

Genetic Influence on Early Age-related Maculopathy

A Twin Study

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Objective: Age-related macular degeneration (AMD) is the most common cause of blindness in industrialized countries. There has been considerable interest in the genetics of early age-related maculopathy (ARM) and AMD, because they have phenotypes similar to inherited diseases where mutations have been identified, but the heritability of ARM and AMD is unknown.

Design: A classical twin study was performed to compare the concordance in monozygotic (MZ) and dizygotic (DZ) twins in an unselected sample of female volunteer twins.

Participants: Five hundred six twin pairs, 226 MZ and 280 DZ, with a mean age of 62 years, were examined.

Methods: ARM was graded from stereoscopic macular photographs of 501 of the twin pairs (99%) according to the International ARM Epidemiologic Study Group grading system. The casewise concordance was calculated for twin pairs from 2×2 contingency tables of affected/unaffected twins, and these tables were used in maximum likelihood genetic modeling to estimate the heritabilities of phenotypes graded.

Main Outcome Measures: Prevalence of ARM; concordance in MZ and DZ twins of the phenotypes of ARM, soft drusen $>63 \mu\text{m}$ and $\geq 125 \mu\text{m}$ diameter, pigmentary changes and hard drusen (<20 and ≥ 20 in number); heritability of ARM and subphenotypes.

Results: The overall prevalence of ARM was 14.6% (95% confidence interval [CI], 12.4%–16.8%). The concordance for ARM in MZ twins was 0.37 compared with 0.19 in DZ twins, suggesting a role for genes. Modeling confirmed a genetic effect for phenotypes of ARM, soft drusen, pigmentary changes, and ≥ 20 hard drusen, although there was little genetic effect for scattered (<20) hard drusen. The heritability of ARM was estimated as 45% (95% CI, 35%–53%). The most heritable phenotypes were soft drusen $\geq 125 \mu\text{m}$ (57%) and ≥ 20 hard drusen (81%), with the latter being dominantly inherited.

Conclusions: This study confirms a significant genetic influence in ARM and suggests that future genetic studies should examine phenotypes of large ($\geq 125 \mu\text{m}$) soft drusen and ≥ 20 hard drusen, because these seem to be the most heritable components. *Ophthalmology* 2002;109:730–736 © 2002 by the American Academy of Ophthalmology.

Age-related macular degeneration (AMD) is the most common cause of low vision and blindness registration in the

Western world, and there is evidence that the incidence may be increasing in the United Kingdom at a rate higher than would be expected on the basis of aging alone.^{1–3} The pathogenesis of early age-related maculopathy (ARM) and late AMD is multifactorial, but candidate gene studies of hereditary retinal dystrophies that have a similar phenotype to that of ARM or AMD have so far not identified significant susceptibility genes.^{4–7} Clearly it is important to determine to what degree genes influence a person's susceptibility to ARM or AMD.

Sibling and parent–offspring case–control studies have demonstrated familial aggregation of ARM and AMD,^{8–12} supporting the role of genetic factors, although shared environmental factors cannot be discounted in these studies. Moreover, there may be heterogeneity of genetic risk, with only a few families having significantly increased risk (Klaver CC, et al. *Invest Ophthalmol Vis Sci* 2000; 41[Suppl]:120). Twin studies, mostly small case series of largely monozygotic (MZ) twins, have shown remarkable degrees of concordance, on the order of 90%, particularly

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for AMD.^{13–18} However, these can be criticized as not being population-based and therefore subject to ascertainment bias.

Twin and family studies published to date therefore suggest a genetic component but are hampered by potential biases and have not quantified the relative importance of genes and environment. A classical twin study comparing the concordance of MZ and dizygotic (DZ) twin pairs provides the ideal design to estimate the heritability of a disease or trait using modern genetic modeling techniques.¹⁹ We performed a twin study on unselected twin volunteers to examine the role of genes and environment in early ARM.

Subjects and Methods

A total of 506 twin pairs, 226 MZ and 280 DZ, between the ages of 49 and 79, were examined. They were all from the St Thomas' UK Adult Twin Registry, ascertained from the general population through national media campaigns in the United Kingdom.²⁰ Historically, the Registry was set up to examine postmenopausal women, and volunteers are predominantly Caucasian, so for this study only female Caucasian twin pairs (all raised together) were examined. The twins were initially recruited after local ethics committee approval was obtained, unaware of any proposals for an eye examination. They were subsequently invited to attend an eye examination involving pupil dilatation and fundus photography and gave informed consent. Zygosity was determined by standardized questionnaire^{21,22} and confirmed by DNA fingerprinting when doubt existed. The AmpFl STR Profiler kit (PE Applied Biosystems, Foster City, CA), which complicates the repeat regions of nine short tandem repeat loci (D3S1358, vWA, FGA, D8S1179, D21S11, D18S51, D5S818, D13S317, D7S820) and a segment of the X-Y homologous gene amelogenin, was used. This test is primarily a test of identity or paternity used by the forensic community and can be used to confirm MZ twins.

To grade the amount of ARM, stereoscopic macular photographs were taken of both eyes of all the twins. Fundus photographs were taken according to the International ARM Epidemiologic Study Group guidelines,²³ with two photographs of each macula taken by a Kowa camera (Kowa-Europe, Dusseldorf, Germany) on a 30° width of field setting and developed on Ektachrome 64 film (Kodak, Rochester, NY). The same individual took all photographs, using the same camera, and film was processed by the same company to ensure as much consistency as possible.

Photographs were assessed using stereoscopic viewing spectacles on an x-ray viewing light-box and graded according to the International ARM Epidemiologic Study Group classification. Data were entered directly into a database. Grading training was supervised by an experienced reader (ACB) and from use of the Wisconsin grading system example slides.²⁴ All macular photographs were graded separately by two ophthalmologists (CJH and ARW), masked to the pairing and zygosity of subjects and to the results of the other grader. When the two assessments differed in any way, the graders reviewed photographs together, and a consensus was reached. If any uncertainty or disagreement remained, final arbitration grades were given by a different ophthalmologist (ACB), and these results were used in the analysis. The grade of the worse eye of each individual was used in the analysis.

The International ARM Epidemiologic Study Group classification is now adopted as the standard protocol to allow comparison between studies.²³ This system quantifies the size and type of drusen, as well as their location and frequency within defined regions of the macula. In addition, areas of hypopigmentation and hyperpigmentation are noted. Late-stage disease (AMD) includes

geographic atrophy or subretinal neovascularization. ARM is defined as the presence of soft drusen greater than 63 μm diameter in the macular area or the presence of hypopigmentation or hyperpigmentation in association with any type of drusen, both in the absence of AMD or other coexisting retinal pathology.

Analytical Approach

The variance of a phenotype in a population is due to genetic and environmental factors. Most traits or diseases occur more commonly in the families of affected individuals than in the general population, but because families share both genes and environment, it is difficult to separate out the effects of each. Because identical or MZ twin pairs share the same genes, and nonidentical or DZ twins share on average half of their segregating genes, any greater concordance or correlation between MZ twins can be attributed to this additional genetic sharing. Twin models assume that both MZ and DZ twins share the same common family environment (the equal environment assumption).²⁵

The phenotypes included in the International ARM Epidemiologic Study Group classification system are binary, because the features are either present or absent. Although drusen are counted (and categorized into numbers of 1–9, 10–19, and more than 20), most of the twins with soft drusen of $>63 \mu\text{m}$ size fell into one category (1–9 drusen), and so analysis using categorical data with multiple thresholds was not possible. However, quantitative genetic model fitting in twin studies can be performed using binary outcome data, and the standard techniques are fully described elsewhere.²⁶ These maximum likelihood modeling methods assume there is an underlying normally distributed susceptibility to disease and that a threshold has been reached when disease is present. Complex diseases such as ARM are multifactorial, involving multiple genetic and environmental factors. Therefore the assumption of a normally distributed liability is plausible, and it is this underlying liability that is subject to quantitative modeling techniques.

The analysis was performed by calculating concordance tables to estimate the correlations between twin pairs. The correlation in liability among twins can be estimated from the frequencies of disease-concordant and disease-discordant pairs, using 2×2 contingency tables.^{26,27} Casewise concordance for MZ and DZ twin pairs can be calculated from the formula $2C/(2C + D)$, where C is the number of concordant pairs and D the number of discordant twin pairs. A higher concordance for MZ pairs compared with DZ suggests a genetic role in the trait being analyzed. Data handling and preliminary analyses were undertaken using STATA.²⁸

Model fitting approaches involve solving a series of simultaneous structural equations to estimate genetic and environmental parameters that best fit the observed twin concordances. Age, an important risk factor in ARM, is the same for twins and so would inflate both MZ and DZ correlations if not accounted for.²⁹ Therefore, polyserial correlation matrices, including correlations between age (a continuous trait) and ARM (binary data), were calculated for MZ and DZ twin pairs using PRELIS.³⁰ These polyserial correlation matrices were used in the Mx genetic modeling program.³¹ The technique is based on the comparison of the covariances (or correlations) within MZ and DZ twin pairs. It allows separation of the observed phenotypic variance into additive (A) or dominant (D) genetic components, and environmental components, both shared within the family (common environment [C]) and individual or unique environment (E), and age. E also contains measurement error. The broad-sense heritability, which estimates the extent to which variation in liability to disease in a population can be explained by genetic variation, can be defined as the ratio of genetic variance (A + D) to total phenotypic variance (A + D + C + E + age).

Table 1. Prevalence (%) of Age-related Maculopathy, Pigmentary Changes, and Drusen in the Twin Eye Study

Age (yrs)	N	(%) Age-related Maculopathy	Drusen >63 μm	Drusen $\geq 125 \mu\text{m}$	Pigmentary Change	Hard Drusen n <20	Hard Drusen n ≥ 20
49–54	108	10.2	7.4	2.8	10.2	56.5	5.6
55–64	562	12.8	9.4	5.2	7.5	47.8	11.5
65–74	328	18.7	16.6	8.6	10.1	50.3	14.7
75+	8	(38)*	(38)*	(38)*	(25)*	(38)*	(25)*
Overall	1006	14.6	11.8	6.3	8.7	49.5	11.9

*Note only eight individuals in this age category, so interpretation is difficult.

μm = diameter in microns; N = number of individuals; n = number of drusen.

The significance of variance components A, C, and D and age was assessed by removing each sequentially in submodels and testing the deterioration in model fit after each component was dropped from the full model. This leads to a model explaining the variance and covariances with as few parameters as possible. Submodels were compared with the full model by hierarchic chi-square tests. The difference in chi-square values between submodel and full model is itself approximately distributed as chi-square, with degrees of freedom equal to the difference in degrees of freedom of submodel and full model. Thus, if a component is removed from the model and there is a significant change in chi-square for the change in degrees of freedom, then this component is significant and is retained in the final model. The best fitting model is calculated by the use of the Akaike Information Criterion (AIC). The AIC describes the model with best goodness of fit combined with parsimony (fewest latent variables) and is calculated as $2 \times$ the degrees of freedom – the model fit chi-square. The submodel with the lowest AIC is the best fitting.

Results

There were 226 MZ twin pairs and 280 DZ twin pairs. The mean age of MZ twins was 62.4 years (standard deviation, 5.7), with a range of 51–75 years, and the mean age of DZ twins was 62.1 years (standard deviation, 5.7), ranging from 49 to 79 years. MZ and DZ twin pairs had similar exposures to known potential risk factors such as smoking (14% MZ and 14% DZ twins were current smokers), hypertension (mean blood pressure 131/79 for MZ twins and 130/80 for DZ). Photographs were available for grading for 1006 individuals of the 506 pairs (99%): 6 missing sets of photographs were from both eyes; four came from two pairs of twins (1 camera failure, 1 lost), and 2 individuals from different pairs (photographs lost). A further 24 photographs were judged ungradeable, 12 from right and 12 from left eyes. The reasons were 14 photographs of poor quality, 5 with media opacity resulting in insufficient detail being visible, 4 with coexistent retinal pathology precluding grading (2 central retinal vein occlusions, 2 previous retinal detachments), and 1 eye had been enucleated. However, from these 24 ungradeable eyes, a grade was obtained for the other eye in 22 individuals; the photographs from both eyes of only 1 individual were deemed ungradeable. Because the grading for the worse eye of each individual was used in the analysis, comparison data were therefore available for 501 pairs of twins of the 506 pairs entered into the study (99%).

Reproducibility of macular photographs was assessed by comparison of the two graders' findings as detailed in the "Methods" section. There were 162 separate disagreements (often small, such as 34 eyes graded as having small hard drusen $< 63 \mu\text{m}$ diameter

by one grader and not the other, which did not influence the actual prevalence of ARM). After reviewing all differences, the graders did not reach agreement (or were uncertain of the grading) on 25 individuals' photographs, which were reviewed by the adjudicator for a "final" opinion, and grades entered as the final grades.

Because the findings were graded categorically, the two graders' performance was compared using the kappa statistic.³² The kappa statistic for the two graders for presence or absence of ARM was 0.63, indicating substantial agreement, and it was 0.75 and 0.78 for each compared with the final agreed grade. For the actual drusen size, graded on a scale of 2 to 7 per the International ARM Epidemiologic Study Group classification,²³ the weighted kappa statistic for the two graders was 0.50, indicating moderate agreement.

The prevalence of ARM was 14.6% (95% confidence intervals [CI], 12.4%–16.8%). The prevalence of other phenotypes assessed is detailed in Table 1. The overall prevalence of pigmentary changes was 8.7%, the prevalence of soft drusen $> 63 \mu\text{m}$ size was 11.8% and of drusen $\geq 125 \mu\text{m}$ was 6.3%. In addition, 49.5% of individuals had fewer than 20 hard drusen, and 11.9% had 20 or more hard drusen within the macula area. Numerous hard drusen were included as a phenotype in this study, because they have been shown to be an independent risk factor for visual loss from AMD.³³ No individuals in this study had features of late AMD.

The MZ and DZ concordances are detailed in Table 2, and show that the MZ twins were more concordant than DZ twins for most phenotypes, supporting a genetic influence. The MZ twin concordance for ARM was 0.37 compared with 0.19 for DZ twins. For the phenotype of scattered (< 20) hard drusen, the MZ concordance of 0.53 was not significantly greater than the DZ concordance of 0.51, suggesting little or no genetic influence. Only one DZ pair was concordant for pigmentary retinal changes, reducing the power of maximum likelihood modeling to separate genetic and environmental influences.

Univariate maximum likelihood modeling results for the different phenotypes involved in ARM are detailed in Table 3. For all phenotypes, the analysis showed the best fitting model was one involving genetic effects (additive and in some dominant) and individual environmental factors, and age, although for the phenotype of < 20 hard drusen the effect of age was not significant. These results mean that all the phenotypes involve some genetic influence. For ARM, AE and CE models could be discriminated, confirming that the familial effect is due to shared genes rather than shared environment. Dominant genetic effects could be eliminated with no significant loss of fit for some phenotypes such as soft drusen and < 20 hard drusen, which may reflect the low power of twin studies to detect nonadditive genetic effects³⁴ rather than the actual absence of these effects on the phenotypes. The modeling and concordance results for hard drusen suggest the genetic component to low numbers of scattered hard drusen is small. In

Table 2. Concordance of Phenotypes within 223 Monozygotic and 278 Dizygotic Twin Pairs Graded for Age-related Maculopathy

Phenotype	Zygotity	No. Concordant Affected Pairs	No. Discordant Affected Pairs	Concordance*	Risk Ratio Monozygotic/Dizygotic
ARM	MZ	11	38	0.37	1.95
	DZ	8	70	0.19	
Drusen >63 μm	MZ	8	32	0.33	1.43
	DZ	8	54	0.23	
Drusen $\geq 125 \mu\text{m}$	MZ	5	17	0.37	2.17
	DZ	3	30	0.17	
Pigment change	MZ	7	30	0.32	7.0
	DZ	1	42	0.05	
<20 Hard drusen	MZ	55	96	0.53	1.04
	DZ	74	142	0.51	
≥ 20 Hard drusen	MZ	13	18	0.59	4.54
	DZ	5	66	0.13	

*Casewise concordance calculated.

ARM = age-related maculopathy; DZ = dizygotic; MZ = monozygotic.

contrast, more than 20 hard drusen seems to be strongly genetic, and dominant genetic effects are involved.

Parameter estimates for the heritability (h^2), the environmental influence (e^2) and the effect of age are given in Table 4. The heritability of ARM in this study was 45% (95% CI, 35%–53%). One of the most heritable phenotypes was large ($\geq 125 \mu\text{m}$) soft drusen, with an estimated heritability of 57% (95% CI, 50%–64%). The least heritable component was scattered (<20) hard drusen, with a heritability of 19%. Pigmentary changes had a heritability of 46% (95% CI, 35%–54%). The most heritable phenotype analyzed was 20 or more hard drusen, and all 81% (95% CI, 77%–84%) of the genetic effects were estimated to be due to dominant genetic effects. Age accounted for 4% of the variance of ARM.

Discussion

This twin study suggests that genetic influences are important in the origin of ARM in the general population, with an overall heritability of 45%. One aim of this study was to determine which aspects of the ARM phenotype are most heritable. The success of future genetic studies, such as sib-pair linkage studies and case-control association studies, will depend on a similar separation of distinctly measurable aspects of the ARM and AMD phenotypes, with separate analysis of those that have been found to be most genetically determined. Moreover, genes involved in the susceptibility to each subcomponent of ARM may be distinct, so that inclusion of different components together in the same analysis might impede the discovery of those genes.

Subdivision of the phenotypes shows that large soft drusen (57% heritability) are more heritable than smaller soft drusen; occasional hard drusen are probably not genetic. This suggests that for candidate gene studies of early ARM, attention should be paid to phenotypes with large soft drusen, or >20 hard drusen, because these phenotypes seem “more” genetic. The phenotype of greater than 20 hard drusen seems to be strongly genetic and dominantly inherited, with a heritability of 81%. The gene for dominant

drusen associated with Malattia-Levantine/Doynes honeycomb retinal dystrophy has been characterized, although no coding region mutations have been identified for AMD in one study.³⁵ The authors are unaware of any analyses of this gene in cohorts of patients with early ARM or multiple hard drusen.

The relatively low concordance between twins for the early features of ARM in this population sample might seem surprising, given earlier studies in smaller series of twins that have shown a greater similarity. For example, the largest previous twin study of 134 pairs showed a pairwise concordance of 1.0 in 25 pairs of MZ twins with ARM or AMD (although the stage of ARM was not always the same) and a concordance of 0.59 in the 12 pairs of DZ twins with ARM, supporting the role of genes.³⁶ The only population-based twin study, of 50 MZ pairs from Iceland, found a casewise concordance of 0.78 for MZ twins (and 0.22 with their spouses), but unfortunately did not study DZ twins to exclude shared family environment as the cause of the greater concordance.³⁷ Population-based twin studies often have a lower concordance than more selected twin samples and require large numbers of twins to gain sufficient statistical power for calculation of heritability, particularly for binary traits.³⁸ As an example, a recent cancer analysis of more than 44,000 Scandinavian twins ascertained 1700 cases of breast cancer, and the MZ concordance was 0.14, with a heritability of 27% (95% CI, 4%–41%).³⁹

The traits examined in this study were binary, and the subsequent analysis performed on the basis of the affected or unaffected status of each twin. Each trait was rendered as binary by either the use of a threshold definition (ARM and pigmentary change), a threshold dimension (soft drusen size), or a threshold number (hard drusen). With this method, persons just bordering each side of a threshold, who in reality are phenotypically similar, are treated as discordant, whereas those twins with largely different values, who are phenotypically distinct but who happen to be on the same side of a threshold, are treated as concordant. An alternative approach would have been to treat those same traits quantitatively, which is more powerful in anal-

Table 3. Univariate Modeling Results for Phenotypes Associated with Age-related Maculopathy

Phenotype	Model	χ^2	$\Delta\chi^2$	df	vs.	P
ARM	1) ADE & age	14.889		—		
	2) ACE & age	22.998	8.109	—	—	—
	3) AE & age	22.998	8.109	1	1	0.004
	4) CE & age	42.885	27.996	1	2	<0.001
	5) E & age	72.042	57.153	2	1	<0.001
	6) ADE no age	49.245	34.356	1	1	<0.001
Soft drusen >63 μm	1) ADE & age	11.219		—		
	2) ACE & age	11.467	0.248	—	—	—
	3) AE & age	11.467	0.248	1	1	0.62
	4) CE & age	22.887	11.668	1	2	<0.001
	5) E & age	74.917	63.698	2	1	<0.001
	6) ADE no age	71.101	59.882	1	1	<0.001
Soft drusen $\geq 125 \mu\text{m}$	1) ADE & age	11.234		—		
	2) ACE & age	11.956	0.722	—	—	—
	3) AE & age	11.956	0.722	1	1	0.40
	4) CE & age	41.315	30.081	1	2	<0.001
	5) E & age	137.017	125.78	2	1	<0.001
	6) ADE no age	60.625	49.391	1	1	<0.001
Pigmentary changes	1) ADE & age	36.506		—		
	2) ACE & age	54.683	18.177	—	—	—
	3) AE & age	54.683	18.177	1	1	<0.001
	4) CE & age	77.195	40.689	1	2	<0.001
	5) E & age	87.620	51.114	2	1	<0.001
	6) ADE no age	39.204	2.698	1	1	<0.001
<20 Hard drusen	1) ADE & age	4.111		—		
	2) ACE & age	6.479	2.368	—	—	—
	3) AE & age	6.479	2.368	1	1	0.12
	4) CE & age	10.002	5.891	1	2	0.02
	5) E & age	12.819	8.708	2	1	0.01
	6) E no age	12.994	8.883	3	1	0.03
	7) ADE no age	4.266	0.155	1	1	0.70
≥ 20 Hard drusen	1) ADE & age	18.720		—		
	2) ACE & age	69.691	50.971	—	—	—
	3) AE & age	69.691	50.971	1	1	<0.001
	4) CE & age	192.527	173.81	1	2	<0.001
	5) E & age	258.818	240.10	2	1	<0.001
	6) ADE no age	29.772	11.052	1	1	<0.001

ARM = age-related macular degeneration; A, D, C, E = additive genetic, dominant genetic, common environment and unique environmental effects, respectively; χ^2 = chi-square goodness of fit statistic; $\Delta\chi^2$ = change in χ^2 comparing submodel with full ADE or ACE model; df = change in degrees of freedom between submodel and full model; P = probability that $\Delta\chi^2$ is zero. Best fitting models are shown in bold, based on calculations using the Akaike Information Criterion (not shown).

ysis of heritability.²⁶ However, the quantification of drusen number, size, area, pigment area, or density and the ranking of ARM is not straightforward, although future computerized quantitative scoring of digital fundus images might be a valuable tool in the reanalysis of studies such as this.

Heiba et al⁹ attempted to improve power in his family segregation study from the Beaver Dam Eye Study by

grading all individuals on a 15-point ordered categorical scale, which included all phenotypes from 1 hard druse through soft drusen to disciform scarring. This was not repeated in this twin study, because this form of categorization is not supported biologically: patients do not progress through these levels, and so they do not reflect a true categorical scoring. For example, soft drusen (level 6) may

Table 4. Parameter Estimates (and 95% Confidence Interval) of Broad-sense Heritability, Age, and Environment Effect in Age-related Maculopathy

	h^2	95% Confidence Interval	e^2	95% Confidence Interval	Age ²	95% Confidence Interval
ARM	45	35–53	51	43–61	4	2–7
Soft drusen >63 μm	41	32–49	51	43–60	8	4–11
Soft drusen $\geq 125 \mu\text{m}$	57	50–64	36	30–43	7	4–10
Pigmentary changes	46	35–54	54	45–65	0.3	0–2
<20 Hard drusen	19	6–30	81	70–94	—	—
≥ 20 Hard drusen	81	77–84	18	15–22	2	0–4

age² = age influence; ARM = age-related maculopathy; e^2 = environmental influence; h^2 = heritability.

occur without hard drusen (level 4), and the evidence that small hard drusen with pigmentary changes (level 9) are "more severe" than soft indistinct drusen (level 7) is unclear.

A concern of this twin study lies in the representativeness of the severity or prevalence of macular degeneration. There was no late AMD in this series of twins, but other major population-based studies have shown AMD in a similarly aged sample. For example, the overall prevalence of AMD in women was 1.9% in the Beaver Dam Eye Study in the United States⁴⁰ and 1.7% in the Blue Mountains Eye Study in Australia,⁴¹ with a prevalence of 1.5% (95% CI, 0.6%–2.4%) and 0.9% (95% CI, 0.2%–1.6%) for those aged 65 to 74 years, respectively. Several reasons may underlie the lower prevalence figure for AMD. Recruitment bias might have occurred so that only twins with early disease were examined, because twins with late-stage AMD and visual loss might not volunteer to travel to London to participate in research.

For early ARM (the outcome studied in this twin sample) it is unlikely that serious recruitment bias occurred, because the twins were asymptomatic and unaware of potential outcomes being studied. It is difficult to compare the prevalence of ARM with previous studies, because they used different definitions. The overall prevalence of ARM in the twin study was 14.6% (95% CI, 12.4%–16.8%), which is not dissimilar to 17.2% in the Beaver Dam Eye Study (7.2% for the more strict criteria of the Blue Mountains Eye Study). Comparing figures for women up to the age of 75 years, the prevalence of soft drusen in the twin study was 9.9% compared with 10.0% in the Blue Mountains Eye Study and 15.9% in the Beaver Dam Eye Study. Twins who had some pigmentary change were 8.6% compared with 9.3% in the Blue Mountains Eye Study and 9.1% in the Beaver Dam Eye Study. The prevalence of ARM therefore seems to be broadly comparable.

The effect of age was modest, explaining only 4% of the susceptibility to ARM (8% for large soft drusen). The mean age of the twins in this study was only 62 years (standard deviation, 5.7 years), and it would be expected that age might have a greater effect in an older sample of twins, with a greater standard deviation for age.

Another potential bias is that the twins are volunteers, and volunteers tend to be more aware of health than nonvolunteers, so it is possible that they are healthier than a true sample of the population, which may have influenced the prevalence of ARM or AMD. In general, twins show similar morbidity and mortality to the rest of the population, and the assumption that MZ and DZ pairs share equal environments has stood up to testing.²⁵ The twin volunteers have been compared with a population sample of similarly aged women from the Chingford Study, a longitudinal study of aging and osteoporosis, and are similar.⁴² The only consistent difference is that DZ twins tend to be heavier than MZ twins and approximately 0.5 kg lighter than the general population, but this factor is not believed to be particularly important in the origin of ARM.

Another explanation of the lower prevalence in our study might be that the prevalence of AMD really is lower in the United Kingdom than in the United States and Australia. No

prevalence data from a comparably aged population in the United Kingdom are currently available. The estimate of heritability derived from this study, as from all studies, reflects the population studied and could be different for other populations. Finally, twins might have a lower rate of macular degeneration compared with singletons. This is difficult to explore. MZ twins are more likely to be mono-chorionic than DZ twins, so if ARM was related to factors in utero, a different prevalence between MZ and DZ twins might be expected if antenatal factors were involved. In this study the prevalence rate of ARM was 13.4% (95% CI, 10.2%–16.6%) for MZ twins and 15.4% (95% CI, 11.7%–19.1%) for DZ twins, which was not significantly different.

In conclusion, early ARM has a major genetic component with a heritability of 45%, with certain phenotypes such as large soft drusen >125 μm and multiple hard drusen showing stronger genetic influences (heritability 57% and 81%, respectively). The further success in finding genes for rare familial AMD-like diseases should continue to identify novel susceptibility genes. These will further advance understanding of the mechanisms of ARM, as well as future interventions for prevention or treatment of this common disabling condition.

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