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Genetic analysis of cover test measures and AC/A ratio in human populations with varying incidences of strabismus

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The purpose of this study was to investigate the nature of genetic differences for the phoria or dissociated position and for the accommodative convergence to accommodation (AC/A) ratio within three populations defined on the basis of the incidence of subtypes of diagnosed strabismus. This approach is designed to determine the importance of genetic differences influencing individual differences for these variables (Falconer, 1960) and, hence, the importance of those gene differences in the aetiology of strabismus.

Subjects and methods

SUBJECTS

Families included in this analysis were contacted *via* designated propositi. Propositi were selected from two sources: the strabismus clinic at the University of Iowa Hospital, and the local school population. Only unoperated cases of nonparetic strabismus were included. The propositi were classified on the basis of their deviation (either eso or exo deviation), and members of their immediate families were assigned to the eso (E) or exo (X) population, respectively. Children from the local school population were randomly selected with some restriction to achieve approximate age matching; members of their immediate families were assigned to the random (R) population. More detailed descriptions of the sampling procedure as well as the summary group statistics are given by Smith, Grützner, Colenbrander, Hegmann, and Spivey (1972). The sampling produced 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 ophthalmological measures, plus various attribute scores relating to attributes and information on the patient's history. Assessments for individuals were as complete as possible considering differences in age and other conditions. The variables considered here were assessed during the same test period.

The cover test was used to detect any manifest or latent deviation. While the patient fixed a distance target, the examiner covered one eye and observed the other. The procedure was repeated, first leaving both eyes uncovered, then covering the second and observing the first. If either uncovered eye moved to fix the target, a manifest deviation was indicated. If no movement occurred, a procedure of rapid alternation of the cover was used to break up fusion. Under these conditions, if the covered eye had moved and, on uncovering, was observed to move (to refix the target), a phoria was indicated. The magnitude of the deviation, whether manifest or latent, was measured by the dioptric power of a prism which was sufficient to stop the movement when placed in front of one of the eyes. If the movement of the eye was in a temporal direction, indicating a convergent position of the eyes, a positive angle was recorded. A medial movement indicated a correction for a divergent position and a negative angle was recorded.

AC/A ratio was assessed by the lens gradient method. The amount of accommodative convergence exerted was determined in response to different amounts of required accommodation (for a fixed viewing distance of 33 cm) while the subject accommodated a target of 20/20-size printed numbers. A measure of the amount of phoria in prism dioptres (PD) was made with the prism cover test while the subject was wearing each of three different powers of lenses, +3, 0, and −3 dioptres (D), which imposed the requirement of 0, 3, and 6 D, respectively, of accommodation.

Regression of the measured phorias on the amounts of required accommodation expresses the amount of convergence (in PD) per dioptre of required accommodation exerted by the subject to maintain fusion of the target while stimuli for proximal and tonic convergence are held constant.

This method of determination of the AC/A ratio 'provides the closest approximation to the true AC/A ratio that we can obtain by simple, rapid clinical measurement' (Breinin, 1971). Other methods tend to confound proximal convergence factors and other elements associated with the vergence mechanism with the accommodative convergence response.

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ANALYTICAL METHODS

Estimates of heritability of the characters were obtained from regression of mean offspring scores on parent values and from intraclass correlations among full sibs. All analyses excluded the scores of propositi.

Regression analyses follow the rationale discussed by Fisher and Gray (1937). Least-squares estimates of regressions and partial regressions were obtained stepwise separately for female and male offspring on parents. Thus, for each variable the regression of offspring scores by sex on female parent, male parent, female parent independent of male parent, male parent independent of female parent, and on midparent have been estimated. In addition, an estimate of dominance bias is provided by the interaction term fitting the total model, discussed in detail by Fisher and Gray (1937).

All regressions are 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 parent scores.

Procedures employed to estimate regressions, partial regressions, and their standard errors are those of Harvey (1960).

Results and discussion

The means and standard errors for the cover test measure are presented in Table I for the three populations. Parent and offspring means from the R-population tend to be slightly positive (esophoric) but the values do not differ from zero. E-population means indicate greater esophoric tendency than shown in the R-population, while X-population means reflect an exophoric tendency. These represent significant differences among populations (indicated by an F-value of 2·3, degrees of freedom (df) = 11:756 for comparison of parent scores, and F = 4·4, df = 5:378 for offspring comparison). These mean levels are all within the range of what we have considered as normal or physiological heterophoria: 5 PD of exophoria to 2 PD of esophoria (Adler, 1959). In Table II, the relative frequency distributions (categorized as normal-range heterophoria, esophoria greater than 5 PD (XP), or esophoria greater than 2 PD (EP) of progeny scores (sexes combined) are displayed for the three populations. Population differences are evident here also ($\chi^2 = 26$; df = 4). This distribution of R-population individuals is in very close agreement with a sample of 4880 individuals presented by Tait (1951) which, when categorized in this way, show percentages of 1.1, 91·5, and 7·4 for the XP, normal-range, and EP categories. It is interesting to note that the X-population shows increased proportions in both of the more 'extreme' categories relative to the R-population while the E-population shows an increase in only the +3 category. These population differences are of interest in the investigation of the aetiology of nonparalytic strabismus (heterotropia) since it has been postulated

Table I *Means and standard errors for cover test measure (in PD)*

Population		*Male parent*	*Female parent*	*Progeny*	*N**
R	Male	0·23±0·24	−0·02±0·33	0·19±0·33	113
	Female	0·50±0·28	0·08±0·42	0·24±0·16	88
E	Male	1·72±0·84	1·40±0·50	0·94±0·64	74
	Female	1·39±0·82	1·29±0·55	2·02±0·64	73
X	Male	−1·34±0·86	−0·76±0·50	−2·19±1·55	20
	Female	−1·37±1·00	−0·82±0·48	−1·87±1·61	16

* N refers to the number of families used to estimate parameters

Table II *Proportion of each population grouped according to magnitude (in PD) of cover test measure*

Population	*Greater than 5 XP*	*5 XP to 2 EP*	*Greater than 2 EP*	*No. of families*
R	0·02	0·91	0·07	201
E	0·03	0·81	0.16	147
X	0·17	0·72	0·11	36

that there is no basic difference between the causes leading to heterophoria and those resulting in strabismus (Burian, 1950; Scobee, 1950; Adler, 1959). This hypothesis implies that the difference between normality and abnormality in the binocular function is a matter of the degree of heterophoria present and the individual's ability to compensate for it. If the fusional reflexes are not adequate to counteract or compensate for a tendency toward misalignment (a phoria), the deviation will become manifest (a tropia). The functional failure could result from too great a strain on normally developed fusional reflexes or from a lesser strain on either poorly developed or disrupted fusional reflexes.

Estimates of heritability for the cover test measure are presented in Table III for the three populations by sex of offspring. These estimates indicate negligible heritability (for all but one) when based on male parent, but moderate heritability when based on offspring resemblance to female parent. The best estimate of heritability, based on pooling the similar estimates of the father-offspring resemblance, is $-0{\cdot}02 \pm 0{\cdot}09$. Heritabilities derived from the partial regressions of offspring measures on mothers' values were consistent ($F = 1{\cdot}9$, df = 5:366) and were pooled to yield a best estimate of female parent heritability, $0{\cdot}42 \pm 0{\cdot}12$. This suggests a fairly high degree of resemblance between offspring and their mothers for the amount of phoria detected by the cover test measure.

There is no indication of dominance variance for the cover test measure in any of the populations. There is, however, some evidence of a X-linked gene or genes influencing the expression of this character in our R-population. X-linkage for quantitative characters is indicated by a pattern of differences in heritabilities estimated using relatives of different sexes (Mather and Jinks, 1971, p. 292). For our data these values are totally consistent with those required for sex linkage (see Table III).

Differences among populations for the parent-pair correlations ($\chi^2 = 15{\cdot}9$, df = 5) resulted from the apparent positive assortative mating with respect to this character within the E-population (pooled estimate of $0{\cdot}41 \pm 0{\cdot}07$) relative to the zero correlation within the pooled R- and X-population. This suggests that when both parents display an esophoric tendency, they are more likely to have an esotropic child. However, the greater probability of having an exotropic child (in this X-population) is apparently not dependent on a similarity between parents for an exophoric tendency.

AC/A ratio is of interest to the study of nonparalytic strabismus because an abnormal amount of accommodative convergence can contribute to a tendency towards ocular motor imbalance.

Means and standard errors for AC/A ratio are presented in Table IV. There are no demonstrable population differences among progeny ($F = 0{\cdot}5$, df = 5:174) or among parents ($F = 1{\cdot}1$, df = 11:348). Estimates were pooled to yield overall means of $2{\cdot}87 \pm 0{\cdot}06$ for progency and $2{\cdot}68 \pm 0{\cdot}06$ PD for parents.

Various studies have indicated that AC/A ratio varies with age although there is some disagreement concerning the nature of this relationship (Alpern, 1950; Davis and Jobe, 1957; Eskridge, 1973). Since neither age of offspring nor that of parents was controlled in the sampling procedure, the presence of variance due to age could artificially reduce or inflate parent-offspring covariances. Individual measures were regressed on age separately for each sex within generation and population. Regression estimates were not pooled across populations because differences among mothers did not allow a consistent method of pooling estimates. Regression techniques were used to adjust scores to mean group age (within population, generation, and sex).

The difference in mean levels between the two generations ($t = 2{\cdot}1$, df = 538) may reflect, in part

Table III *Estimates ± standard errors of population parameters describing variation in cover test measure*

Population		*N*†	*Heritability estimated from regression of mean offspring* measures on:* *Male parent*	*M/F*‡ *parent*	*Female parent*	*F/M*‡ *parent*	*Midparent*	*Dominance*§ *bias*	*Parent pair correlation*
R	Male	113	0·08±0·26	0·07±0·25	0·31±0·19	0·31±0·18	0·22±0·15	−0·07±0·08	0·02±0·09
	Female	88	0·63±0·10	0·63±0·10	0·20±0·08	0·19±0·06	0·32±0·06	0·05±0·03	0·03±0·11
E	Male	74	0·15±0·23	−0·10±0·19	0·87±0·28	0·94±0·32	0·24±0·13	−0·01±0·01	0·44±0·09
	Female	73	−0·02±0·18	−0·06±0·20	0·16±0·27	0·19±0·29	0·03±0·13	0·00±0·01	0·33±0·11
X	Male	20	−0·11±0·85	−0·06±0·88	0·64±1·45	0·63±1·51	0·19±0·57	−1·28±9·99	−0·15±0·22
	Female	16	−0·23±0·86	−0·03±0·86	2·22±1·71	2·20±1·82	0·26±0·84	0·77±9·99	−0·19±0·24

* Propositi excluded
† N refers to the number of families used to estimate parameters
‡ M/F and F/M indicate the partial regressions of offspring on male parent independent of female parent and offspring on female parent independent of male parent
§ The interection term fitting the total model of Fisher and Gray (1937):

$$Y_{ijk} = \bar{Y} + F_i + M_j + F_i M_j + E_{ijk}$$

Table IV *Means and standard errors for age-adjusted AC/A ratio (in PD/1 D)*

Population		*Male parent*	*Female parent*	*Progeny*	*N**
R	Male	2·50±0·11	2·82±0·18	2·93±0·12	55
	Female	2·48±0·11	2·79±0·20	2·76±0·10	50
E	Male	2·69±0·18	2·60±0·18	2·90±0·18	32
	Female	2·50±0·14	2·94±0·17	2·86±0·17	31
X	Male	2·99±0·49	2·57±0·52	2·69±0·22	6
	Female	3·55±0·50	3·55±0·50	3·23±3·34	6

* N refers to the number of families used to estimate parameters

at least, the age-associated change (decrease) in AC/A ratio from approximately 11 years to 35 years.

Estimates of heritability of this character, displayed in Table V, indicate no difference among populations or between parents (F = 0·9, df = 11:324). A best estimate of heritability, calculated from the pooled partial regression on each parent separately, is 0·38±0·09. There is no suggestion of dominance variance for AC/A ratio.

Parent-pair correlations did not differ among populations (χ^2 = 2·8, df = 5). A pooled estimate (calculated from *z*-transformed correlations, weighted and adjusted according to group size (Snedecor and Cochran, 1967) do not indicate any tendency toward assortative mating with respect to this character.

Summary

The genetic analyses of indices relating to distance alignment and accommodative convergence are presented. This approach is important in understanding the contribution of genetic factors to observed individual differences for these measures. Abnormalities of either of these two components results in a tendency towards either a convergent or divergent position of the eyes (relative to the position of fusional demand) and thus places an additional load or strain on the other components of the binocular mechanism which must compensate for this potential disruption. If compensation is inadequate to maintain alignment of the eyes, a manifest deviation will result. Consequently, an understanding of the aetiology of such factors underlies an understanding of the aetiology of nonparalytic strabismus.

The three populations displayed different tendencies in the cover test measure. The average tendency for each of the populations was consistent with the type of deviation common to all propositi of families within each of the respective populations. The heritability of this character was similar in the three populations and was dependent on the contribution of the female parent only, but to a substantial degree (h^2 = 0·42±0·12). The nature of the sex difference is at present

Table V *Estimates ± standard errors of population parameters describing variation in AC/A ratio*

			Heritability estimated from regression of age adjusted mean offspring measures on:*						
Population		*N*†	*Male parent*	*M/F*‡ *parent*	*Female parent*	*F/M*‡ *parent*	*Midparent*	*Dominance*§ *bias*	*Parent pair correlation*
R	Male	55	0·25±0·32	0·37±0·31	0·42±0·18	0·45±0·18	−0·43±0·16	−0·05±0·11	−0·15±0·13
	Female	50	0·64±0·26	0·65±0·27	−0·01±0·15	0·03±0·14	0·15±0·14	0·06±0·07	−0·12±0·14
E	Male	32	0·69±0·34	0·72±0·30	0·84±0·33	0·87±0·31	0·79±0·22	−0·15±0·19	−0·04±0·18
	Female	31	0·55±0·42	0·50±0·42	0·44±0·35	0·40±0·35	0·44±0·25	−0·15±0·28	0·09±0·18
X	Male	6	0·39±0·40	0·32±0·48	0·29±0·39	0·19±0·45	0·25±0·23	0·26±0·27	0·35±0·39
	Female	6	−0·29±0·68	−0·34±0·90	−0·05±0·59	0·09±0·77	−0·10±0·37	0·80±1·39	0·50±0·34

See footnotes to Table III

open to speculation.

The population means within generations were similar for the gradient measure of AC/A ratio. The heritability of this character (0·38 ± 0·09) suggests that the genetic component is of substantial importance underlying individual differences for AC/A ratio.

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