Nuclear Cataract Shows Significant Familial Aggregation in an Older Population after Adjustment for Possible Shared Environmental Factors

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PURPOSE. To quantify the association between siblings in age-related nuclear cataract, after adjusting for known environmental and personal risk factors.

METHODS. All participants (probands) in the Salisbury Eye Evaluation (SEE) project and their locally resident siblings underwent digital slit lamp photography and were administered a questionnaire to assess risk factors for cataract including: age, gender, lifetime sun exposure, smoking and diabetes history, and use of alcohol and medications such as estrogens and steroids. In addition, blood pressure, body mass index, and serum antioxidants were measured in all participants. Lens photographs were graded by trained observers masked to the subjects’ identity, using the Wilmer Cataract Grading System. The odds ratio for siblings for affectedness with nuclear cataract and the sibling correlation of nuclear cataract grade, after adjusting for covariates, were estimated with generalized estimating equations.

RESULTS. Among 307 probands (mean age, 77.6 ± 4.5 years) and 434 full siblings (mean age, 72.4 ± 7.4 years), the average sibling size was 2.7 per family. After adjustment for covariates, the probability of development of nuclear cataract was significantly increased (odds ratio [OR] = 2.07, 95% confidence interval [CI] 1.30–3.30) among individuals with a sibling with nuclear cataract (nuclear grade ≥ 3.0). The final fitted model indicated a magnitude of heritability for nuclear cataract of 35.6% (95% CI: 21.00%–50.3%) after adjustment for the covariates.

CONCLUSIONS. Findings in this study are consistent with a genetic effect for age-related nuclear cataract, a common and clinically significant form of lens opacity. (Invest Ophthalmol Vis Sci. 2004;45:2182–2186) DOI:10.1167/iovs.03-1163

Age-related cataract is the leading cause of blindness in the world1 and the leading cause of low vision in the United States,2 where it consumes approximately 60% of the Medicare budget for vision.3 It has been suggested that any intervention that could delay cataract for even 10 years may reduce the number of cataract surgeries in the United States by 45%.4 The potential impact of cataract prevention may be appreciated when we remember that 1 in 20 Americans over the age of 40 years have undergone cataract surgery.5 In the face of current knowledge about cataract and its causes, smoking prevention has been suggested as the most effective prevention strategy.5 Still, the simple clinical observation that some individuals survive very late in life without visually significant lens opacity has recently prompted several investigations into the genetics of age-related cataract as an avenue of research for novel prevention strategies.

Available evidence from population-based studies6–9 suggests that cataract does in fact aggregate in families. However, such associations might result either from shared genes or shared environment. Twin studies provide a potentially powerful tool to distinguish between “nature” and “nurture,” and have been consistent with the idea of a genetic influence on age-related cataract.10,11 However, such studies are dependent on assumptions about the shared environment of different types of twins, and such assumptions are inherent in the models used to analyze these data.

A practical difficulty in inferring the genetics of cataract, as with all age-related diseases, is that unaffected status at the time of examination may mean that the individual is truly unaffected or that he or she has simply not manifested the phenotype yet. Misattribution can thus be a serious problem in all but the oldest populations. An additional difficulty in performing studies to ascertain the degree of heritability of age-related cataract in the United States is that general access to cataract surgical services leads to systematic censorship of the most affected persons in the population, with attendant loss of power and possible introduction of bias.

In the current investigation, we studied the heritability of nuclear cataract in a cohort of older sibships recruited through the Salisbury Eye Examination (SEE) on Maryland’s Eastern Shore. We attempted to overcome some of the mentioned difficulties in studying the genetics of age-related cataract. To distinguish between familial aggregation of cataract due to environmental and genetic causes, information was collected on major personal and environmental cataract risk factors, including cigarette, alcohol, exogenous estrogen and other medication use, lifetime ultraviolet-B light exposure, serum antioxidant levels, history of diabetes and other relevant medical conditions, and body mass index (BMI). To minimize misattribution due to as yet unaffected individuals who will eventually manifest the phenotype, we chose to work in an older population, with the minimum age for probands of 72 years. Finally, to reduce the impact of censored data from bilaterally pseudophakic individuals, we relied on previous study photographs and records from operating ophthalmologists to assign cataract grades for individuals without a native lens in either eye at the time of enrollment in the study.

MATERIALS AND METHODS

The Salisbury Eye Evaluation (SEE) initially recruited 2520 persons aged 65 to 84 years on a population basis from Medicare roles in the Salisbury area.12 This cohort has been observed with regular measure-
ment of various cataract risk factors through a total of four rounds of visits to date, with lens photographs having been obtained at rounds 1, 2 and 4. At rounds 3 and 4, all surviving subjects (n = 1504) were administered a family history questionnaire, and were eligible for the SEE Cataract Genetics (SEECAT) study if they had one or more full or half siblings living within 100 miles of Salisbury or Baltimore (Fig. 1). Consent was obtained from eligible SEE participants (probands) to contact their siblings. These siblings were then sent letters describing the study and containing stamped, self-addressed postcards that they could return to study headquarters if they did not want to be contacted further. Siblings from whom no card was received after 2 weeks were contacted by telephone and administered the family history questionnaire. Interested eligible siblings were invited to study headquarters.

After giving informed consent, all probands and siblings gave full medical and ophthalmologic histories and also answered questionnaires regarding their age; gender; lifetime ultraviolet-B exposure (methodology documented elsewhere); medical history including diabetes; and use of tobacco, alcohol, estrogen supplements, and other prescription and over-the-counter drugs. In addition, height was measured in stocking feet with a height board, and weight was obtained in kilograms on a digital scale. Seated blood pressure was measured (average of two readings) in the right arm with a mercury sphygmomanometer. Three 7-mL EDTA tubes of blood were drawn by sterile venipuncture, two for later DNA analysis, and one that was centrifuged within 8 hours for 20 minutes at 2200 rpm, with plasma being drawn off, labeled, and frozen at −20°C. Plasma samples were shipped in batches of 100 on dry ice to the laboratory for measurement of antioxidant levels. α-Carotene, β-carotene, β-cryptoxanthin, lycopene, lutein, zeaxanthin, retinol, and α-tocopherol were measured in 100 μL of plasma by high-performance liquid chromatography using a modified method from the Nutrition Laboratory, Inorganic Toxicology and Nutrition Branch, Division of Laboratory Sciences, National Center of Environmental Health, Centers for Disease Control and Prevention (Atlanta, GA). The internal standards used were tocot (Hoffmann-La Roche, Nutley, NJ) at 300 and 325 nm and all-trans-ethyl-β-apo-8’-carotenoate (purified sample courtesy of Fred Khachik, U. S. Department of Agriculture) at 450 nm. Quality control was assessed by repeated analysis of pooled human plasma control samples run at the beginning and end of each analysis. Standard curves were run periodically, using standard reference material 986C (National Institute of Standards and Technology, Gaithersburg, MD). The mobile phase consisted of one pump in acetonitrile with 0.1% triethylamine and a second pump in ethanol with 0.1% triethylene. A gradient method was applied by varying the solvent concentrations from 85% acetonitrile-triethylamine to 50% acetonitrile-triethylamine and again to 85% acetonitrile-triethylamine.

A full ocular examination including dilation of the pupil was performed by an optometrist (HB), and slit lamp (D1 digital camera; Nikon, Melville, NY; and Photograph Slit-lamp SL-7E; Topcon, Paramus, NJ) and digital retroillumination (Marcher Instruments Ltd., Hereford, UK) photographs were obtained through a dilated pupil using slit lamp and ambient light parameters that have been described in detail elsewhere. These photographs were then graded by a team of five trained and experienced graders after an initial period of standardization. The Wilmer Cataract Grading System was used for all grading. Briefly, a decimal grade for nuclear opalescence between 0.1 and 4.0 was assigned by two graders for each phakic eye on the basis of digital slit lamp photographs with reference to four photographic standards (representing grades of 1.0, 2.0, 3.0, and 4.0). Nuclear color was not considered in assigning this grade. The final nuclear grade for an eye consisted of the arithmetic mean between the grades assigned by the two graders, unless the grades differed by more than 0.2 units, in which adjudication involving at least one senior investigator (NGC, SKW) was conducted. All grading was performed under subdued lighting on one of two cathode ray tube (CRT) computer screens which had initially been standardized against one another (Do It Interactive, Inc., Baltimore, MD).

In the circumstance in which a digital lens photograph could not be obtained in either eye (insufficient media clarity, inability to comply with the photographic protocol, bilateral pseudophakia), an attempt was made to assign a cataract subtype(s) for one or both eyes based on photographs from a previous round of SEE or information obtained from the surgeon’s preoperative clinical evaluation of the lens in the subject’s chart. A bilaterally pseudophakic subject was deemed to be affected by nuclear cataract for the purposes of analysis if either eye had nuclear grade ≥3 on a previously graded SEE photograph or had nuclear cataract graded by the surgeon as 2+ or greater (on a scale of 6), or characterized as “dense,” “significant,” or similar terminology in the chart. Clinician grades may come several years after the most recent previous study photograph and so frequently provided new information.

Senior graders reviewed bilateral photographs for 20 subjects in whom both digital and film images were captured before beginning the study. Interobserver and intraobserver agreement in comparing digital and film images of the same eye was similar to that observed in previous testing using film images alone. This protocol was approved in its entirety by the Joint Committee on Clinical Investigations, the Institutional Review Board for the Johns Hopkins University School of Medicine. The study was performed in accord with the Declaration of Helsinki.

**Statistical Methods**

Nuclear cataract was treated in both quantitative (Wilmer decimal grade 0.1−4.0) and binary fashion (with an individual defined as “affected” if the photograph grade was ≥3 or the assigned grade was “present” in either eye). The degree of family association for nuclear cataract was assessed in the binary analysis by the odds ratio (OR)
TABLE 1. Characteristics of Participants in the Salisbury Eye Evaluation Study (Probands) and Their Siblings, with Regard to Demographics, Cataract Risk Factors, Nuclear Cataract Status, and Pseudophakia

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Probands</th>
<th>Siblings</th>
<th>Unadjusted Difference</th>
<th>Age-Adjusted Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (y)</td>
<td>77.6 ± 4.5</td>
<td>72.4 ± 7.4</td>
<td>&lt;0.001</td>
<td>—</td>
</tr>
<tr>
<td>Gender (female)</td>
<td>180/307 (58.6)</td>
<td>254/434 (58.5)</td>
<td>1.0</td>
<td>—</td>
</tr>
<tr>
<td>Race (black)</td>
<td>86/307 (28.0)</td>
<td>119/434 (27.4)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Mean body mass index</td>
<td>28.4 ± 5.5</td>
<td>29.4 ± 6.1</td>
<td>0.016</td>
<td>0.34</td>
</tr>
<tr>
<td>Smoking status (%)</td>
<td>45/42/12</td>
<td>43/47/10</td>
<td>0.43</td>
<td>0.86</td>
</tr>
<tr>
<td>Alcohol status (%)</td>
<td>30/48/21</td>
<td>29/45/25</td>
<td>0.51</td>
<td>0.49</td>
</tr>
<tr>
<td>Systolic or diastolic hypertension (%)</td>
<td>198/302 (66)</td>
<td>239/434 (55)</td>
<td>0.005</td>
<td>0.065</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>77/302 (25)</td>
<td>83/434 (19)</td>
<td>0.046</td>
<td>0.097</td>
</tr>
<tr>
<td>Current or recent steroid use (%)</td>
<td>22/27/6 (6)</td>
<td>41/432 (9)</td>
<td>0.59</td>
<td>0.24</td>
</tr>
<tr>
<td>Bilateral pseudophakia (%)</td>
<td>78/907 (25.4)</td>
<td>69/434 (15.9)</td>
<td>0.002</td>
<td>0.83</td>
</tr>
<tr>
<td>Able to assign cataract grade (among pseudophakics)</td>
<td>50/78 (64.1)</td>
<td>50/69 (72.5)</td>
<td>0.29</td>
<td>0.61</td>
</tr>
<tr>
<td>Nuclear cataract in either eye (%)</td>
<td>141/274 (51)</td>
<td>121/406 (30)</td>
<td>&lt;0.001</td>
<td>0.036</td>
</tr>
</tbody>
</table>

* Includes persons with nuclear cataract grade ≥3.0 on SEE round 3 photographs and also persons determined to be “affected” by nuclear cataract on the basis of clinical records and/or old photographs.

Table 2. Association of Various Covariates with Nuclear Cataract Grade among a Population of Older Persons and Their Siblings in Salisbury, Maryland

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Beta Coefficient (95% Confidence Interval)</th>
<th>Standard Error</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per year)</td>
<td>0.045 (0.036-0.054)</td>
<td>0.0046</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Female gender</td>
<td>0.212 (0.092-0.332)</td>
<td>0.061</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>White race</td>
<td>0.289 (0.150-0.428)</td>
<td>0.071</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Smoking (per pack-year)</td>
<td>0.0025 (0.0005-0.0045)</td>
<td>0.0010</td>
<td>0.014</td>
</tr>
</tbody>
</table>

The heritability of nuclear cataract in this population was 35.6% (95% CI: 21.0%-50.3%), suggesting that some 36% of the variance in nuclear cataract grade can be attributed to genetic causes (Table 3).

DISCUSSION
Our results provide evidence that genetics plays a significant role in nuclear cataract, the most prevalent type of cataract in European-derived populations, and the cataract subtype most commonly requiring surgery. The finding that nuclear cataract is genetically as well as environmentally determined in consistent with previous population-based investigations and twin studies. The fact that several independent lines of investigation in different populations have supported the heritability of nuclear cataract.
TABLE 3. Odds Ratio of Development of Nuclear Cataract among Persons with a Sibling Having Nuclear Cataract Compared with Those without Affected Siblings and Adjusted and Unadjusted Heritability of Nuclear Cataract

<table>
<thead>
<tr>
<th>Nuclear Cataract</th>
<th>Unadjusted</th>
<th>Adjusted*</th>
</tr>
</thead>
<tbody>
<tr>
<td>OR</td>
<td>2.08 (1.39–3.10)</td>
<td>2.07 (1.30–3.30)</td>
</tr>
<tr>
<td>Heritability</td>
<td>54.9% (31.5–78.3)</td>
<td>35.6% (21.0–50.3)</td>
</tr>
</tbody>
</table>

* Adjusted for age, gender, race, body mass index, use of tobacco and alcohol, blood pressure, diabetes, use of steroids, total serum carotenoids, and lifetime ultraviolet-B light exposure. Only age, gender, race, and smoking status were significantly associated in the model and were used for the final adjustment.

The heritability of nuclear cataract suggests that this finding is comparatively robust. The 36% heritability estimate for nuclear cataract in our study, an index of the proportion of cataract variation controlled by genetic causes, is comparable to that which has been reported in other studies. Hammond et al. reported a heritability figure of 48% in their twin study of nuclear cataract, and Heiba et al. estimated that a single major gene may account for 35% of nuclear cataract variation in the Beaver Dam Eye Study population.

In the regression model used in the present study, advancing age, female gender, white race, and smoking history were associated with nuclear cataract grade. All these factors have been identified previously in epidemiologic studies. Certain other covariates that have been found to be positively or negatively associated with nuclear cataract in the past, including alcohol intake, BMI, serum antioxidant status, and steroid use, were not found to predict nuclear cataract outcome significantly in our models. The list of covariates found to be predictive in our model included factors that have been most robust across numerous studies, whereas the associations with nutrition and alcohol, BMI, serum antioxidant status, and steroid use, were not found to predict nuclear cataract outcome significantly in our models. 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between studies in an effort to increase power. Large, population-based studies of cataract in which investigators have not concentrated on the collection of families, but have obtained blood samples, are likely to be in the position to contribute best through case-control studies of positional candidates in areas highlighted by genome-wide scans. It is to be hoped that such efforts will take the field from where it is now, where most information about cataract has come from traditional, population-based studies not organized to explore genetic issues, toward a better understanding of the genes contributing to cataract development. The minimal data currently available from genetic studies of other ocular diseases of aging, such as age-related macular degeneration, suggest that such genes may be numerous, and their individual impact modest.

In view of such a complex model, what likely practical benefits can we expect from cataract genetic studies? It seems unlikely that this ubiquitous, late-onset disease with an existing surgical cure will provide a practical forum for resource-intensive strategies such as gene therapy or population or clinic-based screening of potentially affected persons. A more likely scenario is that studies of the cataract genetic studies will eventually yield knowledge of the protein pathways involved in lens opacity, so that discovery of anticataract agents may proceed in a rational fashion, rather than through the current process of hit or miss. To be practical, such agents probably should be delivered on a mass basis as supplements, which sets a high standard indeed for safety and low cost. However, the future work in the area of cataract prevention.

**References**