been offered to explain the development of astigmatism. In addition to genetics, eyelid pressure, extraocular muscle tension, and visual feedback are thought to be reasons for astigmatism. Various corneal diseases, eye surgery affecting the cornea, or other surgical procedures—for example, cataract, glaucoma, and retinal ablation surgery—may induce astigmatism. The amount and direction of astigmatism has been shown to vary with age.2–5 Asano and colleagues, for example, found mean astigmatism in the right eye of 0.77 D and 1.25 D among 40- to 49-year-olds and 70- to 79-year-olds, respectively.2 The direction of astigmatism tends to change with age, the main trend being an increase against the rule (ATR) and a decrease with the rule (WTR).6 Differences in the prevalence of astigmatism also seem to occur between different ethnic groups.7

The classical twin model is commonly used to determine the relative contribution of the genetic and environmental components of a disease or traits. Thus far, most twin studies examining refraction and ocular biometrics have mainly comprised populations across a wide age spectrum. Grijibovski et al.8 studied the occurrence and heritability of astigmatism in a population-based sample of Norwegian twins through self-reported history of astigmatism from birth to age 31 years in 8045 twins. The best-fitting biometrical model suggested that genetic effects due to dominance explained 54% (95% CI, 20–69 years) and additive genetic effects explained 9% (95% CI, 60–40 years) of the variation in the liability to astigmatism. In the study of Hammond et al.9 among twin pairs aged 49 to 79 years (mean age, 62.4 years), genetic effects due to dominance accounted for 47% to 49% (95% CI, 37%–55%) and additive effects for 1% to 4% of the variance of total astigmatism (95% CI, 0%–13%). Dirani et al.10 studied CA in 18- to 86-year-old Australian twins (mean age, 52.11 ± 15.85 years). Heritability estimates were as high as 60% for CA. In our recent article, quantitative genetic modeling showed that heritable factors explained 83% of the variance in spherical equivalent in 63- to 76-year-old Finnish female twins.11 In the same population, genetic factors explained 81% of the variance in corneal refraction, additive genetic factors 62% (95% confidence interval [CI] 44%–86%), and dominant genetic factors 19% (95% CI 7%–49%).12 For CA, it was not possible to construct a meaningful model, although the values of the intraclass correlation coefficient (ICC) were higher for monozygotic...
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METHODS

Design and Patients

This study forms part of the Finnish Twin Study on Aging (FITSA), the purpose of which is to investigate genetic and environmental effects on the disablement process in older women. A detailed description of the recruitment process has been published earlier.13-14 Schematically, the recruitment process was the following:

2. In the year 2002, there were 1260 surviving pairs of female twins born between 1924–1937.
3. Of that number, 414 pairs were invited to participate.
4. A total of 217 pairs attended the study center examinations. To be included, both co-twins had to agree to participate. Reasons for nonparticipation were one or both sisters’ unwillingness to participate (106 pairs), and disease or poor health status (91 pairs).
5. A total of 47 pairs were excluded due to cataract or glaucoma operation.
6. The final analyses comprised 170 twin pairs (88 MZ and 82 DZ).

Zygosity had initially (1975) been determined by a validated questionnaire15 and later confirmed by applying a battery of 10 highly polymorphic gene markers at the National Public Health Institute to DNA extracted from a sample of venous blood. The subjects ranged in age from 65 to 75 years, with a mean age of 68 years (SD ± 3.2).

The study was approved by the ethics committee of the Central Hospital of Central Finland and both twins gave their written informed consent. Our research adhered to the tenets of the Declaration of Helsinki.

Examination

Refraction, including the amount and direction of astigmatism, were measured with an autorefractor (Topcon AT; Topcon, Tokyo, Japan). On the basis of the values given by the autorefractor, subjective spheral refraction was then measured by the fogging method, and final spherical refraction was measured with an autorefractor, subjective spherical refraction was then measured from a chart with Landolt rings at a distance of 6 m. The examination was performed for both twin sisters by the same nurse, but on separate occasions, during the one-day assessment in a laboratory at the University of Jyväskylä.

Direction of astigmatism was classified into three groups: WTR = axis of the correcting cylinder between 60 to 120°, ATR = between 0 to 30° or 150 to 179°, and oblique (all remaining cases).

For the vectorial analysis, we converted the astigmatism from the spherocylindrical notation to J0 and J45 power vectors by applying a Fourier transformation using the following equations: J0 = |C × cos(2A)|/2, J45 = |C × sin(2A)|/2, C = Power of cylinder, A = Axis of cylinder.16 J0 refers to cylinder power set orthogonally at the 0 and 90° meridians and represents WTR or ATR astigmatism. Positive values of J0 indicate WTR astigmatism, and negative values ATR astigmatism. J45 refers to a cross-cylinder set at 45 and 135°, representing oblique astigmatism. Negative values of J45 indicate astigmatism of around 15° and positive values astigmatism of around 135°.

Statistical Methods

Data were analyzed using statistical software (Stata, version 12; StataCorp, College Station, TX; SPSS version 19.0; IBM Corp., Endicott, NY). The equality of the means of the continuous variables and equality of the distributions of the categorical variables between the MZ and DZ twins were analyzed with the adjusted Wald test, taking into account the fact that the data consist of twin pairs rather than unrelated individuals. The significance of differences in the amount of astigmatism between the ATR, WTR, and oblique directions was tested by one-way ANOVA with Sheffe’s post hoc procedure for the pairwise comparisons of means. ICCs were computed for the MZ and DZ twin pairs separately to estimate the level of within-pair similarity. ICCs can be used to obtain indicative estimates of the genetic and environmental components of variances. Higher ICC values among the MZ than among the DZ pairs indicate the presence of an underlying genetic contribution. The associations between continuous variables (e.g., amount of astigmatism between right and left eye) were analyzed by Pearson’s product moment correlation coefficients. The significance of differences was tested by cross-tabulation and Pearson’s χ² test in the case of discrete variables (e.g., direction of astigmatism).

The classical twin study provides an opportunity to determine whether individual differences in a trait arise from genetic or environmental factors or both. MZ twins share all their genes (100%), whereas DZ twins share, on average, 50% of their segregating genes. Consequently, in MZ pairs, genes contribute only to similarity in a trait, whereas in DZ twin pairs, they contribute both to similarity and to differences. Greater similarity in MZ pairs than in DZ pairs provides evidence for genetic influence on the trait.17 In quantitative genetics studies, genetic effects are typically classified into additive genetic effects (A) and nonadditive genetic effects (D). Environmental effects are classified into shared environmental effects (C) and nonshared environmental effects (E). Shared environmental effects are common to both members of a pair while nonshared effects refer to external exposures affecting only one sibling, such as accidents, surgery, or measurement error. Quantitative genetic modeling is based on necessary similarities and differences in the correlations of the A, D, C, and E factors explaining the variability among MZ and DZ twins. The correlations for additive and nonadditive genetic effects are defined as 1.0 in MZ pairs, and as 0.5 and 0.25, respectively, in DZ pairs. The correlation for shared environmental effects is defined as 1.0 and for nonshared environmental effects as 0, among both MZ and DZ pairs. The aim of genetic modeling is to construct a model that explains the data well and has as few explanatory components as possible. When using bivariate modeling it is necessary to separate effects that are common for both variables included in the model and effects that are only specific for one variable in the model. To sharpen this difference small letters c (common) or s (specific) are used with letters A, D, C, and E.

The full independent pathway model consists of genetic and environmental effects that are common to both eyes (common additive genetic effect [Ac], common shared environmental effect [Cc]/common nonadditive genetic effect [Dc], and common nonshared environmental effect [Ec]) as well as effects that are specific to the right or left eye only (specific additive genetic effect [As]-1, As2, specific shared environmental effect [Cs]-1/specific nonadditive genetic effect [Ds]-1, Cs2/Ds2, and specific nonshared environmental effect [Es]-1, Es2). To obtain a more parsimonious model, the full
model was modified by dropping the weakest nonsignificant parameters one at a time, until the model with the best fit was achieved.

The ICCs for astigmatism and polar value J45 among MZ were significantly higher than among DZ, predicting that the ADE model would show the best fit to the data. Our subsequent analyses showed, however, that nonadditive genetic effects (D) were not significant, and hence the final AE model showed the best fit for astigmatism and for polar value J45. The data from both eyes were analyzed simultaneously with bivariate models. Using a bivariate model instead of a univariate model (with only the right or left eye in the model) results in narrower confidence intervals of estimates, and thus produces more precise results. In the present study, astigmatism showed a high phenotypic correlation between the right and left eye. Hence, eyes were treated as a single, correlated trait in the analyses. The present analyses were carried out using matrix algebra software (Mx program, version 1.52a; Michael Neal, Virginia Commonwealth University, Richmond, VA).

RESULTS

For all the study subjects, the mean spherical equivalent (SE ± SD) was +1.67 D (±1.93) in the right eye and +1.66 D (±1.86) in the left eye. There were no significant differences between MZ and DZ in SE between the right and left eyes. The SE was negative (myopic) in 12.9% and 10.6% of cases in the right and left eye, respectively. Corrected distant vision of the right eye was 0.75 (±0.21), and the corresponding value for the left eye was 0.78 (±0.21).

Mean astigmatism of the right eye between MZ and DZ was 0.77 D (±0.68) and 0.71 D (±0.46), respectively; the corresponding values for the left eye were 0.73 D (±0.65) and 0.70 D (±0.47). Mean astigmatism of the more astigmatic eye was 0.95 D (±0.58), with a maximum of 4.00 D. Astigmatism of at least 0.25 D, 0.5 D, 0.75 D, or 1.0 D in the more astigmatic eye was present in 99.7%, 88.8%, 66.4%, and 46.1% of cases.

There were no statistically significant differences in the amount of astigmatism between either the left and right eyes (P = 0.22) or between MZ and DZ individuals (P = 0.42). The correlations between the amount of astigmatism and age were nonsignificant. The correlations between the amount of astigmatism and spherical equivalent in the whole dataset and separately among those with positive or negative SE were nonsignificant in each eye.

Axis of Astigmatism and Polar Values of Astigmatism

There were no significant differences in the means of astigmatism in the different main axis directions between the right and left eye. Table 1 shows the distribution and means of astigmatism in the main directions for both eyes.

In the right eye, the mean astigmatism in the oblique direction was smaller than that in the WTR (P < 0.001) or ATR (P = 0.001) directions. The correlations in the left eye did not reach significance.

There were no significant differences in the distribution of the axis of astigmatism between those with positive and those with negative SE (χ² test, P = 0.124 for right eye, and P = 0.060 for left eye).

Table 2 shows polar values J0 and J45 for both eyes. All means were slightly negative. Negative J0 indicated ATR astigmatism, but all the means of J0 and J45 were so close to the value zero that no significant mean predominance was found.

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DISCUSSION

All but one subject in the present study had astigmatism of at least 0.25 D in one eye or the other. While this is more than has commonly been reported earlier, in most studies astigmatism has usually begun from a level of either 0.5 D or 0.75 D. Although our study design does not permit general conclusions to be drawn on the prevalence of astigmatism in the population, the prevalence of astigmatism of ≥0.5 D (71.2% in the right and 70.0% in the left eye) found in the present

TABLE 1. Distribution and the Means ± SD of Astigmatism in the Main Directions

<table>
<thead>
<tr>
<th>Direction of Astigmatism</th>
<th>Right Eye</th>
<th></th>
<th>Left Eye</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Prevalence, %</td>
<td>Mean, D (±SD)</td>
<td>Prevalence, %</td>
<td>Mean, D (±SD)</td>
</tr>
<tr>
<td>WTR</td>
<td>29.9</td>
<td>0.78 (±0.66)</td>
<td>29.5</td>
<td>0.74 (±0.66)</td>
</tr>
<tr>
<td>ATR</td>
<td>50.9</td>
<td>0.73 (±0.52)</td>
<td>48.9</td>
<td>0.68 (±0.46)</td>
</tr>
<tr>
<td>Oblique</td>
<td>19.2</td>
<td>0.61 (±0.50)</td>
<td>21.6</td>
<td>0.66 (±0.42)</td>
</tr>
</tbody>
</table>

TABLE 2. Polar Values J0 and J45 ± SD With Minimum and Maximum Values for Right and Left Eyes

<table>
<thead>
<tr>
<th></th>
<th>J0, right</th>
<th>J0, left</th>
<th>J45, right</th>
<th>J45, left</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>Minimum</td>
<td>Maximum</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td>Right eye</td>
<td>−0.015 (±0.328)</td>
<td>−1.65</td>
<td>+1.60</td>
<td>−0.008 (±0.315)</td>
</tr>
<tr>
<td>Left eye</td>
<td>−0.007 (±0.339)</td>
<td>−1.47</td>
<td>+1.37</td>
<td>−0.015 (±0.347)</td>
</tr>
</tbody>
</table>

Right eyes, n = 186. Left eyes, n = 178.
study does not differ greatly from that reported by Schellini et al.,\textsuperscript{20} in a Brazilian population aged 70 years or older (71.7% had astigmatism of $\geq 0.5$ D). In the National Health and Nutrition Examination Survey, the prevalence of astigmatism of $\geq 1.0$ D was 50.1% in persons aged 60 years or older; whereas in our study, this grade of astigmatism was found in 46.5% of cases.\textsuperscript{21} Thus the main difference between the prevalence found here and that reported in most previous studies is probably due to the fact that astigmatism in our study started at 0.25 D.

Some studies have shown a positive relationship between the amount of astigmatism and ametropia and myopia.\textsuperscript{1,2,22} In the present study, no significant correlations between astigmatism and SE were found. The small proportions of myopics and cases of high ametropia in this study could be one explanation for the nonsignificant relationships observed between the amount of astigmatism and spherical ametropia.

The main aim of this study was to calculate the impact of heredity on refractive astigmatism. In the present study, only approximately one-third of the variation of astigmatism was explained by additive genetic effects, which is less than in some previous studies among somewhat younger subjects. Moreover, no significant dominant effects could be calculated. In a population-based sample of Norwegian twins, aged from birth to 31 years, additive genetic effects explained 9% (95% CI, 0.4 to 5.0 years), and dominant genetic effects 54% (95% CI, 20.69 years) of the variance in the liability to self-reported astigmatism.\textsuperscript{8} In the study of Hammond et al.,\textsuperscript{9} among 49- to 79-year-old twins, additive genetic effects accounted for 1% to 4% (95% CI, 0% to 13%) and dominant effects for 47% to 49% (95% CI, 37% to 55%) of the variance of total astigmatism. In the Hammond et al.\textsuperscript{7} study and our study, the MZ correlations for astigmatism were very similar (0.4 to 0.5), while the DZ correlations in Hammond et al.\textsuperscript{9} were 0.2 to 0.10 and in ours negative. Despite the larger sample size in Hammond et al.,\textsuperscript{9} neither study had the power to distinguish unambiguously between additive and nonadditive genetic sources of variation. Given the differences in sample size and in characteristics resulting in some variation in the actual variance/covariance matrices underlying the pairwise correlations, it was not unexpected that the best-fitting model differed in the two studies. Both studies point to the importance of genetic factors, but whether additive or nonadditive factors are more important cannot be stated. Thus, in Hammond et al.,\textsuperscript{9} an ADE model for astigmatism fit better than an AE model for the left but not the right eye in the univariate models. In the bivariate models, Hammond et al.\textsuperscript{9} only present results for an ADE model and no results for an AE model. Higher ICC values were observed between the MZ pairs of sisters for astigmatism in the WTR and ATR subgroups of astigmatism than in the whole sample. Thus, it could be supposed that the heredity of astigmatism could be higher in those subgroups; but due to the small sample size, it was not possible to calculate a meaningful model.

As far as we know, there are no previous studies on the heredity of the polar values of astigmatism. In the present study, significant ICC values between the twin pairs emerged only for the value of J45. Further, the ICC values for J45 between the MZ sisters were lower than those for the amount of astigmatism, suggesting that the heredity of polar values is lower than the amount of astigmatism alone.

In our earlier studies on the same subjects, 83% and 81% of the variance in spherical equivalent and corneal refraction, respectively, were explained by heritable factors.\textsuperscript{11,12} Based on the results of this study and the results of our earlier studies on the same subjects, it is reasonable to conclude that the impact of heredity among elderly females is highest on spherical equivalent refraction and corneal refraction, while environ-

mental factors have a stronger influence on the amount of corneal and refractive astigmatism.

The amount and direction of astigmatism has been shown to vary with age.\textsuperscript{2,3,5} The low impact of heredity on astigmatism found in the present study with elderly females would support the theory that the influence of environmental factors on astigmatism increases at older ages. Possible changes in astigmatism should be taken into account when controlling for refraction and prescribing new glasses, and when planning refractive surgery, especially when doing costumed corneal ablations. Emmetropic nonastigmatic refraction achieved by refractive surgery at a young age may turn to astigmatic refraction later on during the life course.

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