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ORIGINAL CONTRIBUTIONS

Polygenic Effects and Cigarette Smoking Account for a Portion of the Familial Aggregation of Nuclear Sclerosis

Alison P. Klein[1], Priya Duggal[1], Kristine E. Lee[2], Jennifer A. O'Neill[1], Ronald Klein[2], Joan E. Bailey-Wilson[1], and Barbara E. K. Klein[2]

[1] Statistical Genetics Section, Inherited Disease Research Branch, National Human Genome Research Institute, Baltimore, MD.
[2] Department of Ophthalmology and Visual Sciences, University of Wisconsin Medical School, Madison, WI.

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Cataract is the most common cause of blindness worldwide. Nuclear cataract, an advanced stage of nuclear sclerosis, is the most common type of age-related cataract. The authors assessed data from 2,089 persons within 620 extended pedigrees who participated in the 1988–1990 Beaver Dam Eye Study in Wisconsin to determine whether the observed familial aggregation of nuclear sclerosis could be explained by inheritance of a major gene. Familial correlations were examined and segregation analyses were performed on nuclear sclerosis measurements adjusted for age, sex, and pack-years of cigarette smoking. There was modest correlation among close family members after adjustment for age, sex, and pack-years of cigarette smoking: 0.084 between parents and offspring, and 0.198 between sibling pairs. Although results do not support involvement of a single major locus in the etiology of nuclear sclerosis, models that allowed for familial correlation, attributable in part to polygenic effects, did provide a better fit to the observed data than models without a polygenic effect. This finding suggests that several genes of modest effect may influence development of nuclear lens opacity, possibly in conjunction with environmental factors. Cigarette smoking was an important covariate in these analyses. Overall, results highlight the complex etiology of nuclear sclerosis.

cataract; eye diseases; family; genes; genetic predisposition to disease; heredity; smoking

Abbreviation: SD, standard deviation.

Cataract is the leading cause of blindness worldwide. In the United States, cataract surgery is the most commonly performed ophthalmologic procedure, and the annual cost is about $3.4 billion (1). Nuclear cataract, an advanced stage of nuclear sclerosis, is the most common form of age-related cataract (2, 3).

Previous studies, including those conducted within this cohort, the Beaver Dam Eye Study, have indicated that

Correspondence to Dr. Barbara E. K. Klein, Department of Ophthalmology and Visual Sciences, University of Wisconsin-Madison, Ocular Epidemiology, 610 North Walnut Street, Room 409, Madison, WI 53726 (e-mail: kleinb@epi.ophth.wisc.edu).

a family history of nuclear cataract (4, 5), cigarette smoking (6–10), female gender (11–13), and increasing age are associated with an increased risk of nuclear cataract. A recent study by McCarty et al. (14) found that the population attributable risk of cataract due to smoking was 17 percent (95 percent confidence interval: 16 percent, 18 percent).

Studies have shown that inherited genetic factors may also play a role in the development of age-related nuclear cataract. Hammond et al. (5) examined 506 pairs of female twins (226 monozygotic and 280 dizygotic) and concluded that additive genetic factors may explain 48 percent of the variation in the severity of nuclear sclerosis. There was no evidence in these data to support the influence of dominant genetic effects. Additionally, age explained 38 percent of the variation in nuclear sclerosis, and smoking accounted for 14 percent (5). Previous analysis of 1,247 participants in the Beaver Dam Eye Study who could be classified into one of 564 sibships found that measurements of nuclear sclerosis for the right eye, the left eye, and the sum of the right and left eyes were highly correlated between siblings (4). Segregation analysis of the sum of nuclear sclerosis measurements for the right and left eyes, adjusted for age and sex effects, supported the involvement of a major gene accounting for 35 percent of the variability in nuclear sclerosis within these 564 sibships (4). However, because only sibship data were available previously, correlations between other pairs of relatives (parent-offspring, avuncular pairs, and cousins) as well as regressive familial effects (polygenic/multifactorial effects) within the segregation analysis could not be directly estimated. Additionally, the influence of cigarette smoking, a known risk factor for nuclear sclerosis, was not included in these analyses.

Therefore, to confirm results of the previous analyses, to further examine the influence of additional shared familial effects, and to examine the impact of incorporating cigarette smoking in the analysis, we examined familial correlations and performed segregation analyses on the extended pedigree data now available as part of the Beaver Dam Eye Study.

MATERIALS AND METHODS

This study was reviewed and approved by the institutional review board of the University of Wisconsin School of Medicine. In addition, informed consent was obtained from all study participants.

Study population

Of the 5,924 persons aged 43–84 years who resided in the township of Beaver Dam, Wisconsin, 4,926 participated in the baseline examination of the Beaver Dam Eye Study conducted between 1988 and 1990 (15). The recruitment methods and study procedures have been described in detail elsewhere (16). At baseline, complete eye examinations were given, including photography of the lens, and family relationship information was obtained from all participants. At the first follow-up visit, conducted between 1993 and 1995, family relationships, including extended pedigree information, were confirmed (17). For the participants of the baseline examination, data on family relationships were available for 2,783 participants, 2,089 of whom had complete information on age, sex, and cigarette smoking (pack-years) and nuclear sclerosis measurements. Pack-years of cigarette smoking were determined by number of cigarettes smoked per day divided by 20, multiplied by the number of years of smoking.

Measurement of nuclear sclerosis

Nuclear sclerosis measurements were obtained by grading slit-lamp photographs of the lens. The details, including reliability, of these grading procedures have been described elsewhere (8, 18). In brief, photographs were taken of each eye by using a Topcon SL5 photo slit-lamp camera (Topcon America Corp., Paramus, New Jersey). Each photograph was then graded for severity of nuclear sclerosis by comparing it to four standard photographs of increasing severity of nuclear sclerosis. The severity grades were defined as follows: grade 1, as clear or clearer than standard 1; grade 2, not as clear as standard 1 but as clear or clearer than standard 2; grade 3, not as clear as standard 2 but as clear or clearer than standard 3; grade 4, not as clear as standard 3 but as clear or clearer than standard 4; and grade 5, more severe than standard 4. Monocular cases and pseudophakic cases were excluded from the analyses. Only phenotype information from persons who participated in the baseline examination of the Beaver Dam Eye Study was included in this analysis.

Statistical analysis

Familial correlation analysis was performed by using FCOR, version 4.1 of S.A.G.E., and segregation analysis was performed by using REGC, version 2.1 of S.A.G.E. (19), and REGCHUNT (20).

FCOR is used to compute the correlations in trait values between pairs of relatives. Correlations were calculated between the following relative pairs: parents and offspring, siblings, avuncular, and cousins. Equal weight was given to each pair of relatives (21) (i.e., each pair of siblings in a sibship of size two was given the same weight as each pair of siblings in a sibship of size three or larger).

REGC is used to perform segregation analysis of continuous traits and is based on the regressive models proposed by Bonney (19, 22, 23). These analyses test for autosomal inheritance of a single biallelic major locus that influences nuclear sclerosis by obtaining maximum likelihood estimates for parameters that describe the distribution of nuclear sclerosis in this population. If models in which these parameters are fixed to what is expected under Mendelian law describe the data as well as a more general model, then there is evidence for the influence of a major gene in the etiology of nuclear sclerosis. To estimate whether a single normal distribution with mean and variance denoted μ and σ, respectively, provides an adequate description of the data, or whether a mixture of two or three normal distributions provides a significantly better description of the data, mixtures of distributions are fit to the

TABLE 1. Demographics of families in the Beaver Dam Eye Study, Wisconsin, 1988–1990

	Male ($n = 926$)	Female ($n = 1,163$)	p value
Mean age (years)	60.81 (10.47)*	63.60 (11.21)	
Mean nuclear sclerosis grade			
Right eye	2.33 (0.86)	2.64 (0.92)	<0.001
Left eye	2.34 (0.85)	2.64 (0.92)	<0.001
Sum of the right and left eyes	4.67 (1.57)	5.28 (1.72)	<0.001
Smoking status (no.)			
Never smoker	274	722	
Ever smoker	652	441	
Mean pack-years of smoking	37.87 (32.81)	25.32 (22.80)	<0.001

* Numbers in parentheses, standard deviation.

observed data. Box-Cox transformation of the data is estimated as part of the analysis, denoted by parameters λ_1 and λ_2, respectively, to ensure that data are on the proper scale (24).

Additionally, the proportion of persons in each of the distributions, known as the ''type'' frequencies, must also be estimated. This ''type'' represents an underlying discrete trait that influences nuclear sclerosis score (i.e., a person with a ''low risk type'' would have, on average, a lower degree of nuclear sclerosis than a person with a ''high risk type'') (23). In the models that test for inheritance of a major gene, type represents a genotype; however, for models that test for nongenetic factors, type is interpreted as levels of exposure to an unmeasured major environmental risk factor that is not correlated between family members. Three possible types are considered, which, for Mendelian inheritance, represent the two homozygotes AA and BB and the heterozygote AB. However, given that these types must sum to 1, only two parameters are estimated, denoted q_A and q_B. When Hardy-Weinberg equilibrium is assumed ($q_A^2 + 2q_Aq_B + q_B^2 = 1$), only a single parameter q_A is estimated.

To test whether each person's type is shared between parent and offspring in the proportions anticipated under Mendelian expectation, transmission parameters (denoted by τ) are estimated. These parameters represent the probability that a parent will transmit A, given his/her own type (i.e., the probability that a parent with a given genotype will transmit an A allele for genetic models), to his/her offspring. Under Mendelian expectation, transmission parameters are fixed to 1 for parents of type AA, 0.5 for parents of type AB, and 0 for parents of type BB, denoted as τ_{AA}, τ_{AB}, and τ_{BB}, respectively. All of these transmission parameters not being constrained to their expectation under Mendelian law represent environmental factors influencing the phenotype.

Analysis was performed under class D models, which assume that dependency between sets of siblings is equal (i.e., not impacted by birth order, etc.) but not due to common parentage alone. Thus, additional familial correlations can be estimated within these analyses to account for other genes of small effect (polygenes) or other environmental factors shared among family members that influence the degree of nuclear sclerosis. These additional correlations include spousal (ρ_{fm}), parent and offspring (ρ_{po}), and sibling (ρ_{ss}). Furthermore, because age and sex are known to be important determinants of nuclear sclerosis, they were included in the analysis. Analysis was performed by including and excluding pack-years of cigarette smoking exposure as a covariate.

Likelihood ratio tests and Akaike Information Criterion A were used to select the most parsimonious model that adequately described the observed nuclear sclerosis data. Likelihood ratio tests were computed as -2 times the difference in lnLikelihood of the general model compared with a nested model. This test statistic was then compared with a χ^2 distribution in which the degrees of freedom were equal to the difference in the number of parameters estimated in the general compared with the nested model. When parameters in the general model maximized at a boundary, a mixture of χ^2 distributions was used to compute p values (25). Akaike Information Criterion A allows nonnested models to be compared by taking 2 lnLikelihood of the model plus a correction of 2 (degrees of freedom of the model) to estimate additional parameters (26).

Given that these data were obtained through a population-based survey, no correction for ascertainment was necessary in these segregation analyses.

RESULTS

Overall, 2,089 participants in the baseline examination of the Beaver Dam Eye Study were members of families and had complete data on age, sex, and cigarette smoking and nuclear sclerosis measurements. An overview of the demographics of this study population is presented in table 1. Of the 2,089 persons included in these analyses, 1,163 (55.7 percent) were female and 926 (44.3 percent) were male. Mean age at examination was 63.6 (standard deviation (SD), 11.21) years for women and 60.8 (SD, 10.47) years for men. For each participant, grade of nuclear opacity was highly correlated between the right and left eyes

TABLE 2. Familial correlation of baseline nuclear sclerosis measurements in the Beaver Dam Eye Study, Wisconsin, 1988–1990

Relationship	No. of pairs	Correlation (standard error)		
		Crude	Adjusted for age and sex	Adjusted for age, sex, and pack-years of cigarette smoking
Parent-offspring	380	0.180 (0.055)	0.107 (0.051)	0.084 (0.051)
Sibling	943	0.401 (0.038)	0.201 (0.038)	0.198 (0.038)
Avuncular	584	0.049 (0.069)	0.046 (0.053)	0.042 (0.052)
Cousin	1,421	0.275 (0.043)	0.063 (0.034)	0.061 (0.034)

(0.74 and 0.70 for females and males, respectively). On the basis of these results, and to allow comparison with previous studies, we chose to examine the sum of the nuclear sclerosis grades for the right and left eyes. As was observed in the entire Beaver Dam Eye Study cohort, the mean grading of the sum of nuclear opacity in the subgroup used for these analyses was greater for females compared with males: 5.27 (SD, 1.72) and 4.67 (SD, 1.51), respectively (*t*-test $p < 0.001$).

Familial correlation analysis

The results of the familial correlation analysis are presented in table 2. Overall, correlations were higher before adjustment for age, sex, and pack-years of cigarette smoking, which is unsurprising given that certain risk factors may also be correlated among some relative pairs (i.e., smoking among all family members and age among siblings and cousins). Among the 2,089 persons in the 620 extended pedigrees, there was moderate positive correlation in nuclear sclerosis measurements after adjustment for age, sex, and pack-years of cigarette smoking between siblings (0.198) and between parents and offspring (0.084). Avuncular pairs and cousin pairs also showed a positive correlation (0.042 and 0.061, respectively) but to a lesser extent than more closely related pairs. These results support the involvement of genetic influences in the etiology of nuclear sclerosis because correlations are highest among closely related pairs of relatives and are lower among more distant relatives.

Segregation analysis

The results of the complete segregation analysis with regard to smoking are presented in table 3. Models including smoking as a covariate provided a much better fit to the observed data than models that ignored the influence of smoking ($p < 0.0001$: model L vs. M). Overall, the three-distribution models (models F, G, I, K, L, M) provided a better fit to the observed data than the single- or two-distribution models (models A–E, H). Additionally, models that allowed for polygenic/multifactorial effects through estimation of additional familial correlations provided a better fit to the data than models that did not allow for these correlations (models A and K vs. C and M, respectively). All of the no-major-effect, Mendelian, and environmental models were rejected as not providing an adequate fit to the data when compared with the general model (models A–J vs. M). However, the codominant (three genotypic means) major locus plus polygenic/multifactorial model was only borderline rejected ($p = 0.035$) and had the second lowest Akaike Information Criterion A (model G). A model with three genotypic means and a polygenic/multifactorial component in which τ_{AB} was estimated but τ_{AA} and τ_{BB} were fixed to 1 and 0, respectively (their expected values under Mendelian inheritance), was not rejected compared with the general model ($p > 0.10$) (model J vs. M). This model also had the lowest Akaike Information Criterion A score (6,677.19). This is a genetic model that allows deviation from what is expected if the trait under investigation is not a simple Mendelian disorder (a trait under the control of a single gene with little impact of environmental factors).

These study results suggest that no *single* major gene is involved in controlling the severity of nuclear sclerosis. However, they suggest the involvement of multiple genes of more modest effect or more complex environmental models (beyond what can be modeled with these data and using these analytical methods) or any combination thereof in controlling nuclear sclerosis.

DISCUSSION

Our analysis confirmed that nuclear sclerosis is moderately correlated among family members. Although we did not find evidence supporting the involvement of a single major gene or of a purely environmental model (after adjusting for personal smoking) in the etiology of nuclear sclerosis, our results suggest that the etiology of nuclear sclerosis is quite complex and may be due to a variety of genes of modest effect and environmental factors. Because models that included a polygenic/multifactorial component provided a better fit to the data, several genes of small-to-modest effect may be involved in the development of nuclear sclerosis. The observation that smoking did improve the fit of these models indicated that smoking may be an important confounder or modifier of risk and should be considered in any genetic analysis of nuclear sclerosis. Similar patterns of results have been observed for other complex disorders, for which further studies demonstrated that multiple loci influence the trait (e.g., hereditary nonpolyposis colorectal cancer) (27).

Unlike the previous segregation analysis performed on a subset of these data, which was limited to sibship data only and did not take into account personal cigarette smoking

TABLE 3. Segregation analysis of baseline nuclear sclerosis measurements in the Beaver Dam Eye Study, Wisconsin, 1988–1990*

Model and covariate(s)	q[A]†	τ_{AA}	τ_{AB}	τ_{BB}	μ_{AA}	μ_{AB}	μ_{BB}	σ^2	ρ_{PO}	ρ_{SS}	λ_1	Age	Sex	Pack-years of smoking	−2lnL‡	df	χ^2	p value	AIC‡
A. No major gene + smoking	[1.000]				4.1509	$= \mu_{AA}$	$= \mu_{AA}$	1.4472	[0]	[0]	0.8489	0.1020	−0.4123	0.0059	6,700.49	6	49.94	<0.0001	6,712.49
B. No major gene + correlations	[1.000]				3.9844	$= \mu_{AA}$	$= \mu_{AA}$	1.4687	0.1151	0.1468	0.8760	0.1045	−0.3016	[0]	6,706.70	5	56.15	<0.0001	6,718.70
C. No major gene + correlations + smoking	[1.000]				3.9267	$= \mu_{AA}$	$= \mu_{AA}$	1.4450	0.0919	0.1462	0.8832	0.1043	−0.4015	0.0058	6,675.05	8	24.5	0.0003	6,691.05
D. Dominant major gene + correlations + smoking	0.4972	[1.0]	[0.5]	[0]	3.3047	$= \mu_{AA}$	4.7674	1.0568	0.0437	0.0834	1.0618	0.1028	−0.3905	0.0055	6,663.93	10	13.4	0.007	6,683.93
E. Recessive major gene + correlations + smoking	0.5028	[1.0]	[0.5]	[0]	4.7675	$= \mu_{BB}$	3.3050	1.0568	0.0437	0.0834	1.0617	0.1029	−0.3905	0.0059	6,663.92	10	13.4	0.007	6,683.92
F. Codominant major gene + correlations	0.4000	[1.0]	[0.5]	[0]	5.1900	$= \mu_{BB}$	3.7375	0.8872	−0.0679	0.0235	1.1080	0.1025	−0.2833	[0]	6,688.38	10	37.83	<0.0001	6,708.38
G. Codominant major gene + correlations + smoking	0.4243	[1.0]	[0.5]	[0]	5.1251	3.8545	2.9095	0.8825	−0.1218	0.0163	1.0238	0.1023	−0.3846	0.0056	6,658.41	11	7.85	0.035	6,680.41
H. Environmental −2 means + correlations + smoking	0.0674	0.000	$= \tau_{AA}$	$= \tau_{AA}$	2.3562	$= \mu_{BB}$	3.8248	1.4227	0.0945	0.1505	0.8809	0.1061	−0.4074	0.0058	6,670.19	11	19.4	0.0001	6,692.19
I. Environmental −3 means + correlations + smoking	0.6969	0.0725	$= \tau_{AA}$	$= \tau_{AA}$	2.8430	4.7069	3.6054	1.2463	0.1170	0.1560	0.9558	0.1048	−0.3959	0.0057	6,661.99	12	11.4	0.002	6,685.99
J. τ_{AB} estimated + correlations + smoking	0.4769	[1.0]	0.0680	[0]	2.7326	4.8827	3.9378	1.1370	0.1497	0.0525	0.8132	0.1027	−0.3950	0.0056	6,653.19	12	2.63	0.187	6,677.19
K. General + smoking	0.4205	0.1596	0.7230	0§	5.3341	3.9211	2.9438	0.8389	[0]	[0]	1.1042	0.0982	−0.3746	0.0055	6,658.40	11–12	7.85	0.019	6,682.40
L. General + correlations	0.4897	1.0§	0.9562	0.1068	4.0284	5.0091	2.6775	1.1286	0.1907	0.0599	0.7902	0.1031	−0.2962	[0]	6,679.17	12–13	27.17	<0.0001	6,705.55
M. General + correlations + smoking	0.4739	1.0§	0.9494	0.1110	3.9088	4.8850	2.6837	1.1060	0.1572	0.0599	0.8096	0.1031	−0.3910	0.0055	6,650.55	13–14			6,684.55

* Refer to the Materials and Methods section of the text for more detail on parameter definition. Briefly, q[A] represents "type" frequency, τ (τ_{AA}, τ_{AB}, τ_{BB}) represents transmission frequency, μ (μ_{AA}, μ_{AB}, μ_{BB}) represents the mean adjusted nuclear sclerosis score by type, σ^2 represents the variance, ρ_{PO} and ρ_{ss} represent residual correlations, and λ_1 represents the power parameter of the Box-Cox transformation (24). λ_2, the scale parameter of the Box-Cox transformation, was fixed to 6.10.

† Brackets ([ ]) indicate that a parameter is fixed at the value given.

‡ L, likelihood; AIC, Akaike Information Criterion A.

§ Indicates that the parameter maximized the boundary.

exposure (4), our results did not support the involvement of a recessive major gene. Even when smoking was not included in the analysis, recessive (results not shown) and codominant Mendelian ($p = 0.02$: model F vs. L (table 3)) models were rejected compared with the general model. Inclusion of additional pairs of relatives and linking of sibships to form larger pedigrees may have resulted in greater power to observe deviations from the patterns expected if there was a recessive major gene that influenced severity of nuclear sclerosis. This increased power could have resulted in rejection of the recessive model in favor of a more complex polygenic model.

The higher familial correlations observed between relative pairs in the same generations (siblings and cousins) compared with relative pairs in different generations (parents-offspring and avuncular pairs) even after adjustment for age, sex, and cigarette smoking indicated the potential for a cohort effect possibly due to shared environmental factors that we did not include in our analyses. Additionally, the differences could in part be due to residual confounding by age or smoking. When we examined the proportion of smokers by age, we found that about 70 percent of males smoked regardless of age group (above 65 years vs. 65 years or less). However, only 27 percent of females above the age of 65 years were ever smokers, whereas 48 percent of females aged 65 years or less were smokers. The total number of pack-years of smoking was similar among the older and younger women: 24.5 (SD, 28.9) and 24.7 (SD, 19.0), respectively. The younger male smokers had not yet had as much cumulative cigarette smoking exposure as the older men had: 34.8 (SD, 28.2) vs. 43.5 (SD, 39.4) pack-years. However, this difference could be due in large part to their younger age and thereby a fewer number of years of active smoking.

Although the overall reliability of our nuclear sclerosis grading procedure was high, weighted kappa = 0.76 (95 percent confidence interval: 0.70, 0.82) (18), there are limitations to categorizing a continuous trait (nuclear lens opacity) into five categories. Although a Box-Cox transformation of these data did enable us to adjust for the nonlinearity of the data, a certain amount of misclassification is inherent in the binning process. Nondifferential misclassification of nuclear sclerosis grade would bias the results toward the null by reducing the difference between persons with high and low nuclear lens opacity. In order for differential misclassification to be present in segregation analysis, the misclassification must be differential with respect to both nuclear cataract grade and family history of nuclear cataract grade. Therefore, because grading was performed without knowledge of family history, it is unlikely that differential misclassification would impact the results of these analyses.

Cigarette smoking has been shown to be an important risk factor for the development of both nuclear sclerosis and subsequent nuclear cataract. Although models in which we did not incorporate smoking as a covariate were also examined, they did not provide as good a fit to the observed data as did the models that included smoking ($p < 0.0001$; models B, F, and L vs. C, G, and M, respectively (table 3)). However, as with any adjustment, we may not have completely controlled for the influence of smoking on nuclear sclerosis in part because we did not adjust for current smoking, length of time since former smokers quit smoking, and passive smoke exposure, all of which may influence nuclear sclerosis. Cigarette smoking will be an important confounder to control for in future studies aimed at identifying the genes involved in nuclear sclerosis.

Our results suggest that the etiology of nuclear sclerosis is quite complex and may be due to a variety of genes of modest effect and environmental factors. These results are consistent with the findings of Hammond et al. (5), who found evidence supporting the involvement of additive genetic factors in the development of nuclear sclerosis. Although our major gene models were rejected, models with a polygenic component, which could be due to the additive effects of several genes, did provide a better fit to the data than did models that ignored the impact of polygenes. Linkage and association studies aimed at localizing the genes involved in the development of nuclear sclerosis are currently under way.

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