

The Heritability of Age-Related Cortical Cataract: The Twin Eye Study

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PURPOSE. A classical twin study was performed to establish the relative importance of genes and environment in cortical cataract.

METHODS. Five hundred six pairs of unselected female twin volunteers (226 monozygotic and 280 dizygotic) with a mean age of 62 years (range, 49–79 years) were examined. Cortical cataract was assessed using the slit-lamp–based Oxford Clinical Cataract Classification and Grading System (clinical grading) and the Wilmer Automated Grading System, which analyzed digital retroillumination images of subjects' lenses (digital grading). The worse eye categorized score for each individual was used in maximum likelihood path modeling of the correlations within twin pairs. These correlations were used to determine the underlying liability to cortical cataract.

RESULTS. Prevalence of significant cortical cataract ($\geq 5\%$ of lens area) was similar in monozygotic and dizygotic twins, occurring in 19.4% and 20.6% with the clinical grading system and 24% and 23% using the digital grading system, respectively. Modeling suggested liability to cortical cataract is explained by additive and dominant genes, individual environment, and age. Estimates of the broad sense heritability of cortical cataract were 58% (95% confidence interval [CI], 51%–64%) for the clinical grading system and 53% (95% CI, 45%–60%) for the digital system. Dominant genes were estimated to contribute to 38% (95% CI, 1%–64%) of the genetic effect with the clinical grading and 53% (95% CI, 28%–60%) with the digital grading. Individual environment explained 26% and 37% and age 16% and 11% of cortical cataract variance in clinical and digital gradings, respectively.

CONCLUSIONS. Genetic effects are important in the development of cortical cataract and involve the action of dominant genes. (*Invest Ophthalmol Vis Sci.* 2001;42:601–605)

Age-related cataract is common and is the commonest cause of blindness worldwide. The World Health Organization has recently commenced a global initiative, one of the main aims of which is to reduce the number of people blinded by cataracts, a number which is projected to reach 50 million by the year 2020 at current levels of service provision.¹ Currently,

there are no known preventive measures, and in the United States approximately 1.5 million cataract extractions are performed each year.² In the United Kingdom a backlog of visual impairment due to cataract has built up, requiring an additional 346,000 cataract operations on eyes with a visual acuity of $< 6/12$ over the next 5 years to stop the backlog from increasing.³ Cortical cataract is the commonest type of lens opacity occurring in the population under the age of 75 years, occurring in up to 13% of those aged 55 to 64 years, and in more than 40% of those aged 75 to 84 years.^{4–6}

To date most epidemiologic research into the etiology of cortical cataract has concentrated on environmental risk factors. Age is an important risk factor, and women seem to be more at risk.^{4,5,7} The odds of having cortical opacities are four times greater among African Americans than among whites.⁸ Sunlight has been associated with cortical cataracts in a general population study⁹; a doubling of exposure to UV light increased the risk of cortical cataract by 60% in a population with high UV exposure.¹⁰ Although oxidation of lens proteins is associated with cataract formation, evidence for protection by antioxidant vitamin supplementation is conflicting.^{7,11–13} Smoking,^{7,14} hormonal status,¹⁵ and hypertension¹⁶ seem not to be related to cortical cataract.

There has been little research into genetic factors in cortical cataract. A segregation analysis of more than 500 sibships (1275 individuals) from the Beaver Dam Eye Study suggested a major gene could account for 75% and 45% of the variability among men and women, respectively, for cortical cataract.¹⁷ There are now several reported mutations in congenital cataract,¹⁸ and genes may be involved in adult cataract either directly or by increasing susceptibility to environmental risk factors.

Twins provide the ideal design to study and quantify the relative importance of genetic and environmental factors.¹⁹ To our knowledge, this is the first classical twin study set up to examine the heritability of cortical cataract. Cortical cataract was systematically graded in a large sample of female twins aged over 49 years to estimate the relative role of genes and environment.

METHODS

Subjects

A total of 506 twin pairs, 226 monozygotic (MZ) and 280 dizygotic (DZ), between the ages of 49 and 79 were examined. They were all female, white twin pairs from the St. Thomas' United Kingdom Adult Twin Registry, which is ascertained from the general population through national media campaigns in the United Kingdom.²⁰ The research followed the tenets of the Declaration of Helsinki. The twins were initially recruited after local ethics committee approval was obtained, were unaware of any hypotheses and proposals for an eye examination, and gave informed consent. Zygosity was determined by standardized questionnaire²¹ and was confirmed by DNA short tandem repeat fingerprinting when doubt existed.

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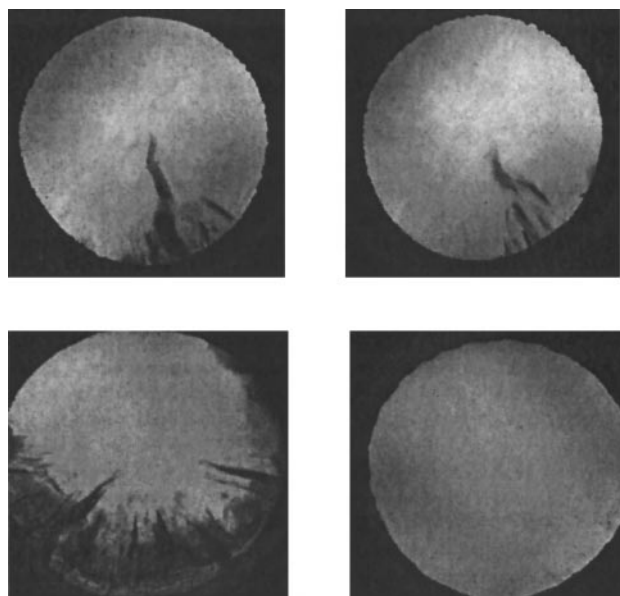


FIGURE 1. Examples of retroillumination photographs of cortical cataract. The *top* two images: right eyes of a pair of 62-year-old monozygotic twins, which show strong concordance. *Bottom* images: right eyes of a pair of 64-year-old twins who are discordant for cortical cataract.

Measurements

The amount of cortical cataract in each eye was graded by a single investigator (CJH) using the subjective Oxford Clinical Cataract Classification and Grading System ("clinical grading"),²² approximately 1 hour after dilation using 1% tropicamide and 10% phenylephrine. Each lens was given a "cortical spoke" score from 0 to 5 in decimalized steps,²³ based on the area of lens within the pupil opaque due to cortical cataract. The clinical grading system is reproducible²⁴ and cortical cataract scores are comparable to those from other subjective grading systems, for example, the Lens Opacity Classification System (LOCS).^{25,26}

An objective grading system was also used because of potential bias due to knowledge of twins' zygosity, because they were seen together. A digitized retroillumination camera system²⁷ (Marcher Enterprises Ltd., www.marcher.co.uk) was used and was focused on the pupil edge, with exposure set to maximize differences in contrast between cataractous and clear lens. Images were stored on computer and analyzed using the Wilmer Automated Cortical Cataract Grading System ("digital grading").²⁸ This automated evaluation procedure consists of a pupillary segmentation algorithm, a secondary segmentation algorithm that identifies regions of opacification based on gray level and texture, and finally a procedure that extracts various classification features. Fuzzy decision concepts are used in identification of cataractous regions. Opacification metrics include area, position, and morphology. Examples of retroillumination photographs are shown in Figure 1.

Of the 1012 subjects (2024 eyes), 30 eyes were excluded from clinical grading analysis: 24 eyes were pseudophakic (had previous cataract surgery) and 6 were ungradeable because of previous eye surgery or injury. Of the remaining 1994 eyes, images of 51 were unavailable for automated digital grading, leaving 1943 eyes undergoing both clinical and digital grading. To use the most informative data, the score for each individual's worse eye was used for subsequent analysis, or if one eye had already had a cataract extraction, then the score from the other eye was used.

Analytical Approach

The variance of a phenotype in a population is due to genetic and environmental factors. Most traits or diseases occur more commonly in

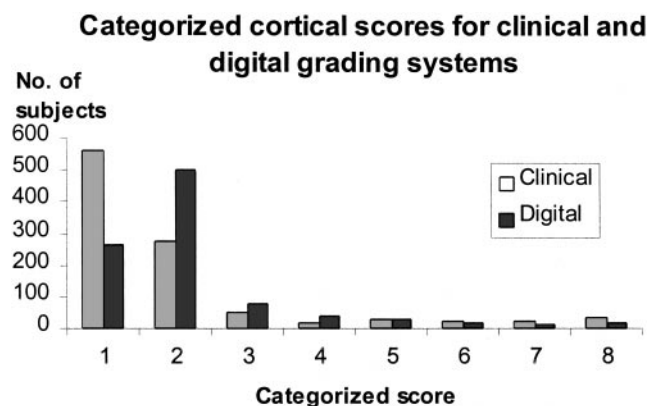


FIGURE 2. The distribution of categorized cortical cataract scores for the clinical and digital grading systems in the worse eye of each individual. The grades are 1, no cortical cataract; 2, <5% area of lens covered by cataract; 3, $\geq 5\%$ and <10%; 4, $\geq 10\%$ and <20%; 5, $\geq 20\%$ and <30%; 6, $\geq 30\%$ and <40%; 7, $\geq 40\%$ and <50%; 8, $\geq 50\%$.

the families of affected individuals than in the general population, but as families share both genes and environment, it is difficult to separate out the effects of each. Because identical or MZ twin pairs share the same genes and nonidentical or DZ twins share on average half of their segregating genes, any greater concordance or correlation between MZ twins can be attributed to this additional genetic sharing. Twin models assume that both MZ and DZ twins share roughly the same common family environment (the equal environment assumption).²⁹

Model Fitting Procedure

Use of quantitative genetic model fitting in twin studies is now standard and is fully described elsewhere.^{30,31} The technique is based on the comparison of the covariances (or correlations) within MZ and DZ twin pairs. It allows separation of the observed phenotypic variance into additive (A) or dominant (D) genetic components and common (C) or unique (E) environmental components. E also contains measurement error. The broad-sense heritability, which estimates the extent to which variation in liability to disease in a population can be explained

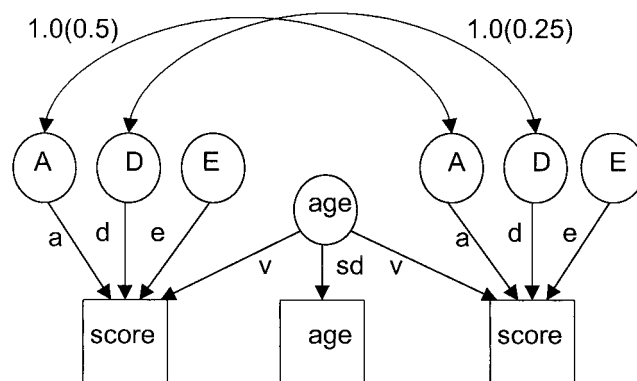


FIGURE 3. Path model for the cataract scores for twin 1 and twin 2 (score 1 and score 2) and age. Observed scores are represented in *squares*; latent factors are represented in *circles*. A, D, and E, the additive genetic, dominant genetic, and unique environmental influences, respectively. C, the common environmental influence, was also tested but is omitted to simplify the diagram. The correlation between the latent additive genetic factors is 1 for monozygotic twin pairs and 0.5 for dizygotic twin pairs. For the dominant genetic factors the correlation is 1 and 0.25 for the monozygotic and dizygotic twin pairs, respectively. Regression coefficients of the observed variables on the different latent factors are shown in *lower case*: a, additive genetic effect; v, age-effect; d, dominant genetic effect; e, unique environmental effect; sd, the SD of age.

TABLE 1. Prevalence of Cortical Cataract in the Worse Eye of MZ and DZ Twins

Grading	MZ: Area of Cataract			DZ: Area of Cataract		
	<i>n</i>	≥5%	≥10%	<i>n</i>	≥5%	≥10%
Clinical grading	443	19.4	13	549	20.6	13
Digital grading	424	24	16	534	23	14

n, number of subjects analyzed.

by genetic variation, can be defined as the ratio of genetic variance (A + D) to total phenotypic variance (A + D + C + E).

The maximum likelihood modeling methods used in twin analysis (modeling twin covariances) assume that the trait being analyzed must be normally distributed. This is not true for cortical cataract (see Fig. 2). The genetic and environmental contributions can, however, be quantified by assuming there is a continuous underlying liability to disease (involving multiple genetic and environmental factors). The correlation in liability among twins can be estimated from the frequencies of disease-concordant and disease-discordant pairs, using a multiple threshold model.^{30,32} Multiple thresholds were created by categorizing the amount of cortical cataract into eight categories for both clinical and digital grading systems, rather than using continuous data of cortical scores. Age, an important risk factor in cortical cataract, is the same for twins and so would inflate both MZ and DZ correlations if not accounted for.³³ Therefore, polyserial correlation matrices, including correlations between age (a continuous trait) and cataract (categorical data), were calculated for MZ and DZ twin pairs using PRELIS.³⁴ These polyserial correlation matrices were used in the Mx genetic modeling program.³⁵ Figure 3 illustrates the twin model used for analysis.

The significance of variance components A, C, and D and age was assessed by removing each sequentially in submodels and testing the deterioration in model fit after each component was dropped from the full model. This leads to a model explaining the variance and covariances with 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. Data handling and preliminary analyses were done with STATA.³⁶

RESULTS

There were 226 MZ twin pairs and 280 DZ twin pairs. The mean age of MZ twins was 62.4 ± 5.7 years (mean \pm SD; range,

51–75 years), and the mean age of DZ twins was 62.1 ± 5.7 years (range, 49–79 years). The prevalence of cortical cataract (worse eye) for the two grading systems and number of eyes graded by each are given in Table 1. The prevalence of cortical cataract was similar for MZ and DZ twins for both grading systems. Prevalence of significant cortical cataract ($\geq 5\%$ and $\geq 10\%$ of the lens area visible within the pupil for MZ and DZ twins, respectively) was similar for both grading systems.

The subjective clinical and objective digital grading systems were correlated with a (Spearman) correlation coefficient of 0.6.³⁷ The twin correlations were significantly higher for MZ than for DZ pairs: 0.74 and 0.36 for the clinical gradings and 0.64 and 0.20 for the digital gradings, respectively. Both scores were categorized into eight categories, details of which are given in Figure 2.

Results of the modeling analysis are illustrated in Table 2. They show that for both grading systems, the best-fitting model was the ADE model including age. This means the effects of additive and dominant genes, individual environment, and age explain the variance of liability to cortical cataract within this population. There was a significant loss of fit if any of these were excluded from the model, but if the effect of common environment (C) was removed, the fit of the models did not change.

The broad-sense heritability (additive and dominant genetic effect) was estimated to be 58% (95% confidence interval [CI], 51%–64%) for the clinical grading and 53% (95% CI, 45%–60%) for the digital grading. Dominance accounted for all the genetic effect in the digital grading, and 38% of the clinical grading, both with wide but similar confidence intervals. Parameter estimates of the components and their 95% CIs for the best-fitting models are given in Table 3. Age explained 16% and 11% of the variance, and individual environment 26% and 37% of the variance of cortical cataract in clinical and digital gradings, respectively.

DISCUSSION

We have demonstrated that genes are important in cortical cataract, with a heritability of 53% to 58% in this population and that the inheritance of cortical cataract appears to involve dominant genes. Unique environment explained 26% to 37% of the variance. Compared with our twin study of nuclear cataract,³⁸ heritability was similar at 48%, with a lower environmental effect of 14%. Age effects were more important in nuclear cataract, explaining 38% of the variance compared with 11% to 16% of the variance of cortical cataract. The importance of genetic factors may explain the racial differ-

TABLE 2. Model-Fitting Results for Analysis of Cortical Cataract Scores Using Clinical and Digital Grading Systems

Measure	Model	χ^2	$\Delta\chi^2$	df	Versus Model	<i>P</i>
Clinical grading	1. ADE	4.752	—	—	—	—
	2. ACE	8.829	4.077	—	—	—
	3. ACE no age	122.325	113.496	1	2	<0.001
	4. AE	8.829	4.077	1	1	0.04
	5. CE	57.904	49.075	1	2	<0.001
Digital grading	1. ADE	1.843	—	—	—	—
	2. ACE	13.355	11.512	—	—	—
	3. ACE no age	90.012	76.657	1	2	<0.001
	4. AE	13.355	11.512	1	1	<0.001
	5. CE	48.587	35.232	1	2	<0.001

A, D, C, and E, additive genetic, dominant genetic, common environment, and unique environmental effects, respectively; χ^2 , chi-square goodness-of-fit statistic; $\Delta\chi^2$, change in χ^2 comparing submodel with full ADE or ACE and age model; df, change in degrees of freedom between submodel and full model; *P*, probability that $\Delta\chi^2$ is zero. All models include age, except the ACE no age model.

TABLE 3. Standardized Parameter Estimates and 95% CIs of the Best-Fitting Models of Cortical Cataract for Clinical and Digital Grading Systems

Measure	a ²	d ²	e ²	Age
Clinical grading	0.20 (0-0.57)	0.38 (0.01-0.64)	0.26 (0.22-0.31)	0.16 (0.12-0.21)
Digital grading	0 (0-0.24)	0.53 (0.28-0.60)	0.37 (0.30-0.43)	0.11 (0.07-0.15)

Values in parentheses are 95% CIs.
 a², proportion of variance due to additive genes; d², proportion of variance due to dominant genes;
 e², proportion due to individual environmental effects; age, proportion due to age effects.

ences in cortical cataract; risk factors for African-Americans behave in the same way as whites, but cortical cataract is four times as common.⁸

The only other family study of cortical cataract used comingling analysis and showed that two transformed distributions fitted better than one, which would fit with a dominant or recessive transmission hypothesis.¹⁷ However, its complex segregation analysis predicted a major recessive gene accounting for 45% of the variance in women, different from this study's estimation of additive and dominant genetic effects. Complex segregation analysis may have little ability to distinguish among the many possible modes of inheritance for complex traits.³⁹ Twin studies do not provide useful data on segregation and do not estimate possible major gene effects but assume that the liability to cortical cataract is influenced by multiple genetic and environmental effects.

The two grading systems correlated reasonably with each other and came up with similar prevalences, reducing concern about bias in the subjective clinical grading (the zygosity of the twins was obvious at the time of observation). However, the two approaches did differ for the lower categories of cortical cataract affecting less than 5% of the pupillary area (Fig. 2); this difference is because the objective classification using the digital grading system graded minor noncortical peripheral lens changes (such as coronary flakes or shadow due to corneal arcus) as evidence of opacity, whereas the subjective clinical grading did not. For significant levels of cataract the grading systems agreed more closely; for example, the clinical grading system estimated a prevalence of 13% and the digital 14% for twins with lens area of cataract equal to or greater than 10% (\geq grade 4), as in Table 1.

The heritability estimates for the two grading systems were similar at 53% and 58%, and model-fitting analysis of both suggested dominant genes are important in cortical cataract inheritance. In general, twin studies have low power to detect dominance because of the low DZ correlation,⁴⁰ which explains the wide CIs (Table 3). Although the estimates of dominant genetic effect were different for the two grading systems (38% and 53%), the CIs are similar for both and in neither could the effect of dominant genes be removed without significant loss of fit (Table 2). Although the CIs of additive genes include zero, it is generally accepted that both additive and dominant genes must be included in total heritability,⁴¹ so the effect of removing additive genes from the model cannot be tested.

In general twins show morbidity and mortality similar to the rest of the population, and the assumption that they share equal environments has stood up to considerable scrutiny.²⁹ In this study 35% of eyes had some cortical cataract, similar to the prevalence of 36% in a study of similar British adults aged 55 to 74 years.⁶ The results from this twin study therefore are probably generalizable to the population, but it should be noted that heritability is population-specific and might be different for a different population, for example, one more exposed to UV radiation from sunlight. All twins in this study were volunteers, but they were initially recruited unaware of the eye test or of its reason when asked to attend for the eye examination to reduce potential bias.

In conclusion, we have demonstrated that genetic effects are important in the development of cortical cataract in this twin population, with a heritability of 53% and 58% for the two grading systems used. Dominant genetic effects seem to be significant. These results may lead to the search for genes involved in cortical cataract, to further elucidate the mechanisms in cataract formation and to identify potential disease-modifying agents or environmental interventions to reduce disease in susceptible individuals.

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