The US Twin Study of Age-Related Macular Degeneration

Relative Roles of Genetic and Environmental Influences

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Context: Age-related macular degeneration (AMD) is the leading cause of irreversible blindness among older individuals in many parts of the world. The relative importance of genes and environment in the etiology of this major public health problem is not well understood.

Objective: To investigate the impact of genetic and environmental factors.


Methods: Twins were surveyed for the known presence of macular degeneration. Enrolled twins underwent a standardized examination and fundus photography. Age-related macular degeneration evaluation was completed for 840 elderly male twins, 210 monozygotic and 181 dizygotic complete twin pairs, both concordant and discordant for presence or absence of AMD, and 58 singletons. A bivariate twin model incorporating initial screening ascertainment and age effects was employed to partition variation in liability to AMD and signs of maculopathy into additive genetic, common environment, and unique environment components.

Main Outcome Measure: Heritability of AMD grade and signs of maculopathy based on clinical examination and fundus photographs.

Results: Of the 840 twins, 331 had no signs of maculopathy and 241 had early signs, while 162 had intermediate AMD and 106 had advanced AMD. Heritability (additive genetic) estimates were significant for overall AMD grade (0.46) and for intermediate (0.67) and advanced (0.71) AMD. Significant unique environmental proportions of variance were also observed for these AMD variables (0.37, 0.19, and 0.24, respectively). Shared or common environmental contributions were not significant (0.05-0.17). For specific macular drusen and retinal pigment epithelial characteristics, significant genetic (0.26-0.71) and unique environmental (0.28-0.64) proportions of variance were detected.

Conclusions: Genetic factors play a substantial role in the etiology of AMD and associated macular characteristics, explaining 46% to 71% of the variation in the overall severity of the disease. Environmental factors unique to each twin also contribute to the occurrence of this disease. This quantification of relative genetic and environmental contributions to the development of AMD should guide future research on this important cause of blindness.

report herein, to our knowledge, results of the largest twin study of AMD to date and the only US study using a population-based registry of elderly twins. Results add new information regarding heritability and quantify for the first time the genetic contribution to advanced stages of AMD.

### METHODS

#### STUDY POPULATION

The study population was derived from the National Academy of Sciences—National Research Council World War II Veteran Twin Registry. This registry is the largest population-based twin registry in the United States and includes information for 159,244 white male twin pairs born between 1917 and 1927 who served in the US armed forces. This cohort of elderly twins is ideal for the study of genetic and environmental risk factors for age-related diseases, including AMD.

In total, 12,126 individuals in this registry were surveyed by telephone (n=9,920) or mail (n=2,806) for a prior diagnosis of AMD. Of those surveyed, 5.6% (n=684) reported having been diagnosed. In some cases both twins in a pair screened positive for AMD, yielding 639 potentially eligible pairs in which one or both twins reported a diagnosis of AMD. Medical records were reviewed to confirm AMD status and eligibility. Among the 639 pairs approached for participation, in 209 pairs (32%) one or both twins could not be located (n=42), were deceased (n=152), or were in poor health (n=15). Of the remaining 430 twin pairs, 340 (79%) participated.

We also enrolled and examined pairs from the oldest age group to select those past the typical age of disease onset in which both twins screened negative for AMD (51 pairs; mean±SD age, 77±1.2 years). These twins not only provide zygosity-based age-correction information for the screen-negative group, but also provide estimation of the heritability components of AMD in the screen-negative group, since they underwent the same procedures, including an ocular examination and photography. Of the 120 screen-negative pairs identified, 51 (43%) were enrolled. In the 69 pairs (57%) that were not enrolled, one or both twins could not be located (n=15), were deceased (n=39), or were in poor health (n=15).

In some cases, only one twin of 58 eligible pairs (45 in the screen-positive group and 13 in the screen-negative group) was examined because the co-twin refused, was too ill, or died. These singletons were included in the analyses because they provide information about the correlation between traits within individuals, and their inclusion can help control for certain types of selection bias.

A total of 840 twins were included in the final analyses, including 340 pairs (n=680) in which one or both twins reported AMD, 51 pairs (n=102) in which neither twin reported AMD, and 58 singletons. Our bivariate twin model included all screen-negative twins for whom age and zygosity information was available.

#### DATA COLLECTION

The twin’s current ophthalmologist or an ophthalmologist in the same geographic area as the twin was recruited to perform the study examination. We designed detailed protocols and standardized clinical data forms, and these were sent to ophthalmologists to complete. The ophthalmologists were not informed about twins’ age or disease status of co-twins. Refraction and best corrected visual acuity were assessed. Intraocular pressure was measured and iris color was classified according to standard photographs. Cataract status was assessed by comparison with standard photographs. Signs of AMD were recorded using slitlamp biomicroscopy with the aid of example photographs we provided that depicted signs of maculopathy. Retinal photography was performed according to a standard protocol, which required stereo pair 30° fundus photographs centered on the disc and fovea and temporal to the fovea of each eye. We provided film that was returned to us and developed by the same processing laboratory throughout the study. The Massachusetts Eye and Ear Infirmary’s Institutional Review Board approved all study protocols, and appropriate consents were obtained from all participants.

### CLASSIFICATION OF AMD AND SIGNS OF MACULOPATHY

This study of AMD includes all levels of age-related maculopathy, including the early and intermediate stages, usually referred to as age-related maculopathy, as well as the advanced stages of AMD. Classification of specific macular characteristics was based on the grading of color fundus photographs of the macula using a grid with a 3000-µm radius centered on the foveal center, according to an established protocol. The grader was masked to zygosity status and clinical diagnosis. All study examination and photographic data were evaluated and assigned an AMD grade by J.M.S. (masked to zygosity status) using a 5-grade, mutually exclusive clinical age-related maculopathy staging system, as previously described. This system is our modification of the Age-Related Eye Disease Study grading system. Eyes with extensive intermediate drusen (>15 drusen <36 µm), nonextensive intermediate drusen (<20 drusen >63 µm but <125 µm), or retinal pigment epithelial (RPE) abnormalities associated with AMD were assigned grade 2 (early disease). Eyes with extensive intermediate or large (>125 µm) drusen with or without RPE abnormalities were assigned grade 3 (intermediate disease). Eyes with geographic atrophy were assigned grade 4, and eyes with neovascular disease with choroidal neovascular membrane were assigned grade 5 (advanced disease). Eyes were assigned grade 1 if none of these signs was present. Specific signs of maculopathy included area of drusen, presence of soft drusen within a predefined grid, maximum drusen size, increased and decreased RPE pigmentation, and geographic atrophy within 1 disc diameter of the macular center. We analyzed both ordinal and binary measures.

### ZYGOSITY STATUS

In most cases (90%), zygosity status was determined using questionnaire data from the National Academy of Sciences—National Research Council World War II Veteran Twin Registry; these data have 95% agreement with blood typing. Among the 10% of the sample with unknown zygosity, DNA specimens were evaluated and zygosity was established by polymerase chain reaction and microsatellite typing using multiplex analyses of 8 microsatellite loci from 8 different chromosomes with polymorphic information content of 0.8 or greater.

### STATISTICAL ANALYSES

#### Genetic Model

As described elsewhere, the classic twin study, consisting of pairs of twins reared together who can be classified as monozygotic (MZ) or dizygotic (DZ), provides information to partition phenotypic variation into additive genetic (A), common (shared) environment (C), and specific environment (E) sources. Because MZ twins share their complete genetic makeup whereas DZ twins share only about half of their genes, a trait influ-
enced entirely by additive genetic factors should correlate perfectly in MZ twins and approximately 0.5 in DZ twins. Similarly, a trait influenced entirely by common (shared) environmental factors should correlate perfectly in both MZ and DZ twin pairs. In practice, measurement error and unique environmental factors tend to proportionately reduce both MZ and DZ correlations from their population values. The ACE (additive genetic, common environment, and unique environment) model therefore predicts positive correlations for both MZ and DZ pairs, with the DZ correlation ranging from half of the MZ correlation (purely AE [additive genetic and unique environment] model) to being equal to it (purely CE [common environment and unique environment] model).

This ACE model can be applied to continuous data or, by means of a threshold model\(^\text{36, 40}\) to ordinal and binary data. In the present study, maculopathy variables were coded as ordered categories where possible. Statistical power can be substantially improved in the threshold model when variables are scored as multordered categories rather than dichotomies.\(41\) The threshold model is built on the assumption that there is an underlying, normally distributed, latent liability to AMD. Abrupt thresholds on this liability dimension mark the boundaries between the ordered responses. If response categories are scored as \(j = 0, 1, \ldots, J\), then the likelihood of observing an individual in a particular category \(j\) can be obtained by integrating the normal distribution from threshold \(t_j\) to \(t_{j+1}\), where \(t_0 = -\infty\) and \(t_J = +\infty\). The likelihood of observing a pair of twins can be computed by integrating the bivariate normal distribution over the region bounded by the thresholds that corresponds to the observed responses of the pair of twins. The correlation between twins, which is used in computing the likelihood under the bivariate normal distribution, depends on the additive genetic, common environment, and unique environment parameters of the model. By expressing the twin correlation in terms of these parameters and maximizing the likelihood over the whole sample, we obtained maximum likelihood estimates of the additive genetic, common environment, and unique environment variance components.

The ACE model is readily generalized to the multivariate case, in which the covariance between traits can be decomposed into the same 3 sources. This is important because any nonrandom sampling of twin pairs incurred through the screening process requires the bivariate analysis of both screening and AMD examination data. A path diagram of this bivariate ACE model for AMD screening and examination grade is shown in the Figure.

**Ascertainment Correction**

A telephone screening instrument was used to select twin pairs for further examination. All pairs in which at least one member screened positive were eligible for examination. A random sample of the oldest pairs who screened concordant negative was also included. Two separate corrections were made for ascertainment, one for pairs in which at least one twin screened positive and the other for pairs in which neither twin screened positive. By definition, AMD is age related, and therefore we sought to remove any effects of differences in age in this sample. By design, the age range was modest, so large effects were not expected. Statistically, age effects are taken into account during model fitting by making the mean of the latent liability distribution for a concordant unaffected and screen-negative pair

$$\text{Asc} = \int_{-\infty}^{t_0} \int_{-\infty}^{t_1} \phi(x_1, x_2) \, dx_1 \, dx_2,$$

where \(\text{Asc}\) indicates ascertainment and \(\phi(x_1, x_2)\) is the bivariate normal probability density function

$$2\pi \Sigma^{-1/2} \exp \left\{ -\frac{1}{2} \begin{pmatrix} x_1 - \mu_i \end{pmatrix} \Sigma^{-1} \begin{pmatrix} x_1 - \mu_i \end{pmatrix} \right\},$$

where \(\Sigma\) is the population covariance matrix, \(\mu_i\) is the (column) vector of population means of \(x_1\) and \(x_2\), \(\Sigma^{-1}\) denote the determinant and inverse, respectively, of the matrix \(\Sigma\), and \(t_i\) indicates transpose. For the pairs in which at least one twin screened positive, the ascertainment correction is \(1 - \text{Asc}\).

**Age Correction**

Under the liability threshold model with random ascertainment, the likelihood of observing, for example, a twin pair in which neither twin is affected would be simply calculated as the 2-dimensional integral

$$\int_{-\infty}^{t_0} \int_{-\infty}^{t_1} \phi(x_1, x_2) \, dx_1 \, dx_2,$$

In the present case, the joint likelihood of the screen \(s\) and diagnosis \(x\) for a concordant unaffected and screen-negative pair may be written as

$$\int_{-\infty}^{t_0} \int_{-\infty}^{t_1} \int_{-\infty}^{t_2} \phi(s_1, s_2, x_1, x_2) \, dx_2 \, dx_1 \, dx_2,$$

which varies as a function of the parameters of the model. The predicted covariance matrix \(\Sigma\) is a function of the estimated
Modeling Missing Data

Although the assumption that data are missing at random\(^4^3\) encompasses a variety of possible mechanisms, with the inclusion of missing data by design in the present study, there remains the possibility that the missing-at-random assumption will not be satisfied. Nonrandom failure to participate is possible for subjects with advanced stages of AMD, so the proportion of subjects with advanced disease may be underestimated. The impact on estimates of genetic and environmental parameters and of the predicted means that vary as a function of age.

Table 1. Distribution of Age-Related Macular Degeneration (AMD) Grade Based on Severity of Worst Eye According to Zygosity (N = 840)

<table>
<thead>
<tr>
<th>Category</th>
<th>MZ No. (%)</th>
<th>DZ No. (%)</th>
<th>Total No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None (grade 1)</td>
<td>169 (38.4)</td>
<td>162 (40.5)</td>
<td>331 (39.4)</td>
</tr>
<tr>
<td>Early</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small drusen only (grade 2)</td>
<td>89 (20.2)</td>
<td>74 (18.5)</td>
<td>163 (19.4)</td>
</tr>
<tr>
<td>RPE changes with or without small drusen (grade 2)</td>
<td>33 (7.5)</td>
<td>45 (11.3)</td>
<td>78 (9.3)</td>
</tr>
<tr>
<td>Intermediate: extensive intermediate or any large drusen (grade 3)</td>
<td>90 (20.5)</td>
<td>72 (18.0)</td>
<td>162 (19.3)</td>
</tr>
<tr>
<td>Advanced</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Geographic atrophy (grade 4)</td>
<td>24 (5.5)</td>
<td>15 (3.8)</td>
<td>39 (4.6)</td>
</tr>
<tr>
<td>Neovascular disease (grade 5)</td>
<td>35 (8.0)</td>
<td>32 (8.0)</td>
<td>67 (8.0)</td>
</tr>
<tr>
<td>Total No.</td>
<td>440</td>
<td>400</td>
<td>840</td>
</tr>
</tbody>
</table>

Abbreviations: DZ, dizygotic; MZ, monozygotic; RPE, retinal pigment epithelial.

A total of 840 individual twins were included in the analyses: 440 MZ and 400 DZ. Two hundred sixty-eight twins were classified in grade 3, 4, or 5 and 572 in grade 1 or 2. The mean ± SD ages of the twins in these two groups were 74.5 ± 2.95 and 74.1 ± 2.98 years, respectively. There were no significant differences in age across zygosity status within the screened or examined groups.

Table 1 displays the prevalence of AMD for all twins and for MZ and DZ twins separately based on the worst eye. Overall, 39.4% of twins (n = 331) had no signs of maculopathy, 19.4% (n = 163) had small drusen only, 9.3% (n = 78) had RPE abnormalities with or without small drusen, 19.3% (n = 162) had extensive intermediate drusen or large drusen, and 12.6% (n = 106) had advanced AMD with geographic atrophy (n = 39) or neovascular disease (n = 67). There were no significant differences between MZ and DZ individuals in the prevalence rates of any of the AMD measures. Table 2 displays the prevalence of specific macular drusen and pigment characteristics based on the grading of fundus photographs. There were nonsignificant differences in the distributions of maculopathy between MZ and DZ individuals.

Table 2 shows significant differences in concordance of maculopathy grade between MZ and DZ pairs. Among pairs in which one or both twins had AMD, 55% of MZ pairs were classified as concordant whereas 25% of DZ pairs were concordant for AMD (defined as grade 3, 4, or 5). For advanced disease (grade 4 or 5), the corresponding concordance rates were 18% for MZ twin pairs and 6% for DZ twin pairs.

Model-fitting results are shown in Table 3. The heritability (additive genetic) estimates for AMD are 0.46 for the ordinal 5 stage grading and 0.67 (including intermediate and advanced disease) and 0.71 (advanced disease only) for the two binary definitions of AMD grade. Point estimates were all statistically significant (P ≤ .05), with the lower 95% confidence limit greater than 0. Of note, the heritability estimate was low (0.18) when grade 2 (early maculopathy) was included in the binary definition of AMD, which is consistent with the clinical ob-
Table 3. Parameter Estimates for Additive Genetic, Common Environment, and Unique Environment Variance Components in Age-Related Macular Degeneration (AMD) Variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Additive Genetic</th>
<th>Common Environment</th>
<th>Unique Environment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall Severity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AMD grade (5 categories)</td>
<td>0.46 (0.12-0.73)</td>
<td>0.17 (0.00-0.46)</td>
<td>0.37 (0.29-0.48)</td>
</tr>
<tr>
<td>AMD grade 1 vs 2-5</td>
<td>0.18 (0.002-0.61)</td>
<td>0.40 (0.00-0.81)</td>
<td>0.42 (0.28-0.56)</td>
</tr>
<tr>
<td>AMD grades 1, 2 vs 3-5</td>
<td>0.67 (0.31-0.88)</td>
<td>0.14 (0.00-0.46)</td>
<td>0.19 (0.11-0.31)</td>
</tr>
<tr>
<td>AMD grades 1-3 vs 4, 5</td>
<td>0.71 (0.18-0.88)</td>
<td>0.05 (0.00-0.53)</td>
<td>0.24 (0.14-0.42)</td>
</tr>
<tr>
<td><strong>Macular Characteristics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drusen area (4 categories)*</td>
<td>0.37 (0.02-0.75)</td>
<td>0.30 (0.00-0.60)</td>
<td>0.33 (0.23-0.47)</td>
</tr>
<tr>
<td>Drusen area (binary)†</td>
<td>0.71 (0.06-0.86)</td>
<td>0.01 (0.00-0.56)</td>
<td>0.28 (0.14-0.49)</td>
</tr>
<tr>
<td>Soft drusen (binary)‡</td>
<td>0.54 (0.07-0.72)</td>
<td>0.03 (0.00-0.41)</td>
<td>0.42 (0.28-0.60)</td>
</tr>
<tr>
<td>Maximum drusen size (5 categories)*</td>
<td>0.39 (0.02-0.59)</td>
<td>0.09 (0.00-0.39)</td>
<td>0.52 (0.41-0.65)</td>
</tr>
<tr>
<td>Maximum drusen size (binary)§</td>
<td>0.55 (0.01-0.71)</td>
<td>0.00 (0.00-0.46)</td>
<td>0.45 (0.29-0.65)</td>
</tr>
<tr>
<td>Increased RPE pigmentation (binary)‡</td>
<td>0.43 (0.05-0.68)</td>
<td>0.08 (0.00-0.41)</td>
<td>0.49 (0.33-0.68)</td>
</tr>
<tr>
<td>RPE depigmentation (3 categories)*</td>
<td>0.26 (0.02-0.48)</td>
<td>0.10 (0.00-0.34)</td>
<td>0.64 (0.47-0.84)</td>
</tr>
<tr>
<td>RPE depigmentation (binary)‡</td>
<td>0.35 (0.01-0.56)</td>
<td>0.09 (0.00-0.43)</td>
<td>0.56 (0.37-0.79)</td>
</tr>
<tr>
<td>Geographic atrophy (binary)‡</td>
<td>0.87 (0.05-0.86)</td>
<td>0.00 (0.00-0.65)</td>
<td>0.33 (0.13-0.45)</td>
</tr>
</tbody>
</table>

Abbreviation: RPE, retinal pigment epithelial.
*See Table 2 for definitions of the categories.
†Defined as <175 µm.
‡Defined as not present vs present.
§Defined as <25 µm.

To our knowledge, this study represents the largest US population–based sample of twins assembled to study AMD, the leading cause of visual loss among the elderly in many parts of the world. Unlike previous studies, this study had a large number of twins with maculopathy. Of the 840 twins included, 509 had maculopathy, and 106 of these 509 were diagnosed with advanced disease. Heritability estimates for AMD were significant and ranged from 0.46 to 0.71. Estimates of heritability for specific macular characteristics were also substantial, ranging from 0.26 to 0.71. Values for soft drusen, drusen area, and drusen size (0.37-0.71) were somewhat higher than those for increased or decreased pigmentary changes (0.26-0.43) but the confidence intervals for these estimates overlap, indicating that they are not significantly different.

A sizable portion of AMD familial resemblance was attributed to additive genetic factors, with no evidence for shared environmental factors. Because the twins most likely had not been cohabiting for over 50 years, it is not surprising that shared environmental effects were not detected. In contrast, environmental factors unique to each twin accounted for significant proportions of the variance for AMD grade (19%-37%) and other specific AMD variables (28%-64%). Thus, a substantial genetic role was detected as well as a moderate-to-large unique environmental component.

Study strengths include the narrow age range of the cohort (10 years) and standardized data-collection instruments, including assessment of AMD end points by clinical examination and fundus photography. The AMD status was determined independent of knowledge of zygosity or co-twin diagnosis. The statistical power of this classic twin study was enhanced by using a 2-stage screen and follow-up research design, for which we developed and tested new statistical methods to control for non-random ascertainment.

A few smaller studies of volunteer twins have also suggested various levels of heritability for AMD,‡‡-‡‡ An-
other study of maculopathy compared MZ and DZ twins using a volunteer sample of women from a registry recruited from media appeals in the United Kingdom. In this study, 146 cases of early age-related maculopathy (60 MZ and 86 DZ), aged 44 to 79 years, were identified. Compared with our study, there were fewer cases of maculopathy and no advanced cases of AMD, and the underlying study group had a wider age range and was not population based. The heritability of early maculopathy in that study was 0.45, whereas our estimates for intermediate and advanced or only advanced disease were 0.67 and 0.71, respectively, which suggests that more advanced disease may have higher heritability.

This twin study identifies both genetic factors and environmental risk factors not shared by twins as important factors in the development of AMD. It also quantifies the relative contributions of genetic and environmental factors, previously unknown for the whole range of signs of AMD. Although our results indicate a relatively larger role for genetic factors, to date the evidence for environmental risk factors in the etiology of AMD has been more clearly delineated, including behavioral, lifestyle, and medical factors such as cigarette smoking,\textsuperscript{14-16} obesity and abdominal adiposity,\textsuperscript{17} systemic hypertension,\textsuperscript{45,46} elevated cholesterol levels,\textsuperscript{47} and nutritional factors (antioxidants and dietary fats).\textsuperscript{6-13} This cluster of risk factors suggests a cardiovascular risk profile,\textsuperscript{48} which is further supported by a relationship found between C-reactive protein level and AMD.\textsuperscript{49} Some of these factors might also have a genetic component or genetic susceptibility and thus could contribute to the heritability of AMD.

These results add new information and underscore the need to pursue the search for AMD-related genes, despite the difficulties encountered with genetic analyses of this complex disease of late onset. These new findings will encourage our investigative team and others to pursue linkage and association studies to identify AMD susceptibility genes. Some progress has been made toward this goal by various groups\textsuperscript{35,50-56}; however, genetic associations reported to date are related to a small proportion of cases. As with other complex disorders of late onset, gene-environmental interactions are likely—individuals may inherit a susceptible genotype but may not manifest the disease if they practice a protective lifestyle. Our results support and quantify this mechanism and provide evidence that clinicians should inform patients with a known family history of AMD of potential increased risk and should emphasize modifiable behavioral and environmental factors.

Potential limitations should be considered. The study is limited to male twins from a specific birth cohort, and the results may not generalize to women or to other birth cohorts. While the twin cohort is population based, not all eligible twins participated, which may have led to selection bias. Such bias, if it exists, would have been partly controlled by our statistical method, which included individual twins from unmatched pairs. Additionally, undiagnosed cases would have been missed if both twins reported having no AMD. Furthermore, we note that heritability is an average statistic that may mask heterogeneity in the population. It is possible that there is a population-wide liability with relatively low heritability and a subgroup in which the heritability is high, perhaps with more extreme symptoms. That this might be the case was supported by the trend toward higher heritability for the more extreme diagnosis, although a larger sample size would be required to establish this trend as significant.

In summary, based on what is, to our knowledge, the largest twin study of AMD to date and the only population-based twin registry in the United States among elderly individuals, we quantified substantial genetic influences on AMD, contributed new information about the heritability of advanced AMD, and established an important environmental contribution. This twin study underscores the need for a multifactorial approach that incorporates genetic, environmental, and biologic factors in the study of the pathogenesis and clinical management of this increasingly prevalent cause of blindness.

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