Genetic analysis of indices of corneal power and corneal astigmatism in human populations with varying incidences of strabismus

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Heritability estimates for corneal power were found to be high and similar for two populations which differed in their incidence of esotropia. This similarity suggests (1) that genetic differences for corneal power do not contribute to the difference in heritability for spherical refractive error reported for these populations and (2) that this character is not a critical variable contributing to the pathophysiology of esotropia. Heritability estimates for corneal astigmatism were, in most cases, rather low. The pattern of population and sex differences among heritability estimates was consistent with those previously reported for cylindrical refractive error. These population differences in heritability suggest that they contribute to population differences found for cylindrical refractive error.

Key words: strabismus, genetics, heritability, corneal power, corneal astigmatism, esotropia, exotropia, refraction, quantitative genetics.

Clinically, strabismus appears to represent what Falconer1 refers to as a threshold character: the condition itself is discontinuous (diagnosed strabismus or not), but its expression depends on underlying variables (motor and sensory characteristics) which show continuous variability. This variability, resulting from genetic and environmental differences influencing underlying measurable characters, can be assessed and can be subjected to genetic analyses. Such analyses provide information about (1) the relative importance of genetic differences to this variability, and (2) the extent to which offspring resemble parents in the phenotypic expression of these characters. Comparison of genetic parameters estimated from populations which differ in their incidence of and hence liability to, strabismus provides a basis of assessing the importance of genetic differences in-
In previous studies, we have reported differences among population parameters estimated within three samples which differ in their incidence of strabismus subtypes. Among the variables which suggested genetic differences between groups were spherical and cylindrical refractive error. It was concluded that components of familial similarity for strabismus may arise from genetic differences for spherical and cylindrical refractive error and, hence, these refractive characteristics of the eye are implicated as important underlying continuous variables contributing to the pathophysiology of strabismus.

The basis of individual differences in spherical refractive error might involve one or more of the components of ocular refraction which include corneal power, depth of the anterior chamber, lens thickness, depth of the vitreous chamber, and axial length. In this paper we examine the genetic basis of individual differences in corneal power.

One of the components of refractive astigmatism (cylindrical refractive error) is corneal astigmatism resulting from an aspheric anterior surface of the cornea. Other components include error of curvature of the lens, eccentric lens position, and irregularities in the refractive index of the lens.

The purpose of the present study was to examine the nature of gene differences associated with corneal power and corneal astigmatism within three populations differing in their liability to strabismus and to determine the contribution of these components to population differences for refractive error and, hence, for strabismus.

Subjects and methods

Subjects. Families included in this analysis were contacted via designated propositi selected from two sources: the strabismus clinic at The University of Iowa Hospital and the local school population. Only nonoperated cases of nonparetic strabismus served as index cases. These propositi were classified on the basis of their deviation (either eso- or exo-deviation) and members of their immediate families were assigned to the “E” or “X” population, respectively. Children from the local school population were selected at random (with some restriction to achieve approximate age matching) and members of their immediate families were assigned to the “R” population. A more detailed description of the sampling procedures and summary group statistics are presented by Smith and co-workers. The sampling procedures resulted in 118 families (668 individuals) in the “E” population, 27 families (162 individuals) in the “X” population, and 163 families (866 individuals) in the “R” population. Individuals were examined in a standard manner at The University of Iowa Strabismus Clinic.

Clinical methods. The clinical examination consisted of a test battery of approximately 70 orthoptic and 25 ophthalmologic measures plus various attribute scores and patient history information. Assessments for individuals were as complete as possible considering differences in age and other conditions.

Corneal curvatures were measured with a Bausch and Lomb keratometer calibrated in terms of refractive power in units of prism diopters. This is an indirect method that utilizes the optical principle that the size of a reflected image (which can be measured) is a function of the curvature of the reflecting surface. With knowledge of the size of the object and its distance, the radius of curvature can be ascertained and, hence, the refractive power which is also a function of curvature.

Two assessments of curvature were made: either in the horizontal or vertical meridians or in the meridians which yielded the largest and the smallest radii of curvature. Although both eyes were measured, only the measures from the right eye are considered here.

The average value of the readings taken in the two meridians is used as the index of corneal power. The absolute value of the difference between these two readings is the measure of corneal astigmatism. Both measures displayed similar continuous distributions in the three population samples.

Analytical methods. Estimates of heritability for the measures were obtained from regression of mean offspring scores on parent values. All analyses excluded the scores of propositi and regression analyses followed the rationale presented by Fisher and Gray. Least squares estimates of regressions and partial regressions were obtained step-wise separately for male and female offspring mean scores (by sex) on male parent, on female parent, on male parent independent of female parent, on female parent independent of male parent, and on midparent value. In addition, an estimate of dominance bias was provided by the
Table I. Means and standard errors for corneal power

<table>
<thead>
<tr>
<th>Population</th>
<th>Male parent</th>
<th>Female parent</th>
<th>Progeny</th>
<th>N*</th>
</tr>
</thead>
<tbody>
<tr>
<td>R</td>
<td>43.31 ± 0.14</td>
<td>44.00 ± 0.14</td>
<td>43.88 ± 0.13</td>
<td>100</td>
</tr>
<tr>
<td>F</td>
<td>43.58 ± 0.17</td>
<td>44.06 ± 0.17</td>
<td>44.62 ± 0.16</td>
<td>81</td>
</tr>
<tr>
<td>E</td>
<td>43.45 ± 0.21</td>
<td>44.03 ± 0.19</td>
<td>43.41 ± 0.20</td>
<td>55</td>
</tr>
<tr>
<td>X</td>
<td>43.34 ± 0.23</td>
<td>43.92 ± 0.19</td>
<td>44.37 ± 0.21</td>
<td>55</td>
</tr>
</tbody>
</table>

*N is the number of families.*

interaction term fitting the total model discussed in detail by Fisher and Gray.5

All regressions were estimated within the "R", "E", and "X" populations. Within each population the parents of male offspring and those of female offspring are not independent samples. Parent-pair correlations are standard product-moment correlations between male and females parent scores. Procedures employed to estimate regressions, partial regressions, and their standard errors are presented by Harvey.6

Results and discussion

Since variance in characters imposed by age differences can artificially reduce or inflate parent-offspring covariance, both measures were regressed on age (within generation, sex, and population) to assess age effect. No significant association of age with either measure was detected. These findings are in agreement with other studies.7-10

Means and standard errors for corneal power estimated from the three populations are presented in Table I. There are no apparent differences among parents of the same sex across the three populations (F = 0.6 and 0.1, d.f. = 5,312, for fathers and mothers, respectively). However, the average corneal power for fathers is 43.44 compared to 44.00 for mothers. This sex difference is consistent in five of six comparisons and accounts for the difference in the comparison of all parental means (F = 2.4, d.f. = 11;624).

Among progeny, there is a comparable sex difference, at least between males and females of the "R" (t = 3.6, d.f. = 176) and "E" (t = 3.2, d.f. = 108) populations. Male and female progeny of the "X" population display a difference in the same direction but the mean levels cannot be demonstrated as being different. This sex difference in mean levels is also present in data reported by Young and Leary10 for a study involving Eskimo families. Based on the reported means and standard deviations, our comparisons indicated that mean levels for mothers exceeded those for fathers (t = 2.5, d.f. = 140) and female progeny mean tended to exceed that for male progeny (t = 1.9, d.f. = 256, p < 0.054).

Comparison among female progeny of our three populations indicates no differences (F = 0.6, d.f. = 2,146); comparison among male progeny does indicate the presence of population differences (F = 3.2, d.f. = 2,166) which reflects the lower corneal power among "E" males relative to males of the other two populations.

In the normal (emmetropic) eye, the various components that contribute to ocular refraction have developed to levels that are mutually compensatory so that no error of refraction exists. At extreme levels of expression of one of these components, compensation on the part of other components could tend to be inadequate. Hence, the lower corneal power, the greater the tendency toward hyperopia and, alternatively, the higher the corneal power, the greater the tendency toward myopia unless sufficiently compensated by the other components. This suggests that the slightly greater levels of corneal power displayed by females could be associated with either slightly higher levels of negative refractive error (myopia) or slightly reduced levels of positive refractive error (hyperopia) relative to males. A tendency among Caucasian children for females to show an earlier development, a higher proportion, and a greater amount of myopia than males has been reported.11,12 However, for our "R" and "E" samples the opposite association is present for the four parent comparisons and for the two progeny comparisons.5 Alternatively, the slightly greater level of corneal power for fe-
Table II. Estimates ± standard errors of population parameters describing variation in corneal power. Heritability estimated from regression of mean offspring* measures

<table>
<thead>
<tr>
<th>Nf</th>
<th>δ parent</th>
<th>α/δ $ parent</th>
<th>γ parent</th>
<th>δ/γ $ parent</th>
<th>Midparent</th>
<th>Dominance§ bias</th>
<th>Parent pair correlation</th>
</tr>
</thead>
<tbody>
<tr>
<td>δ</td>
<td>100</td>
<td>0.80 ± 0.17</td>
<td>0.71 ± 0.13</td>
<td>1.09 ± 0.15</td>
<td>1.03 ± 0.13</td>
<td>0.87 ± 0.09</td>
<td>0.09 ± 0.04</td>
</tr>
<tr>
<td>γ</td>
<td>81</td>
<td>0.77 ± 0.20</td>
<td>0.68 ± 0.17</td>
<td>1.05 ± 0.18</td>
<td>1.00 ± 0.16</td>
<td>0.84 ± 0.11</td>
<td>-0.06 ± 0.05</td>
</tr>
<tr>
<td>E</td>
<td>55</td>
<td>0.84 ± 0.23</td>
<td>0.79 ± 0.20</td>
<td>1.08 ± 0.25</td>
<td>1.03 ± 0.22</td>
<td>0.90 ± 0.14</td>
<td>-0.08 ± 0.09</td>
</tr>
<tr>
<td>δ</td>
<td>55</td>
<td>1.07 ± 0.20</td>
<td>1.02 ± 0.17</td>
<td>1.04 ± 0.26</td>
<td>0.96 ± 0.20</td>
<td>0.99 ± 0.13</td>
<td>0.01 ± 0.06</td>
</tr>
<tr>
<td>γ</td>
<td>13</td>
<td>0.83 ± 0.39</td>
<td>0.81 ± 0.22</td>
<td>1.17 ± 0.34</td>
<td>1.16 ± 0.24</td>
<td>0.97 ± 0.16</td>
<td>-0.24 ± 0.15</td>
</tr>
</tbody>
</table>

*Propositus excluded.
†Nf refers to the numbers of families used to estimate parameters.
‡δ/γ and δ/γ § indicate the partial regressions of offspring on δ parent independent of γ parent and offspring on γ parent independent of δ parent.
§The interaction term fitting the total model of Fisher and Gray5: Yijk = Y + Fi + Mj + FIMj + Eijk.

males may simply reflect a compensatory difference corresponding to sex differences in the dimension of the eye, in particular, axial length.

Heritability estimates for corneal power (see Table II) do not differ among females (F = 0.5, d.f. = 2;134). Since there are no differences between estimates derived from regression on father and those derived from regression on mother and no suggestion of dominance variance for this character among females, a best estimate of heritability of corneal power among females (0.91 ± 0.08) was obtained by pooling across groups.

Comparison of heritability estimates from male progeny of the three groups presents a different situation (F = 0.5, d.f. = 2;163). Specifically, the "X"-population estimate based on midparent value differs from, and is lower than the pooled estimate of 0.88 ± 0.08 for the other two populations. Within the "X" population, the heritability of this character for males appears to be entirely a function of the mother's contribution. Multiple regressions involving "R" and "X" males indicate the presence of dominance bias, a source of genetic variance not apparent among females. The regression coefficient associated with this interaction term are both positive, indicating a negative bias, i.e., dominance in the direction of the smaller value. The negligible contribution by fathers to the expression of this character in the "X" population could be interpreted to indicate that, in this sample, the mothers, primarily, carry the dominant gene or majority of dominant genes. This could be a stochastic result of the small sample size. It could also suggest genetic differences for the presence of an X-linked gene (or genes) between the "X" population and the other two populations. Comparison of the magnitude of the heritability estimates within the "X" population is consistent with the pattern suggesting X-linked inheritance15; namely, that the magnitude of the regressions of males on mother and females on father are comparable and equal to or greater than the regression of females on mother which is greater than the regression of males on father.

Overall, corneal power is a highly heritable character in all the populations sampled. Pooling across all groups yielded a heritability estimate of 0.89 ± 0.05.

Estimates of correlations presented by Young and Leary10 for a nonclinical Eskimo sample (comparable only to our "R" population sample) also indicate significant levels of covariance between fathers and sons, fathers and daughters, mothers and sons, and mothers and daughters.

Sorsby and Fraser14 reported correlations for a nonclinical Caucasian sample of monozygotic and dizygotic twins for corneal power. Estimates of heritability (broad-sense) can be calculated on the basis of these correlations.15 Using three
different methods, we obtained similarly high and comparable estimates: Holzinger's H index = 0.84, Nichol's HR index = 0.73, and Jensen's $h^2 = 0.69$. Although heritability indices based on twin correlations estimate the ratio of genetic variance (rather than additive genetic variance) to phenotypic variance, the lack of dominance variance would make these broad-sense heritabilities comparable to our (narrow-sense) heritability estimates.

The correlations between parent-pairs (indices of assortative mating) are consistently low and positive and do not differ ($r = 0.3$, d.f. = 5). A pooled estimate of the parent-pair correlation for corneal power, based on $z$-transformed correlations, weighted and adjusted according to group size, is $0.05 \pm 0.06$.

The second variable considered was corneal astigmatism; means and standard errors for the three populations are presented in Table III. Although there are no significant differences among the parents—either between the sexes or among populations ($F = 0.7$, d.f. = 11,624)—mean levels of mothers consistently exceed those of fathers.

Analysis of variance among progeny indicated the presence of group differences ($F = 3.2$, d.f. = 5,312); however, the source of this difference is the high mean level of "R" females compared to the other five groups which are relatively homogeneous ($F = 2.3$, d.f. = 4,232). The pattern of slightly greater mean levels of corneal astigmatism for female parent compared to male parent within all three populations is also present for progeny within the "R" and "E" populations. This parallels the sex pattern for corneal power. No pattern of sex difference was noted for cylindrical refractive error.

The sex difference for corneal astigmatism is in agreement with other studies involving nonclinical, random samples (comparable to our "R" population). In fact, the mean levels for a nonclinical Caucasian sample (ages 7 to 14) reported by Lyle, Grosvenor, and Dean are in close agreement with those presented here: 0.62 and 0.78 for males and females, respectively, compared to pooled ("R" and "E") means of 0.64 and 0.82. It has been suggested that lid pressure induces slightly more corneal astigmatism in females than in males due to the greater softness of the female corneal tissue.

Although we failed to detect an association of corneal astigmatism with age, it is interesting to note that comparison of progeny means with their respective mid-parent values as well as comparison of progeny with their like-sex parent does seem to suggest (with the exception of "X" male progeny) that a slight increase with age does occur. Hirsch noted that approximately 75 per cent of the children in his longitudinal study had a change in astigmatism of less than 0.25 D. during the first eight years of school; Lyle reported that 70 per cent of his subjects of all ages displayed a change of 0.25 D. or less over a ten-year period. Inspection of Lyle's data of mean levels at various age groupings reveals that up to the age of 20 (which would include the age range of progeny in this study), the amount of corneal astigmatism remains relatively constant. Mean levels for age classes ranging from 21 to 50 years of age (approximately the age range of parents in this study) are similar but exceed that of the younger ages. For individuals 51 to 60 years of age and those 61 and older, there is a decrease in astigmatism to levels below the under-20 groups. This pattern of change would explain the slightly higher levels for parents relative to progeny as well as the failure to detect...
Table IV. Estimates ± standard errors of population parameters describing variation in corneal astigmatism. Heritability estimated from regression of mean offspring* measures

<table>
<thead>
<tr>
<th>Parent pair</th>
<th>%Δ parent</th>
<th>%Δ/parent</th>
<th>%Δ parent</th>
<th>%Δ/parent</th>
<th>Midparent</th>
<th>Dominance $\delta^f$ bias</th>
<th>Parent pair correlation</th>
</tr>
</thead>
<tbody>
<tr>
<td>R $\delta$</td>
<td>0.37 ± 0.10</td>
<td>0.34 ± 0.16</td>
<td>0.35 ± 0.14</td>
<td>0.32 ± 0.14</td>
<td>0.33 ± 0.10</td>
<td>-0.14 ± 0.13</td>
<td>0.13 ± 0.10</td>
</tr>
<tr>
<td>R $\gamma$</td>
<td>-0.05 ± 0.17</td>
<td>-0.04 ± 0.17</td>
<td>0.23 ± 0.18</td>
<td>0.23 ± 0.18</td>
<td>0.18 ± 0.13</td>
<td>0.01 ± 0.16</td>
<td>-0.06 ± 0.11</td>
</tr>
<tr>
<td>E $\delta$</td>
<td>0.12 ± 0.15</td>
<td>0.15 ± 0.15</td>
<td>0.24 ± 0.17</td>
<td>0.26 ± 0.17</td>
<td>0.20 ± 0.12</td>
<td>-0.11 ± 0.13</td>
<td>-0.16 ± 0.13</td>
</tr>
<tr>
<td>E $\gamma$</td>
<td>0.15 ± 0.26</td>
<td>0.19 ± 0.24</td>
<td>0.74 ± 0.22</td>
<td>0.75 ± 0.22</td>
<td>0.49 ± 0.17</td>
<td>0.35 ± 0.18</td>
<td>-0.06 ± 0.14</td>
</tr>
<tr>
<td>X $\delta$</td>
<td>-0.61 ± 0.56</td>
<td>-0.66 ± 0.58</td>
<td>0.15 ± 0.36</td>
<td>0.22 ± 0.36</td>
<td>-0.10 ± 0.29</td>
<td>-0.07 ± 0.47</td>
<td>0.15 ± 0.27</td>
</tr>
<tr>
<td>X $\gamma$</td>
<td>0.04 ± 0.39</td>
<td>-0.03 ± 0.36</td>
<td>0.36 ± 0.21</td>
<td>0.37 ± 0.22</td>
<td>0.25 ± 0.18</td>
<td>0.06 ± 0.11</td>
<td>0.12 ± 0.28</td>
</tr>
</tbody>
</table>

*Propositor excluded.

†(N refers to the numbers of families used to estimate parameters.

1$\delta/\gamma$ and $\gamma/\delta$ indicate the partial regressions of offspring on $\delta$ parent independent of $\gamma$ parent and offspring on $\gamma$ parent independent of $\delta$ parent.

The interaction term fitting the total model of Fischer and Gray $Y_{ijk} = T + F_i + M_j + FIMJ + E_{ijk}$.

a significant association with age in this study since regressions were calculated within generations. Hence, our results are not in conflict with studies which do report an effect of age on this measure.

Heritability estimates for corneal astigmatism are presented in Table IV. Each of the three populations presents a somewhat different picture with regard to the heritability of this character. For the "R"-population males, heritability estimates from regression on midparent value as well as the partial regression on both parents indicates substantial resemblance. The heritabilities from males associated with fathers and with mothers are not different, and there is no suggestion of dominance. "R" females, however, failed to show much resemblance to either parent although they tended to be more similar to mothers than fathers' variance accounted for by the two partial regressions (only 2 per cent in both cases). Thus, there appears to be a lack of additive as well as dominance variance for this character among "R" females. The heritability estimates for cylindrical refractive error (refractive astigmatism) also indicated negligible heritability for progeny of both sexes whether based on male or female parent (see Hegmann, Mash, and Spivey, Table VI).2

For the "E" population, estimates are consistently positive; however, standard errors associated with all estimates for "E" males are quite large. "E" females show substantial resemblance to mothers and the presence of dominance variance for this character ($t = 2.6$, d.f. = 1.77). This difference in heritability as a function of sex of parent and the indication of dominance variance for this character are similar to results obtained for refractive astigmatism for "E" females.

For "X" population males and females, estimates on male parent indicate negligible heritability; those on female parent are low with large standard errors. There is no indication of dominance variance in the expression of this character for either sex of progeny. For refractive astigmatism, all estimates for "X" males as well as those for "X" females on mother also indicated negligible heritability; in addition, the heritability estimate for "X" females on father was low with a large standard error. There was no suggestion of dominance bias in the "X" population. In general, estimates from the "X" population display considerable variability and are not well-determined because of the very small sample sizes available.

For the "R" and "E" populations, comparison of heritabilities estimated for corneal astigmatism with those for refractive astigmatism indicated a similar rank order by magnitude of the estimates. The correlation between the eight pairs of heritabilities (those based on the partial regressions) for the two measures was 0.86, indicating substantial similarity ($t = 4.1$, d.f. = 6). In
addition, "E" population females displayed significant levels of dominance variance for both measures.

Parent-pair correlations for this character do not differ (X = 3.5, d.f. = 5) although they are both positive and negative. A pooled estimate, based on z-transformed correlations weighted and adjusted according to group size,10 is -0.01 ± 0.06.

The lower levels of heritability estimates for the refractive measures relative to the keratometric measures are generally to be expected in view of the more "complex" nature of the refractive measures, i.e., the refractive measures involve the net effect of several somewhat independent components.

REFERENCES