

# Inheritance of Astigmatism: Evidence for a Major Autosomal Dominant Locus

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## Summary

Although astigmatism is a frequent refractive error, its mode of inheritance remains uncertain. Complex segregation analysis was performed, by the POINTER and COMDS programs, with data from a geographically well-defined sample of 125 nuclear families of individuals affected by astigmatism. POINTER could not distinguish between alternative genetic models, and only the hypothesis of no familial transmission could be rejected. After inclusion of the severity parameter, COMDS results defined a genetic model for corneal astigmatism and provided evidence for single-major-locus inheritance. These results suggest that genetic linkage studies could be implemented and that they should be limited to multiplex families with severely affected individuals.

## Introduction

Astigmatism (from the Greek “a,” absence; and “stigma,” point) is a condition in which the parallel rays of light entering the eye through the refractive media are not focused on a single point. Both corneal and non-corneal factors contribute to refractive astigmatism. Corneal astigmatism is mainly the result of an aspheric anterior surface of the cornea, which can be measured readily by means of a keratometer; a small fraction (~1/10) of these cases are neutralized by the back surface. The curvature of the back surface of the cornea is not considered, because it is more difficult to measure; moreover, in the case of severe corneal astigmatism, there is evidence that both surfaces have the same configuration

(Bennet and Francis 1962). Noncorneal factors are errors in the curvature of the two surfaces of the crystalline lens, irregularity in the refractive index of the lens, and an eccentric lens position. Since the cornea is the dominant component of the eye's refracting system, a highly astigmatic cornea is likely to result in a similarly astigmatic ocular refraction.

Although astigmatism shows considerable variability among populations (Grosvenor 1978), its inheritance is an unsettled issue. Several studies since the first decades of this century (e.g., see Spengler 1904) have demonstrated familial aggregation, but the mode of inheritance is still uncertain; indeed, polygenic, autosomal dominant, autosomal dominant with variable penetrance, autosomal recessive, and multifactorial threshold (MFT) models were advanced during the years 1920–60 (Powell 1948; François 1958; Waardenburg et al. 1963, pp. 1215–1217). More recently, heritability was estimated in families of affected subjects (Mash et al. 1975) and in twins (Teikari and O'Donnell 1989); Mash et al. (1975) concluded that heritability is low, whereas Teikari and O'Donnell (1989) suggested that genetic factors do not contribute to astigmatism, leaving environmental causes as the major contributors.

To define the mode of inheritance of this refractive error, we conducted a complex segregation analysis of a sample of individuals affected by astigmatism. We present the results of this study.

## Subjects and Methods

### *Population Sample*

Data on astigmatism in our region were drawn from the findings of a photorefractometric screening program that was conducted in an unselected population in a small, well-defined geographic area during 1987 and 1990. The general characteristics of this study have been described elsewhere (Angi et al. 1992). In brief, 1,046 children were born in 1985 to mothers living within the territory of National Health Unit 19 (Cittadella) in the Veneto Region. These children were invited to participate in a screening program for amblyopic defects, based

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on noncycloplegic photorefractometry at the age of 18–20 mo, and were called back for autorefractometry with visual acuity testing at the age of 36–40 mo. In the present study, data from this sample are used to calculate the distribution of astigmatism in the general population. In 1991, the problem of astigmatism was reappraised in the same population, for a doctoral thesis: 29 high-degree-astigmatic ( $>2.5$  D) and 33 normal children were reevaluated, to obtain longitudinal data on the evolution of their refraction error. On this occasion, the astigmatic children were evaluated by means of an autorefractor/autokeratometer (ARK 200S; Nidek) without cycloplegia, to differentiate between corneal and noncorneal astigmatism.

#### Measurements

The autorefractometer has been described elsewhere (Angi et al. 1992). In brief, the eye is viewed by means of an internal television system that enables the reflected mire image to be focused and centered within a ring displayed on a TV monitor. Once accurate focusing and proper alignment of the examined eye are ensured, the operator takes at least five measurements for each eye, and the average value is automatically estimated by the instrument computer. All refractions are recorded in diopters, by means of the minus-cylinder convention. The autokeratometer measures corneal astigmatism by projecting a collimated light from a ring mire onto the cornea. An electronic flash positioned behind the ring mire generates an image on the anterior corneal surface, and the light reflected back is captured by a photodetector system. On the basis of the light distribution in different sectors of the detector, the computer is able to calculate the corneal radii. The differences between the two major radii give the corneal astigmatism and its axis.

Corneal astigmatism was analyzed as an absolute value. The axis of the cylindrical component was regarded as being with the rule if the minus-cylinder axis was at  $180^\circ \pm 15^\circ$ , against the rule if the minus-cylinder axis was at  $90^\circ \pm 15^\circ$ , or oblique (i.e., other than either with or against the rule). To eliminate a possible bias in the classification of the astigmatic eyes, we always considered the difference between corneal astigmatism measured by the autokeratometer and refractive astigmatism simultaneously measured by the autorefractometer.

#### Criteria for Entry in the Present Study

To address the issue of availability of a complete nuclear family for testing, all individuals affected by astigmatism, and referred, for their first evaluation, to the Dipartimento di Oculistica, Università di Padova during the period 1995–96 were interviewed; none belonged to the population sample. In each consenting family, in-

formation regarding the proband, pregnancy, parents, and family history was obtained and recorded.

Since low birth weight was positively correlated with astigmatism, all astigmatic subjects who had a history of premature delivery and/or had been born small for time of gestation were excluded from this study. The proband and his or her first-degree relatives underwent an ophthalmologic examination, including a test of visual acuity, keratometry (Javal-Schiötz keratometer; Haag-Streit Berne), cycloplegic and noncycloplegic autorefractometry, slit-lamp examination of the anterior segment, and indirect ophthalmoscopy of the fundus. Families in which members had eyes with poor fixation (tropias, amblyopia, and dioptric media opacities) or ocular disease were excluded from the study.

#### Study Sample

The sample studied in the present analysis consisted of 125 nuclear families; 103 were ascertained through an affected child (incomplete selection) with both parents living, and 22 others were ascertained through seeking elderly probands with a living unaffected spouse and offspring (complete selection). The total sample therefore consisted of 476 individuals (125 probands and 351 first-degree relatives), 227 of whom were affected.

#### Analytical Methods

The pedigrees of astigmatic subjects of the study sample were analyzed by complex segregation analysis using the mixed (Morton and McLean 1974) and oligogenic (Morton et al. 1991) models. The computer programs POINTER (Lalouel and Morton 1981) and COMDS (Morton et al. 1991) were used on a SUN Sparc Classic X workstation running the UNIX operating system. Astigmatism was analyzed as a qualitative trait (affected/unaffected). Astigmatism of the right eye (REA), left eye (LEA), and either eye (EEA) was studied.

The mixed model in POINTER assumes an underlying scale of liability in which a major locus (ML), a multifactorial transmissible component, and environmental effects operate independently to produce phenotypes. POINTER tests nonfamilial, single ML (SML), polygenic, MFT, and mixed (SML and MFT) models. The ML component is determined by two alleles producing three possible genotypes. The frequency of the disease allele is denoted by " $q$ ," the distance between the two homozygote genotypes is denoted by " $t$ ," and the degree of dominance of the disease allele is denoted by " $d$ ." The MFT component is represented by  $H$  (heritability) and  $Z$  (ratio of adulthood heritability to childhood heritability).

The COMDS program assumes an oligogenic model (a major locus and a modifier locus), and incorporates information on severity and diathesis (Morton et al.

1991). The two-locus model tests whether more than one ML is involved. Transmissible effects not attributable to the major gene are assigned to a second (modifier) locus, with parameters  $qm$ ,  $tm$ , and  $dm$  equivalent, respectively, to  $q$ ,  $t$ , and  $d$  of the major gene. On the hypothesis of no familial transmission the value of  $q = qm = 0$  or  $t = tm = 0$  is expected, whereas on the hypothesis of monogenic inheritance, a value of  $qm = 0$  or  $tm = 0$  is expected. A pseudo-MFT model can be fitted (by fixing  $q = .5$  or  $q = qm = .5$ ) and is the closest approximation to the MFT model fitted in POINTER.

The parameters used to test hypotheses are estimated by maximization of the likelihood (L) of the phenotypes of the families. For monogenic inheritance and a simple phenotype (affected/normal), the POINTER and COMDS programs give identical parameter estimates, and L values differ only by a constant. Covariates with the disease under study, such as age and sex, are controlled by definition of liability classes prior to the analysis, as in the usual formulation of the liability model (Morton and McLean 1974).

In simple phenotype analyses (affected/unaffected), a significant part of the information, such as severity of the disease, is neglected. In COMDS, complex phenotypes are analyzed through an ordered polychotomy among affected individuals (severity classes [SCs]) arranged in order of increasing severity. SCs must be independent of liability classes, because severity should depend only on the genotype, not on situational variables that are considered within the liability classes (Morton et al. 1991). When severity is considered, an additional scaling parameter is introduced into COMDS, for each locus: parameters  $S$  and  $S_m$  model the effects that the ML  $g_i$  and the modifier  $g_m$ , respectively, have on the severity of the disease, through  $Sg_i + S_m g_m$ . Displacement between genotypes for SCs is assessed by these parameter estimates. These parameters describe the contribution of severity to distinguish alternative models. If  $S$  tends toward 0, very little additional information comes from assignment of an SC to each individual. Positive value estimates of  $S$  and improvement in likelihood indicate that the information retrieved by use of the phenotypic classes provides an explicit contribution in definition of the genetic model. Both probit and logistic models are implemented to calculate the conditional probability associated with each class, given genotype and penetrance.

In this study we analyzed severity by considering both the laterality (uni-/bi-) of astigmatism and its level expressed in diopters. When laterality was considered, affected individuals were classified into two different classes: SC 1 if astigmatism was present in one eye only, SC 2 if both eyes were astigmatic. When astigmatism level expressed in diopters was considered, five SCs were defined; the most severe class included astigmatism >4.4 D, and the least severe class included astigmatism of

1.0–1.25 D. The relative prevalence of each SC among affected individuals was obtained from the population sample (table 1). In agreement with the literature, individuals with astigmatism of 0–0.75 D were considered to be unaffected (class 0).

### Application of Models

POINTER and COMDS were used to calculate the likelihood of phenotypes of nuclear families sampled through an affected proband. The likelihood was corrected for ascertainment by conditioning on whether the family was identified through a parent or an offspring (Morton et al. 1991). When families were ascertained through an affected child (incomplete selection), the probability of ascertaining an individual in the population was assumed to be small, because there was, in our sample, only one proband per family (single selection), and an ascertainment probability ( $\pi$ ) approaching zero ( $\pi = .001$ ) was assumed; in families ascertained through an affected parent (complete selection), ascertainment bias was controlled by conditioning the offspring's phenotypes on the parental phenotypes. Joint likelihood was used (in the computer programs, joint likelihood defaults to conditional if a parent is recorded as a proband). The likelihood is expressed as twice the natural log likelihood,  $2\ln(L)$ .

To test the hypotheses, nested models were compared by taking the difference, in  $-2\ln(L)$  values, between models. The difference is distributed as a  $\chi^2$  with df equal to the difference between the parameters estimated in the two models.

The Akaike information criterion (AIC), defined as  $-2\ln(L) +$  twice the no. of estimated parameters (Akaike 1974), was used to compare the likelihood of models.

**Table 1**

**SCs Defined in EEA Sample**

A. SC Defined as Laterality					
SC	Status	Degree of REA	Degree of LEA	Frequency	
0	Unaffected	0–.75	0–.75	...	
1	Affected	>.75	0–.75	.502	
2	Affected	0–.75	>.75	.498	
		>.75	>.75		
B. SC Defined as Degree of Astigmatism					
SC	STATUS	DEGREE OF ASTIGMATISM	FREQUENCY OF		
			EEA	REA	LEA
0	Unaffected	0–.75	...	...	...
1	Affected	1.0–1.25	.467	.517	.491
2	Affected	1.5–2.25	.376	.328	.361
3	Affected	2.5–3.25	.114	.126	.101
4	Affected	3.5–4.25	.026	.017	.030
5	Affected	>4.25	.017	.011	.018

**Table 2**

**Distribution of Population Sample, by Astigmatism Expressed as Diopters in the More Severely Affected Eye**

Maximum Diopters	No. of Subjects
0	97
.25	237
.5	289
.75	151
1	61
1.25	46
1.5	20
1.75	27
2	21
2.25	18
2.5	11
2.75	7
3	7
3.25	1
3.5	3
3.75	2
4.25	1
4.5	1
4.75	2
5	1

By this criterion, the "best" model is considered to be that having the smallest AIC.

## Results

### Population Sample

Of the 1,046 eligible children in the health-unit territory, a total of 1,003 were screened at the ages of 18-20 and 36-40 mo. Of these, 229 had an EEA  $\geq 1.0$  D, giving a prevalence of .23. No differences were found in the degree and axis of astigmatism at ages 4-6 years, in the subsample studied during 1991 (data not published). The distribution of children on the basis of the degree of EEA was significantly skewed (Kolmogorov-Smirnov test,  $P < .0001$ ) (table 2).

A comparison of corneal and total astigmatism disclosed that the degrees of astigmatism were positively intercorrelated. In eyes with  $>.75$  D of total astigmatism, only two eyes (1.6%) showed a noncorneal astigmatism higher (1.25 D and 1.75 D) than the corneal astigmatism, and, consequently, they were reclassified. Therefore, we concluded that the distribution of corneal astigmatism in our population could be effectively evaluated by means of autorefractometry in cases with a refractive astigmatism  $\geq 1$  D. No sex differences were observed ( $P = .81$ ); thus, only one liability class was defined.

### Complex Segregation Analysis

In simple phenotype analyses (affected/unaffected), the hypotheses of no familial transmission, SML (reces-

sive, dominant, additive, and general), MFT, and general mixed model were investigated in the EEA sample by means of POINTER. When astigmatism was defined as EEA  $\geq 1$ , only the hypothesis of no familial transmission ( $\chi^2_1 = 832.09 - 818.77 = 13.32$ ;  $P = .0003$ ) could be excluded. It was not possible to distinguish between SML and MFT models, because the likelihood surface was rather flat (table 3), or to fit the mixed model (SML and MFT component).

Tests of heterogeneity were performed in the EEA sample by means of POINTER. No significant heterogeneity was found between the families in which both parents were unaffected and the families in which either one or both parents were affected, nor was it found between the families with complete selection and the families with incomplete selection (results not shown).

When complex phenotypes (affection status and severity of disease) were considered, the hypotheses of nonfamilial transmission, SML (recessive, dominant, additive, and general), pseudo-multifactorial, and two-locus model were tested by means of COMDS, for the EEA, REA, and LEA samples. When the severity parameter was constrained to 0, the likelihood surface was flat, and only the nonfamilial model could be rejected in all samples. Results for the EEA sample were close to those obtained with POINTER (results not shown). When severity of astigmatism was included ( $S$  estimated), both laterality and degree of astigmatism permitted a significant improvement in likelihood (table 4, models 6-15). However, when the degree of astigmatism was taken into account (table 4, models 11-15), the SML was significantly better than the pseudo-MFT model ( $\chi^2_1 = 285.56 - 275.41 = 10.15$ ;  $P = .0014$ ); when laterality was examined (table 4, model 6-10), the pseudo-MFT model could not be significantly excluded ( $\chi^2_1 = 640.97 - 637.92 = 3.05$ ;  $P = .08$ ).

When severity was estimated with consideration of the degree of astigmatism, the SML dominant model (model 12) provided a more parsimonious fit than did the SML general model (model 15), whereas the SML recessive could be rejected when compared with the SML general model ( $\chi^2_1 = 285.56 - 279.85 = 5.71$ ;  $P = .0169$ ). The SML dominant model with  $S = .31$  was slightly better than the SML dominant model with  $S = 1$  ( $\chi^2_1 =$

**Table 3**

**Results of POINTER Analysis for Affection Defined as EEA**

Model	$q^a$	$t$	$d^a$	$H^a$	$-2\ln(L)$	AIC
1. Sporadic	(0)			(0)	-818.77	-818.77
2. SML dominant	.0712	1.44	(1)	(0)	-833.41	-829.41
3. SML recessive	.5807	1.23	(0)	(0)	-831.37	-827.37
4. SML additive	.0628	2.91	(.5)	(0)	-833.17	-829.17
5. MFT	(0)			.40	-832.09	-830.09

<sup>a</sup> Parentheses denote that the parameter is fixed.

**Table 4**  
**Results of Segregation Analysis (COMDS) for Sample of EEA**

Model	$q^a$	$t$	$d^a$	$S^a$	$-2\ln(L)$	AIC
SC defined as laterality:						
6. Pseudo-MFT	(.5)	1.29	.05	.60	-637.92	-631.92
7. SML dominant	.0238	3.42	(1)	.19	-640.97	-634.97
8. SML recessive	.2838	3.00	(0)	.26	-638.41	-632.41
9. SML codominant	.0239	6.78	(.5)	.18	-640.87	-634.87
10. SML general	.0238	3.42	1	.19	-640.97	-632.97
SC defined as degree of astigmatism:						
11. Pseudo-MFT	(.5)	2.30	.84	1.02	-275.41	-269.41
12. SML dominant	.0181	2.67	(1)	.31	-284.69	-278.69
13. SML recessive	.2259	3.49	(0)	.35	-279.85	-273.85
14. SML codominant	.0175	5.66	(.5)	.29	-284.56	-278.56
15. SML general	.1277	6.86	.06	.29	-285.56	-277.56

<sup>a</sup> Parentheses denote that the parameter is fixed.

284.69 – 280.33 = 4.36;  $P = .0368$ ), thus indicating that this putative gene has more effect on affection than on severity of astigmatism. A gene frequency of .0181 was calculated for the SML dominant model with  $S = .31$ , and its estimated penetrance was very high (98.7%).

In the REA and LEA samples, it was possible to exclude the pseudo-MFT model, but it was not possible not to distinguish among the different SML models (results not shown). When laterality of astigmatism was considered as an increased degree of severity (table 4, models 6–10), it was not possible to distinguish among the different genetic hypotheses, even though an SML dominant model (model 7) was favored and provided the best AIC value (AIC –634.97). The estimated gene frequency for this dominant gene was .0238, and the penetrance was estimated as being complete.

There was no evidence for the presence of a second locus in our samples. The two-locus models did not fit better than the single-locus models, and the likelihood surface was rather flat.

**Discussion**

Astigmatism that is  $\geq 1$  D is a common refractive error, with a frequency of ~20% in the Caucasian population. Several studies have addressed changes in astigmatism during life; the general consensus is that astigmatism present during the 1st year of life decreases as the infant grows, but that there are few small changes after the age of 2 years and that a stable value is reached at age  $\geq 3$  years (Howland and Sayles 1985; Saunders 1995). Our data confirm these observations.

Familial aggregation of astigmatism has been noted since the 1st decade of the 20th century. However, the inheritance of astigmatism has not been extensively examined, and most studies date to the 1940s and 1950s. Several investigations of selected pedigrees and twins have documented that astigmatism is genetically trans-

mitted, but its inheritance alternatively has been found to be autosomal dominant (the result in most studies), autosomal recessive, or X linked. François (1958), Waardenburg (1963, pp. 1215–1217), and, more recently, Mash et al. (1975) have estimated a low heritability value for astigmatism. However, many ascertainment biases (among which are the ways in which pedigrees are selected and the methods that are used to measure astigmatism) may explain these findings.

Teikari and O'Donnell (1989) suggested that genetic factors do not contribute to astigmatism, leaving environmental causes as the major contributors. However, they based their study on the most recent prescription for eyeglasses required to qualify for a driving license, in a sample of 72 twin pairs for whom zygosity was determined on the basis of a questionnaire; since they found that differences in the amount of astigmatism in MZ twins were not significantly different from those in DZ twins, they concluded that genetic factors did not play a role in this defect. Mash et al. (1975) measured the right eye only, as usually is done in ophthalmologic studies, and obtained heritability estimates from regression of mean offspring scores on parent values.

We made a particular effort to examine our sample uniformly; indeed, all family members underwent ophthalmologic evaluation, to exclude noncorneal astigmatisms as well as other refractive or fixation defects. Families with members affected by poor fixation (see Subjects and Methods) also were excluded from the study. In addition, analysis was performed by use of data for REA, LEA, and EEA. When the phenotype was defined as the presence or absence of astigmatism in the samples of REA, LEA, and EEA families, POINTER analysis could not distinguish between alternative genetic models, and only the sporadic model was rejected significantly.

When the parameter  $S$ , defined as either laterality (table 1A) or degree of astigmatism (table 1B), was held at

0, COMDS analysis was equivalent to the dichotomy (affected/unaffected) of POINTER, and the results were very close. Inclusion of this parameter favored the presence of a single dominant gene in the EEA sample. When severity was considered as the degree of astigmatism, the SML dominant model and the SML codominant model provided the best fit. However, the SML model seems more favored, because, by testing for the two-locus model by means of COMDS, we were unable to obtain an improvement in likelihood. In addition, the SML dominant model was the most parsimonious. When severity was considered as laterality, information retrieved from the data was not sufficient to define the best genetic model. Through the likelihood-ratio test procedure, it was not possible to exclude a multifactorial transmission of the defect, in favor of an SML model, although the AIC slightly favored the SML dominant model. In both analyses, estimated frequency of the putative dominant gene was low (.018-.024).

The results of POINTER and COMDS analyses may explain previously published findings. Indeed, if the selection of cases is biased, and if all cases of astigmatism (corneal and non-corneal) are considered, and if only REA (LEA) is taken into account, the analysis does not have enough power to detect the gene responsible for the defect.

Moreover, the analysis of paired organs, like that of most human malformations (i.e., cleft lip, cleft palate, and anophthalmia), raises some methodological difficulties. There is no reason why laterality should be considered by itself and analyzed separately. Astigmatism can be unilateral or bilateral. A genetic study should consider the presence/absence of the astigmatism, and laterality could be used, if necessary, as a liability or severity parameter.

The analysis of *S* indicates that the putative gene has more effect on the presence of astigmatism than on its severity. Nevertheless, astigmatic individuals carrying the disease allele have a higher probability of presenting the more severe form.

Our findings define a genetic model for corneal astigmatism and provide evidence for SML inheritance, thus suggesting that genetic linkage studies could be imple-

mented. Such studies should be limited to multiplex families with severely affected individuals.

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