Genetic Risk of Age-related Maculopathy

Population-Based Familial Aggregation Study

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Objective: To investigate to what extent age-related maculopathy (ARM) is genetically determined.

Design and Setting: Familial aggregation study based on probands derived from the population-based Rotterdam Study.

Participants: First-degree relatives of 87 patients with late ARM, ie, atrophic or neovascular macular degeneration, were compared with first-degree relatives of 135 control subjects without ARM.

Main Outcome Measures: Presence and stage of ARM as diagnosed on fundus transparencies, odds ratio, lifetime risk, risk ratio, and population-attributable risk.

Results: Independent of other risk factors, the prevalence of early (odds ratio = 4.8, 95% confidence interval [CI] = 1.8-12.2) and late (odds ratio = 19.8, 95% CI = 3.1-126.0) ARM was significantly higher in relatives of patients with late ARM. The lifetime risk estimate of late ARM was 50% (95% CI = 26%-73%) for relatives of patients vs 12% (95% CI = 2%-16%) for relatives of controls (P < .001), yielding a risk ratio of 4.2 (95% CI = 2.6-6.8). Relatives of patients expressed the various features of ARM at a younger age. The population-attributable risk related to genetic factors was 23%.

Conclusions: First-degree relatives of patients with late ARM developed ARM at an increased rate at a relatively young age. Our findings indicate that approximately one fourth of all late ARM is genetically determined and suggest that genetic susceptibility may play an important role in determining the onset of disease.


A ge-related maculopathy (ARM) is by far the leading cause of blindness in the elderly in developed countries.1 The prevalence and severity of ARM increase substantially with age. By age 80 years, approximately 10% of patients have developed 1 of the 2 late stages of ARM—atrophic or neovascular macular degeneration.2 Treatment such as laser photocoagulation is available for only a minority of patients, and even then improvement of visual function is limited.3 The growing population of elderly and increased life expectancy necessitate research into the causes and risk factors of this disease.

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The etiology of ARM is largely unknown, but environmental and genetic factors have been implicated in the disease. Environmental factors that have been associated are cardiovascular risk factors such as smoking,4-6 atherosclerosis,7 and estrogens.8,9 A role for genetic factors has been supported by various twin studies10,11 and by a population-based segregation study.12 Recent findings from a molecular study13 suggest that the Stargardt ABCR gene may be associated with ARM.

The presence of a genetic component may be widely acknowledged, but the magnitude of its causative role is controversial. Results of 2 clinic-based studies14,15 show familial aggregation of ARM and estimate a familial risk of 19.3 and 2.4, respectively. Possible explanations for this large difference are the high chance of selection bias with hospital-derived probands, the large range of ARM features that were combined, and the use of family history and self-reported diagnoses.

The purpose of this study was to investigate to what extent ARM is genetically determined on the basis of a collection of population-derived probands ascertained without regard to family history and selected without regard to any known risk factors. We determined the diagnosis of ARM in first-degree relatives by actual examination using a standardized protocol, defined the risk of ARM for these relatives, and identified those factors associated with increased risk. Further...
PARTICIPANTS AND METHODS

COLLECTION OF FAMILIES

All probands were derived from the Rotterdam Study, a population-based prospective follow-up study in the Netherlands of subjects aged 55 years and older. The rationale and design of the Rotterdam Study have been described elsewhere.1,2 In brief, 6775 participants were ophthalmologically examined; the diagnosis of ARM was based on grading of fundus transparencies according to an internationally accepted classification system.2 For the present study, we identified all patients with atrophic or neovascular macular degeneration as patient probands (n = 101). As control probands (n = 154), we randomly selected a sample of study participants who did not have any features of ARM, ie, no soft drusen of intermediate (63-124 µm) or large (≥125 µm) size and no late ARM, ie, no atrophic or neovascular macular degeneration. Probands differed in age (mean age of patients vs controls, 81.9 vs 76.7 years; P < .001) but not in sex (patients vs controls, 63% vs 56% women; age-adjusted P = .64).

Eligible relatives were siblings and offspring of patients and controls living in the Netherlands or Belgium who could be contacted by letter and telephone. Relatives were invited for an extensive screening examination at the research center of the Rotterdam Study, located in Ommoord; those who were homebound were examined at their home. The study was approved by the Medical Ethics Committee of Erasmus University, Rotterdam, the Netherlands, and written informed consent was obtained from all participants.

DIAGNOSIS

The ophthalmologic examination included measurements of best-corrected visual acuity, ophthalmoscopy, and fundus photography. After mydriasis, 20° stereoscopic fundus color transparencies (TRC-SS2 stereoscopic fundus camera, Topcon Optical Co, Tokyo, Japan) and 35° color transparencies (Topcon TRV-50VT fundus camera, Topcon Optical Co) were taken of the macular area. Participants who were examined at their homes were photographed with a portable camera (35° fields, RC-2 fundus camera, Kowa Corp Ltd, Tokyo). Fundus transparencies were graded for the presence of ARM in a masked fashion according to the International Classification System,2 identical to the protocol that was used for probands. In accordance with this system, drusen larger than 63 µm, increased pigmentation, retinal pigment epithelium degeneration, atrophic macular degeneration (geographic atrophy), and neovascular macular degeneration present in the macular grid area (radius, 3000 µm) were considered outcomes of ARM. These lesions were subsequently stratified into 4 exclusive stages of increasing clinical severity: no ARM was defined as the absence of any type of soft drusen (≥63 µm) and atrophic or neovascular macular degeneration4; preliminary ARM as the presence of soft distinct drusen without pigimentary irregularities; early ARM as either the presence of soft indistinct or reticular drusen or the presence of both soft distinct drusen and pigimentary irregularities4,19; and late ARM as the presence of atrophic or neovascular macular degeneration.12

ENVIRONMENTAL RISK FACTORS

To investigate whether familial aggregation of ARM could be caused by clustering of environmental risk factors, we considered smoking, atherosclerosis, and estrogen deficiency as potential correlates of ARM.

Presence of atherosclerosis was noninvasively assessed using ultrasound, as described earlier.20,21 Peripheral arterial disease was judged to be present when the ankle-brachial systolic blood pressure ratio was less than 0.90. Participants were questioned about current and former smoking by interview, and women were asked about age and type of menopause, use of contraceptives, and postmenopausal estrogen therapy.

STATISTICAL ANALYSES

Prevalence of ARM lesions, adjusted for age and sex, was compared between siblings and children of patients and between offspring of both groups. The prevalence odds ratio was estimated for siblings and offspring of patients using multiple logistic regression analysis, with siblings and offspring of controls as reference categories and early and late ARM as outcomes. Odds ratios were adjusted for age and sex and, in additional analyses, for smoking, peripheral arterial disease, early menopause, and exogenous estrogen use. Interaction between genetic factors and smoking was studied by performing a stratified analysis and by performing the analysis on the full data set, including the product term for smoking and proband status (patient or control).

The cumulative risk estimating the lifetime absolute risk of ARM for relatives of patients and controls was calculated using Kaplan-Meier product-limit survival analysis, with early and late ARM as outcomes. Participants older than 85 years were pooled to maintain unbiased estimates.22 Cumulative risks were compared between groups using the log-rank test.

The attributable proportion of genetic factors to the occurrence of late ARM in the exposed and general population was estimated using the formulas presented by Miettinen.23 The attributable proportion for the genetically exposed (Ape) was calculated with the formula Ape = (RR - 1)/RR, where RR is the relative risk. The attributable proportion for the total population (App) was calculated with the formula App = Ape × Pe, where Pe is the proportion genetically exposed in the patients.

RESULTS

FAMILY DESCRIPTION

The overall response of eligible subjects was 83.6%. Of patients, 87 (86.1%) gave permission to contact their families; 34 patients had been diagnosed as having atrophic macular degeneration and 53 as having neovascular macular degeneration. Of controls, 135 (87.7%) consented. Of relatives of patient probands, 73 (85%) of 86 siblings and 113 (86.2%) of 131 children agreed to participate; of relatives of controls, 142 (79.8%) of 178 siblings and 201 (81.0%) of 248 children participated. The frequency of home visits was equally distributed among the participating relatives of patients and controls (16.7% and 17.5%, respectively; P = .90).

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Table 1 shows the distribution of age, sex, and risk factors among relatives. There were no significant differences in these characteristics between groups, except for the age distribution among offspring. Smoking was more frequent among relatives of patients but did not differ significantly from relatives of controls.

The prevalences of the various features of ARM are given in Table 2. Although siblings had higher frequencies of almost all ARM characteristics than offspring, in siblings and offspring these lesions were significantly more frequent among relatives of patients than among relatives of controls. Features given in Table 2 may overlap; hence, we subsequently calculated the prevalence of ARM by exclusive stages of disease. For siblings, the prevalence of no ARM was 35.5% for siblings of patients vs 57.8% for siblings of controls (P = .001, age- and sex-adjusted), the prevalence of preliminary ARM was 41.6% vs 37.1% (P = .52, age- and sex-adjusted), the prevalence of early ARM was 9.5% vs 2.9% (P = .04, age- and sex-adjusted), and the prevalence of late ARM was 13.4% vs 2.2% (P = .001; age- and sex-adjusted), respectively. For offspring, the prevalence of no ARM was 57.4% for offspring of patients vs 72.4% (P = .02, age- and sex-adjusted), the prevalence of preliminary ARM was 34.9% vs 25.7%...
(P = .09, age- and sex-adjusted), the prevalence of early ARM was 6.3% vs 1.9% (P = .05, age- and sex-adjusted), and late ARM was present in only 1.4% of offspring of patients (P = .20, age- and sex-adjusted).

In the nuclear families of patients, 10 siblings and 2 children were identified with late ARM. To investigate whether there was an association with subtype of macular degeneration, we determined the concordance of subtype in the 12 relative-proband pairs with late ARM. The concordance was low because only 3 pairs had the same type of late ARM (neovascular macular degeneration).

**GENETIC RISK ESTIMATES**

Relatives of patients had an increased risk of ARM compared with relatives of controls (Table 3 and Table 4). For siblings, the point estimate of the odds ratio increased with greater severity of ARM (odds ratio point estimate: of early ARM, 4.5; of late ARM, 14.3). However, confidence intervals were wide. For offspring, the odds ratio estimate of early ARM (4.9) was similar to the estimate for siblings. The strength of the associations did not diminish after adjustment for smoking and atherosclerosis or after additional adjustment for early menopause and exogenous estrogen use in women (latter data not shown), indicating that the associations were not confounded by familial clustering of these risk factors. Furthermore, we found no statistical evidence for interaction between familial risk and smoking (data not shown).

Kaplan-Meier product-limit estimates indicated that the lifetime absolute risk of developing early ARM by age 85 years (Figure, left) was 48% (95% confidence interval [CI] = 31%-65%) for relatives of patients, whereas this risk was 23% (95% CI = 10%-37%) for relatives of controls (P = .001), yielding a risk ratio of 2.1 (95% CI = 1.4-3.1) and a risk difference of 25%. The lifetime absolute risk of developing late ARM by age 85 years (Figure, right) was 50% (95% CI = 26%-73%) for relatives of patients vs 12% (95% CI = 2%-16%) for relatives of controls (P <.001), yielding a risk ratio of 4.2 (95% CI = 2.6-6.8) and a risk difference of 38%. Although the pattern was most pronounced for late ARM, both cumulative risk curves showed similar patterns, with an earlier rise in risk for relatives of patients. When relatives were stratified by proband sex, no significant evidence for difference in risk of early or late ARM was obtained. When relatives were stratified by proband subtype of ARM, ie, atrophic or neovascular macular degeneration, there was no significant difference in cumulative risk of early ARM. This showed that genetic risk was not confined to sex or subtype of late ARM.

**Table 3. Odds Ratio of Early ARM for First-Degree Relatives of Patients**

<table>
<thead>
<tr>
<th>Early ARM</th>
<th>No ARM</th>
<th>OR (95% CI)†</th>
<th>OR (95% CI)‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Siblings of patients, No. 15</td>
<td>22</td>
<td>4.5 (1.8-11.3)</td>
<td>4.8 (1.8-12.2)</td>
</tr>
<tr>
<td>Siblings of controls, No. 12</td>
<td>77</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Offspring of patients, No. 8</td>
<td>60</td>
<td>4.9 (1.2-20.6)</td>
<td>6.6 (1.4-31.8)</td>
</tr>
<tr>
<td>Offspring of controls, No. 3</td>
<td>150</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Early ARM indicates age-related maculopathy, defined as either the presence of soft indistinct or reticular drusen or the presence of both soft distinct drusen and pigmentary irregularities; OR, odds ratio; and CI, confidence interval.
†Adjusted for age and sex.
‡Adjusted for age, sex, smoking, and atherosclerosis.

**Table 4. Odds Ratio of Late ARM for First-Degree Relatives of Patients**

<table>
<thead>
<tr>
<th>Late ARM</th>
<th>No ARM</th>
<th>OR (95% CI)†</th>
<th>OR (95% CI)‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Siblings of patients, No. 10</td>
<td>22</td>
<td>14.3 (3.0-67.8)</td>
<td>19.8 (3.1-126.0)</td>
</tr>
<tr>
<td>Siblings of controls, No. 3</td>
<td>77</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Offspring of patients, No. 2</td>
<td>60</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Offspring of controls, No. 0</td>
<td>150</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Late ARM indicates age-related maculopathy, defined as the presence of atrophic or neovascular macular degeneration; OR, odds ratio; CI, confidence interval; and ellipses, not calculated.
†Adjusted for age and sex.
‡Adjusted for age, sex, smoking, and atherosclerosis.

**Figure**

Left, Comparison of cumulative risk of early age-related maculopathy (ARM), ie, either soft indistinct or reticular drusen or both soft distinct drusen and pigmentary irregularities, between relatives of patients and relatives of controls. Right, Comparison of cumulative risk of late ARM, ie, atrophic or neovascular macular degeneration, between relatives of patients and relatives of controls.
ATTRIBUTABLE RISK

We restricted the calculation of the attributable risk related to genetic factors to late ARM because this is the clinically most relevant stage and the diagnosis on which patients had been selected. The attributable proportion, or excess case load, was calculated for the genetically exposed participants and for the total population using the ratio of the cumulative risks of late ARM in relatives as the best approximation of the true relative risk for genetic factors (relative risk = 4.2) in the Ape and App formulas (see the "Participants and Methods" section). The attributable proportion among the genetically exposed (Ape) was 76%, i.e., in 76% of participants with a familial occurrence the disease may be attributed to a genetic component. We estimated the proportion of exposed patients (Pe) as the ratio of patient probands with affected relatives divided by all patient probands with relatives who were at least 68 years old, which was the minimum age of late ARM onset in our study. This proportion was 12 of 39, and subsequently we calculated that the proportion of late ARM in the total population that may be attributed to a genetic component (App) was 23%.

COMMENT

We demonstrated that ARM aggregates in families of a general white population, which we cannot attribute to clustering of known risk factors. Independent of smoking, atherosclerosis, and early menopause, first-degree relatives of patients with late ARM had a substantial excess risk of developing ARM. Their lifetime absolute risk to be likewise affected by late ARM was 50%. Results of our study suggest that almost one fourth of all late ARM in the general population may be caused by a genetic component.

The design of our study has several benefits. First, we took advantage of the database from the Rotterdam Study, which included detailed information about ARM in a population-based setting. This enabled us to ascertain probands without knowledge of family history and without regard to any known risk factors. Previous studies have used hospital registries for sampling probands, where differential referral of patients according to family history or other correlates of disease may have distorted results. Second, in contrast to others, we did not rely on family history but actually examined all first-degree relatives. Third, because ARM is clinically heterogeneous with a large range of variance in its manifestations and an age-dependent penetrance, enforcement of standard clinical criteria is important. We based the diagnosis of ARM on a masked grading of fundus transparencies using internationally accepted criteria. For probands, we used rigorous criteria and selected patients and controls who were at either end of the clinical spectrum to improve classification of truly affected and unaffected participants. By contrast, we registered all characteristics of ARM in relatives and stratified them according to stage of disease to study aggregation of the entire spectrum of ARM in the families.

There are also several limitations to our study. The size of the study was relatively small, which resulted in imprecise risk estimates and low statistical power to detect interaction with environmental factors. Only larger studies can overcome this problem. Another issue is the age distribution of the study participants. Although siblings of both groups were similar in age, offspring of patients were significantly older than offspring of controls. This may have distorted the prevalence odds ratios for offspring estimated with logistic regression analysis. Distortion of other risk estimates is less likely because they were based on the Kaplan-Meier analysis, which carefully accounts for age at examination. The last point is the limited study of potential confounding variables. The environmental factors that we considered were those risk factors identified in the Rotterdam Study. Other environmental factors such as diet and cholesterol level have been suggested, but the risk associations are inconclusive and could not be replicated in the Rotterdam Study (J. R. Vingerling, MD, PhD, and C. C. W. K., unpublished data, 1997). Simple clustering of unknown risk factors may partly account for our findings, but it has been shown that genetic factors are the most likely explanation for strong familial aggregation.

The notion has long existed that genetic susceptibility is one of the strongest risk factors for ARM apart from advanced age. However, it has remained unclear to what extent ARM is genetically determined. We based the relative risk for a genetic component on the proportions affected in relatives of affected and unaffected participants and estimated the odds ratio and the ratio of cumulative lifetime risks. The latter was estimated with Kaplan-Meier product-limit analysis, which censored participants who had not developed the disease at the time of examination and thereby accomplished an adjustment for age-dependent expression. Given this benefit, the 4.2 ratio of cumulative lifetime risks is the better estimate of the true lifetime relative risk of late ARM for first-degree relatives. We based the attributable risk on this ratio and on the proportion of exposed patients, considering those having an affected relative to be exposed. We limited our analysis to patients with relatives aged 68 years or older, but our proportion of 23% may be an underestimation of the true attributable risk if exposed patients have relatives who have not yet developed the disease.

Although both cumulative risk curves of ARM demonstrated an exponential rise in risk, the curve for relatives of patients shifted to the left, suggesting that a strong effect of familial predisposition is an earlier onset of disease. This contention is supported by the observation that the frequencies of ARM features were remarkably similar between offspring of patients and siblings of controls, whereas they differed approximately 20 years in age (Table 2). Unfortunately, our study had no information on age of disease onset, and we, therefore, could not make a distinction in familial risk for probands with early vs late onset of ARM. A higher risk for probands with an early onset would have added to the evidence of an association between age at onset and familial risk. Nevertheless, it is an interesting observation that needs further exploration, for knowledge of this relation will direct
genetic research to focus on subjects with a high familial risk of disease.

Whether differences in phenotypic manifestations of ARM reflect differences in genetic background has been subject for debate. Various reports describe familial occurrence of drusen only \(^{28,29}\) whereas Klein et al\(^{10}\) report a striking similarity of late ARM features in monzygotic twins. On the other hand, a recent publication\(^{30}\) reporting 8 families with a high prevalence of ARM describes a large variance of ARM features among relatives. We compared families of participants with late stages of ARM with families of participants without any manifestations of disease. All early and late manifestations of ARM occurred more frequently among relatives of patients. Concordance of ARM features between family members was low apart from stage of disease, and there was no difference in familial risk between probands with atrophic vs neovascular macular degeneration. Hence, genetic susceptibility to late ARM increased expression of all manifestations of ARM, with the highest risk for either type of late ARM.

In conclusion, we showed that all manifestations of ARM occur at a higher frequency and at an earlier age in relatives of patients with late ARM. The high relative and attributable risks demonstrate that genetic factors play a major role in the cause and overall occurrence of ARM. Further studies are needed to reveal whether this genetic contribution is mainly caused by a major gene, the result of several genes, or involves interaction with other risk factors. This will improve understanding of the molecular basis of this disease and may eventually lead to strategies for prevention and treatment.

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