EPIDEMIOLOGY

Genetic Risk of Rhegmatogenous Retinal Detachment

A Familial Aggregation Study

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Objective: To investigate the magnitude of the genetic risk of nonsyndromic rhegmatogenous retinal detachments (RRDs) in a familial aggregation study.

Design: Two hundred three consecutive patients with RRD and 461 controls without RRD were ascertained at the Department of Ophthalmology of the University Medical Centre Nijmegen in Nijmegen, the Netherlands. Data on family composition, history of RRD, and presence of other risk factors in siblings and offspring were collected by means of a questionnaire. Diagnosis of RRD was confirmed by evaluation of medical records.

Results: One hundred eighty-one patients (89.2% of those eligible) and 408 controls (88.5% of invited controls) with 1090 and 2345 relatives, respectively, were included in the analysis. Thirteen familial RRDs (1.2%) were diagnosed in 10 case probands and 9 RRDs (0.4%) in 8 control probands. Siblings and offspring of cases had a higher incidence of RRD independent of age, sex, and myopia. The cumulative lifetime risk of RRD was 7.7% for relatives of cases and 3.0% for relatives of controls, yielding a risk ratio of 2.6 (95% confidence interval, 1.1-6.2).

Conclusions: Familial occurrence of RRD is a risk factor for RRD. Genetic factors apart from myopia may explain the increased familial risk.


RHEGMATOGENOUS RETINAL detachment (RRD) is a common retinal disorder with an incidence of 1 per 10,000 individuals per year in whites. Untreated, RRD can lead to irreversible damage of the rods and cones, frequently ending in blindness. Conversely, surgical treatment can achieve reattachment of the retina in 90% to 96% of cases when performed in a timely manner. Prevention of RRD, however, is preferable. Preventive laser treatment and encirclement can be used in individuals with a known high risk of RRD.

Known endogenous risk factors for RRD are myopia, lattice degeneration, and posterior vitreous detachment, while acquired risk factors such as trauma and prior cataract surgery can also contribute considerably to the risk of RRD. Furthermore, RRDs are more often found in men (57%-60%) than in women, and race has proven to be an important determinant. A recent study showed that Chinese had an annual incidence of 11.6 per 100,000 individuals, Malays had an incidence of 7.0 per 100,000, and Indians had an incidence of 3.9 per 100,000. Blacks had an extremely low incidence; in black South Africans, the incidence was reported to be as low as 0.46 per 100,000 individuals. These racial differences may result from genetic disparity.

There is now ample evidence that retinal disorders related to RRD carry a genetic component. Case reports and twin studies have shown that retinal dialysis, idiopathic giant tears, lattice degeneration, and myopia can aggregate in families or can show a remarkable resemblance among relatives. The genetic risk for myopia has been studied most profoundly, and a fifth genetic locus for high myopia was found recently. Multiple RRDs, both with and without myopia, have been described in families. Some of these revealed inherited syndromic etiologies such as Wagner disease, erosive vitreoretinopathy, or Stickler syndrome, but others had no known syndromic cause of RRD. Recently, we found evidence for genetic linkage in 2 large autosomal dominant RRD families without systemic abnormalities.

Although genetic susceptibility to RRD appears to be present in specific families, it is currently unknown whether RRD occurring in a general population has a genetic etiology. The purpose of this study was to investigate the magnitude of the genetic risk of common, nonsyndromic RRD. We studied aggregation of RRD in siblings and offspring of probands with RRD that was not
The initial phase of the study, the selection of probands, had a case-control design. This was subsequently followed by construction of 2 cohorts of first-degree relatives for analysis. The control group was composed of white companions of patients who had undergone cataract surgery. Myopia was defined as a spherical equivalent of $-1.00$ diopter or less in at least 1 eye.

Size, composition, and ophthalmologic history of siblings and offspring of the proband were ascertained by questionnaire and subsequent personal follow-up by telephone by 1 of the investigators (S.L.G.). Probands were asked for the ophthalmologic history of each relative (eg, a diagnosis of RRD, name of treating ophthalmologist, cataract extraction preceding RRD, trauma or other ophthalmologic events, and presence of myopia, as well as age at last contact). After informed consent and written permission of the affected relatives or their legal representatives was obtained, medical files of the ophthalmologists were collected in all subjects with histories of RRD and possible RRD-related disorders. A final diagnosis of RRD in relatives was given after evaluation of these records by 2 independent retinal specialists (C.B.H. and C.C.W.K.). Relatives of probands were excluded if they had never had contact with the proband, if their retinal detachment was due to a perforating trauma, or if the RRD was nonrhegmatogenous in origin.

### METHODS

The initial phase of the study, the selection of probands, had a case-control design. This was subsequently followed by construction of 2 cohorts of first-degree relatives for analysis.

### COLLECTION OF PROBANDS

Probands were ascertained at the Department of Ophthalmology of the University Medical Centre Nijmegen in Nijmegen, the Netherlands. The case group was composed of all consecutive patients with RRD who were hospitalized from June to December 2000. Exclusion criteria were nonwhite race; inherited retinal detachment–causing syndromes like Marfan, Wagner, Stickler, and juvenile retinoschisis; and RRD occurring less than 4 years after intraocular operations or ocular traumas.

The control group was composed of white companions of patients who were visiting our department for reasons other than RRD, who were not related to the patient group, and who were matched within a 5-year age range with case probands. Exclusion criteria for control probands were history of retinal detachment or (family) history of retinal detachment–causing syndromes, clinical symptoms of retinal detachment at the time of inclusion, and participation of relatives in the case group. Diagnoses of ophthalmologic disorders among the control group were checked by medical records where appropriate. The study was executed according to the guidelines of the Committee on Research Involving Human Subjects Region Arnhem-Nijmegen, and written consent was obtained from all participants.

### DATA COLLECTION AND DIAGNOSIS OF RRD IN RELATIVES

Probands filled out a questionnaire regarding personal medical history, present symptoms of retinal detachment, and risk factors for RRD. The spherical equivalents of glasses or contact lenses were measured or collected from ophthalmologic records to obtain information about the presence and degree of myopia. The preoperative refractive errors were used to assess myopia in subjects who had undergone cataract surgery. Myopia was defined as a spherical equivalent of $-1.00$ diopter or less in at least 1 eye.

### STATISTICAL ANALYSIS

Demographic and clinical characteristics were compared with $t$ test for continuous variables and with $\chi^2$ test for categorical variables. Cox proportional hazards regression analysis was used to estimate the risk of RRD for first-degree relatives of cases independent of the confounding factors age, sex, and myopia. First-degree relatives of controls served as the reference. Each relative with RRD was tallied as a single event. The cumulative risk estimating the lifetime absolute risk of RRD for first-degree relatives was calculated with Cox proportional hazards analysis at age 85 years. Study participants 85 years or older were pooled to avoid biased estimates.
RISK OF RRD FOR FIRST-DEGREE RELATIVES

Retinal detachments in relatives were initially reported by 13 case probands and 15 control probands. Validation of the diagnosis of RRD by medical reports reduced the numbers to 13 relatives of 10 case probands and 9 relatives of 8 control probands. Misclassification of the reported RRD was caused by confusion with a large range of other ophthalmic pathology, varying from cataract extraction to removal of epiretinal membranes.

The relative group that showed a significant higher absolute RRD frequency between cases and controls was the sibling group (n = 12 [1.6%] vs n = 7 [0.4%]; P = .01); there was no statistically significant difference in absolute RRD frequency in offspring. A summary of the number of all affected first-degree relatives per proband is given in Table 3. Table 4 presents the frequency distribution and the risk of RRD for first-degree relatives. The annual incidence of RRD in relatives of cases was estimated at 23.9 per 100 000 individuals and in relatives of controls, 8.24 per 100 000.

Bilaterality of RRD was present in 1 (8%) of 13 affected relatives of cases. The interval between the RRDs was 2 years. In controls, none of the 9 affected relatives had a bilateral RRD. Retinal breaks without retinal detachment in fellow eyes were found in another 2 relatives of cases (15.4%) and in only 1 relative of controls (11.1%). These breaks were round, atrophic holes in both case relatives and a cribiform area in the control relative. All were seen within 2 years of the event. One patient from the case group had undergone laser treatment.

The Figure shows the cumulative lifetime risk of all types of RRD as a function of age for the total group of siblings and offspring. Relatives of cases had a higher frequency of RRD. Beyond 50 years, an increasing discrepancy was found between the 2 groups. Not only did the risk of RRD appear higher for relatives of cases, the curve had also shifted to the left, implying an earlier onset of RRD among case families. However, before the age of 69 years there was no statistically significant difference. The lifetime absolute risk at age 85 years for case relatives was 7.7% and for control relatives, 3.0%. This resulted in a risk ratio of 2.6 (95% confidence interval, 1.1-6.2).

Case and control probands with myopia had more affected relatives than probands without myopia. Of all 1333 relatives derived from case and control probands with myopia, 1.13% were diagnosed with RRD vs 0.33% of 2102 relatives of probands without myopia. This resulted in an age- and sex-adjusted odds ratio of 4.04 (95% confidence interval, 1.64-9.96). The frequency difference of relatives with RRD between probands with and without myopia was more prominent in the case group: 1.79% vs 0.46% (P = .04) in the case group and 0.56% vs 0.31% (P = .47) in the control group. Moreover, there was a significantly higher frequency of RRD in relatives of case probands with myopia vs control probands with myopia (1.8% vs 0.6%; P = .03), suggesting interaction between myopia and proband status. However, the interaction term (myopia × proband status) did not reach statistical significance when added to the model in Table 4 (P = .60).

Our data show the presence of familial predisposition to nonsyndromic RRD. Siblings of subjects with this type of RRD had a 3-fold increased frequency of RRD compared with siblings of nonaffected subjects. This familial risk was not fully explained by the aggregation of known risk factors myopia, age, and sex.

Our study was designed to compare the risks for RRD between affected relatives of unselected, consecutive RRD patients and healthy controls derived from the same district in the Netherlands. We limited our family data collection to siblings and offspring to enhance the reliability of clinical history. The data collection was performed in an identical fashion among both study groups. All histories of RRD were verified using medical records, and the general diagnostic criteria of good clinical practice were applied. For probands we used stringent criteria and accepted only spontaneous, nonsyndromic RRD, whereas for relatives we registered all types of RRD to examine the entire disease spectrum.

A limitation in our study is the low frequency of the disorder. We investigated a large population of relatives but the number of outcome events was still small among both study groups. This limited the power of the analyses, although we were able to detect significant differences between groups. Another potential drawback was the reliance on family history for ascertainment of RRD. We do not think that this has distorted our results because RRD appears to be a significant ophthalmologic event that has a great and memorable impact on patients and their families. In addition, the intensive validation procedure by medical records and adjudication by retinal specialists facilitated the diagnosis of genuine nonsyndromic RRD. Frequencies of reported RRD among the relatives were comparable with former reports. The annual incidence of RRD of 8.24 per 100 000 individuals in our control group was comparable with the annual incidences mentioned in British epidemiologic studies: 6.3 to 13.0 per 100 000 subjects. Bilaterality of familial RRD appeared to be lower than the 15% to 25% in other family reports. The low frequency of retinal breaks and treatment in the second eye suggested that this could not be explained by higher awareness and preventative treatment. These other reports possibly harbor more high-risk families.

Myopia was an important risk factor for RRD in our study. Although a negative refractive error appeared to enhance the risk of RRD among relatives of both proband groups, the risk was higher for families of case probands. Former reports regarding familial, nonsyndromic RRD predominantly describe myopic families. The genetic background of myopia is still unclear, but linkage in specific families has been found with 5 different loci (Xq28; 18p11.31; 12q21-q23; 7q36; 17q21-q22). Cataract extractions did not precede RRD considerably more frequently in relatives of cases than in relatives of controls, indicating that cataract extraction did not explain familial aggregation of RRD in our study.

Our data suggest that genetic risk factors for RRD, other than those determining axial length, exist because myopia did not fully explain the increased risk in first-
degree relatives in our study. Moreover, our data implying interaction between myopia and proband status may indicate that myopia genes have influence on these other genetic determinants. Additional support for the existence of genes not involving myopia comes from former family reports that describe autosomal dominant occurrence of spontaneous, nonsyndromic RRD without myopia. In a previous report, we presented evidence for linkage with the region containing the COL2A1 gene in 2 unrelated RRD families and identification of the pathogenic mutation in 1 family. COL2A1 codes for the 3α1 and 3α2 chains of collagen type II and for the precursor of the 3α1 chain of collagen type XI, a collagen that forms the core of collagen type II.27-30 This collagen is important for the

### Table 2. General Characteristics of First-Degree Relatives*

<table>
<thead>
<tr>
<th></th>
<th>Siblings (n = 736)</th>
<th>Controls (n = 1572)</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, y, mean (SD)</strong></td>
<td>57.95 (15.9)‡</td>
<td>55.36 (15.8)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>Age group, y</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50</td>
<td>183 (24.9)‡</td>
<td>540 (34.4)</td>
<td></td>
</tr>
<tr>
<td>50-70</td>
<td>395 (53.7)§</td>
<td>753 (47.9)</td>
<td></td>
</tr>
<tr>
<td>&gt;70</td>
<td>158 (21.5)§</td>
<td>279 (17.7)</td>
<td></td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>349 (47.4)</td>
<td>801 (51.0)</td>
<td>.11</td>
</tr>
<tr>
<td>Female</td>
<td>387 (52.6)</td>
<td>771 (49.0)</td>
<td>176 (49.7)</td>
</tr>
<tr>
<td><strong>Ocular pathologic condition</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myopia</td>
<td>187 (25.4)§</td>
<td>337 (21.4)</td>
<td>.05</td>
</tr>
<tr>
<td>Glaucoma</td>
<td>9 (1.2)</td>
<td>15 (1.0)</td>
<td>.56</td>
</tr>
<tr>
<td>Macular degeneration</td>
<td>3 (0.4)</td>
<td>3 (0.2)</td>
<td>.48</td>
</tr>
</tbody>
</table>

*Values are expressed as number (percentage) of relatives unless otherwise indicated.
†Adjusted for age and sex where appropriate.
‡P < .001.
§P < .05.

### Table 3. Frequencies of Rhegmatogenous Retinal Detachment in Siblings and Offspring per Proband

| Total No. of Affected Siblings and Offspring | Case Probands (n = 181) No. (%)| Control Probands (n = 408) No. (%)|
|---------------------------------------------|---------------------------------|----------------------------------|---------------------------------|
|                                             | No. With Affected Siblings | No. With Affected Offspring | No. With Affected Siblings | No. With Affected Offspring |
| 0                                           | 171 (94.4)                  | 0                                | 0                               | 400 (98.1)                  | 0                                | 0                               |
| 1                                           | 8 (4.4)                     | 7                                | 1                               | 7 (1.7)                      | 5                                | 2                               |
| 2                                           | 1 (0.6)                     | 1                                | 0                               | 1 (0.2)                      | 1                                | 0                               |
| 3                                           | 1 (0.6)                     | 1                                | 0                               | 0                            | 0                                | 0                               |

### Table 4. Risk of Rhegmatogenous Retinal Detachment (RRD) for First-Degree Relatives

<table>
<thead>
<tr>
<th>No. of Relatives Without RRD</th>
<th>Relations With RRD, No. (%)</th>
<th>Risk of RRD (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>After Trauma</td>
<td>&lt;4 y After Cataract Extraction</td>
</tr>
<tr>
<td>Siblings of Cases (n = 736)</td>
<td>724</td>
<td>1 (0.14)</td>
</tr>
<tr>
<td>Controls (n = 1572)</td>
<td>1565</td>
<td>1 (0.06)</td>
</tr>
<tr>
<td>Offspring of Cases (n = 354)</td>
<td>353</td>
<td>0</td>
</tr>
<tr>
<td>Controls (n = 773)</td>
<td>771</td>
<td>0</td>
</tr>
</tbody>
</table>

*Adjusted for age, sex, and myopia.
†Not enough events for analysis.

Abbreviation: CI, confidence interval.

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structure of the vitreous and maintenance of the vitreo-retinal interface, and it is likely that dysfunction increases the risk of RRD. Other genes serving similar functions may exist.

Do RRD families require specific clinical care? The current policy for treatment is described in the American Academy of Ophthalmology preferred practice pattern.39 It does not offer specific guidance in clinical management of relatives of patients with RRD. Our demonstration of familial aggregation of RRD suggests that these patients require extra awareness of prodromal symptoms. Further investigation is needed to decide if preventive treatment for retinal detachment should be performed at an earlier stage in these relatives, especially in those with myopia.

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