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A practice-based survey of familial age-related maculopathy

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Abstract *Purpose:* We evaluated the efficacy of a practice-based survey of age-related maculopathy (ARM) to identify potential families for molecular genetic studies. Demographic and ophthalmic features of the eligible study population were compared with responders and with individuals who reported a positive family history of ARM. *Methods:* Individuals seen within a three-year period in a comprehensive ophthalmic practice were identified through billing codes. Clinical records were reviewed, coded, and merged with questionnaire responses. Patient identifiers were removed prior to analyses. *Results:* There were no significant differences between the respondents and the eligible cohort with respect to gender, age, or type of macular degeneration. Comparable percentages of younger and older individuals with ARM reported positive family histories. The distribution of atrophic macular degeneration, choroidal neovascular membranes, and milder forms of the disease among the individuals reporting positive family histories corresponded to the distribution of the entire eligible cohort of patients. *Conclusion:* This recruitment strategy for ARM families is cost-effective and confirmed a high prevalence of familial ARM. The respondents are representative of the general ARM population. This approach is applicable for other ophthalmic genetic conditions.

Key words Family studies; recruitment; age-related macular degeneration; age-related maculopathy

Introduction The hereditary nature of age-related maculopathy (ARM) has been well established by both epidemiologic and family studies.¹⁻⁵ With the advent of new molecular genetic methods and analyses, a number of groups are investigating the genetics of age-related maculopathy in an effort to identify one or more of the genes that may confer susceptibility within families. As part of our recruitment effort for families with ARM, we have established a cost-effective screening program that can be generalized for

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use by many eye care centers and for other complex genetic eye disorders. We have striven to comply with the strict limitations on the design and conduct of genetic studies as proposed by the current guidelines and recommendations regarding genetic studies from the Office for Protection from Research Risks (OPRR) and by the local institutional review board (IRB). In the development of this program, we sought to determine what factors might affect our ability to identify individuals with familial ARM. We also sought to determine what epidemiologic factors might affect the extent to which patients would respond to the survey and report a family history of ARM.

Patients and methods A collaboration was established with a large four-member, general ophthalmology practice in Northwestern Pennsylvania. This practice provides care over a large geographic area through three offices. All members of the practice agreed to assist in this survey. Using the billing codes (Nonneovascular, Macular Degeneration Dry 362.51 and Neovascular, also known as Macular Degeneration, Wet 362.52), the office manager ran a search of the entire practice over the past three years to identify patients with ARM. The list of names, separated by office site, were entered into a Filemaker™ database on a laptop computer. A medical student associated with the practice reviewed the entire chart list to identify miscoded individuals, persons who were deceased, and demographic and ophthalmic information from the records. Individuals who had no evidence of ARM, as determined by documented diagnosis or features (see Table 1), were excluded from the mailing. A cover letter and a return-addressed postcard were mailed from the practice to all living eligible patients. The postcards asked patients to indicate if they were aware of their own diagnosis of ARM, had any family members with ARM, had any living family members with ARM, and were willing to be contacted in regards to the study. Individuals who wished to be contacted and reported that they had other living family members with ARM were identified from the original (name, address, and phone number) database via a code number on the postcards and contacted by our study coordinators. The responses from the postcards and phone contacts were entered into the original database, and then all identifiers were removed before analysis. In this fashion, the confidentiality of the patients could be preserved within the practice. Confidential data from individuals who had not responded to the survey or expressed no desire to participate could be preserved within the practice.

A major objective of this study was to determine whether the use of billing records was a reasonable and effective method of identifying patients with familial ARM. We evaluated the prevalence of billing records that were coded incorrectly or that identified deceased patients at the time of survey. We sought to establish whether the group of respondents to the survey was different from the overall cohort of eligible subjects with respect to age, sex, vision, and type and severity of ARM. We tested the hypothesis that familial ARM might represent a different distribution of ARM types than would be observed in the general population of ARM patients. The ARM features and demographics of the subset of patients who reported a family history were compared with those of the overall cohort of eligible patients as well as the cohort of patients who responded to the survey. Analyses

ARM D (age-related macular degeneration)
Macular degeneration
SMD (senile macular degeneration)
Atrophic macular degeneration
SRNV* (subretinal neovascularization)
Disciform scar*
Drusen
RPE (retinal pigment epithelium) figures
RPE clumping
RPE dropout
PED (pigment epithelial detachment)

*collectively referred to as CNVM (choroidal neovascular membrane).

TABLE 1. Terms and abbreviations identified from the chart records that were used to document the presence of ARM.

were performed using Minitab™ cross-tabulations and comparisons of different groups were conducted with the Fisher exact test.

Results

INELIGIBLE INDIVIDUALS WITHIN THE SELECTED MAILING LIST The billing search identified 1309 patients who had been billed with a diagnosis of ARM over a three-year period. At the time of chart review, 8.2% (107/1309) of these patients were found to be deceased. Thirteen percent (171/1309) of the reviewed charts revealed neither documented features nor a documented diagnosis of ARM. These cases may represent minor pigment changes or drusen that were not documented and were not included in the study. The remaining 996 patients (76.4% of total list) who were living and had documented evidence of ARM were considered eligible for the study.

RESPONSE TO THE SURVEY AND PROFILES OF THE RESPONDERS Mailings were sent to all 996 eligible patients. Twenty-seven letters (2.7%) were returned by the postal service and deemed undeliverable. Postcards were received from 391/996 patients (39.3%) of which 265/391 (67.8%) were female compared to 670/996 (67.3%) females in the eligible cohort. The distribution of ages and visual acuities were quite similar between the responders and the eligible cohort (Figs 1-3).

Patients for whom the presence or absence of certain macular features was not clear from the medical record were excluded from the calculations of prevalence of macular pathology. Review of the macular features, based only on medical records, revealed evidence of drusen/retinal pigment epithelial (RPE) figures in 361/391 (92.3%) responders and 933/996 (93.7%) members of the eligible cohort. There was documentation of a choroidal neovascular membrane or a disciform lesion in 175/391 (44.8%) responders and 399/996 (40.1%) members of the eligible cohort. Geographic atrophy was reported in 100/391 (25.6%) responders and 247/996 (24.8%) members of the eligible cohort (Fig. 3). Many of the individuals had documentation of more than one feature associated with ARM. The distributions of retinal pathology as documented in the medical records among the eligible patients, the individuals who responded to the survey, and the

Fig. 1. Age distribution of respondents and those with positive family histories. Cumulative percentages of the total sample are shown so that one can compare distributions among different sample sizes. The squares indicate all of the individuals who were in the eligible cohort for the screening program. The circles represent those individuals who responded to the survey by sending in completed postcards. The triangles represent the subset of individuals who responded to the survey and indicated that they had a positive family history of ARM.

Fig. 2. Distribution of visual acuities among the eligible subjects, the respondents, and the respondents with positive family histories. The symbols used in the graph are identical to those used in Figure 1.

patients who were identified as having a positive family history of ARM are summarized in Table 2.

ESTIMATED PREVALENCE OF FAMILIAL ARM A family history of ARM was reported by 28.4% (111/391) of the respondents. Sixty-six percent of the respondents (73/111) reported a positive family history of ARM with living affected individuals, 20.7% (23/111) a family history of ARM but no living affected members, and 3.6% (4/111) were unsure which family members also had ARM. Our study coordinators were unable to confirm a family history (living or deceased) of ARM in six of the 95 individuals (6.3%) contacted, although a family history was indicated on the postcard. If these cases are assumed to be representative of the misreporting of family history, then the adjusted prevalence is 26.9% (105/391) of respondents have a family history of ARM. We were unable to confirm a reported family history in nine respondents as they did not wish further contact.

CHARACTERISTICS OF THE PATIENTS REPORTING FAMILIAL ARM COMPARED TO THE OVERALL SAMPLE Comparison of the demographics between those who reported a family history and the eligible cohort reveals 82/111 (73.9%) patients with a family history were female, while 670/996 (67.3%) of the eligible cohort were female. As shown in Figures 1 and 2, comparisons of age and severity of disease between the patients reporting a family history and the eligible cohort is not significantly different.

PROFILES OF THOSE WITH A POSITIVE FAMILY HISTORY OF ARM Review of the macular features, based only on medical records, revealed evidence of drusen/RPE figures in 95/109 (87.2%) patients who reported a family history of ARM compared to 885/1000 (88.5%) members of the eligible cohort. There was documentation of a choroidal neovascular membrane or disciform lesion in 51/109 (46.8%) patients reporting a family history

Fig. 3. Macular features of subjects as determined from ophthalmic records. The most severe feature present in at least one eye was considered. +GA indicates that geographic atrophy was documented. +CNVM: documentation of a choroidal neovascular membrane. +Drusen: the presence of hard or soft drusen (the majority of the records did not provide specific numbers, areas, or types of drusen present in the macula). Bars with diagonal lines indicate the individuals who were in the eligible cohort for the screening program. Cross-hatched bars represent individuals who responded to the survey by sending in completed postcards. The shaded bars represent the subset of individuals who responded to the survey and indicated that they had a positive family history of ARM.

compared to 399/1000 (39.9%) members of the eligible cohort. Geographic atrophy was reported in 31/109 (28.4%) subjects reporting a family history compared to 247/1000 (24.7%) members of the eligible cohort (Fig. 3). There was a tendency for the individuals with positive family histories to have slightly worse visual acuities than the total cohort, but none of these differences were statistically significant.

Discussion

INELIGIBLE INDIVIDUALS WITHIN THE SELECTED MAILING LIST The amount of coding discrepancies and the number of individuals who were deceased accounted for 20% of the initial sample. The percentage of miscodings is likely to vary with different practices as well as the type of practice. We anticipated the possibility of miscodings by carefully stating in the cover letter that was sent to the patients that the diagnosis may be in error. This survey considered only those patients who had been seen within a three-year period. A longer period of inclusion would be likely to cause a significant increase in deceased or relocated individuals. For large-scale screenings, chart review prior to the mailings would be prohibitively time-consuming and labor intensive. In our experience, this percentage of ineligibility would be acceptable in a mass mailing program.

The work demands on the medical practice office staff can be minimized

	<i>Eligible participants</i>	<i>Responded to survey</i>	<i>+ Family history</i>
Drusen	46.0	41.4	36.0
CNVM	3.4	10.0	14.4
GA	1.5	8.7	11.7
Drusen + CNVM	25.8	23.0	21.6
Drusen + GA	12.4	5.1	6.3
CNVM + GA	1.4	5.1	4.5
Drusen + CNVM + GA	9.4	6.6	5.4

CNVM, choroidal neovascular membrane; GA, geographic atrophy.

TABLE 2. Percentage of individuals documented with findings.

by electronically creating the mailing list from billing records. In our program, the study coordinators make telephone contact with the potential probands identified by the survey, provide them with information about the study, and arrange for the probands to initially contact the prospective family members. Once the coordinators have confirmed with the proband that the family members are receptive to the study, then these family members are contacted by phone or mail. The study coordinators initially concentrate their efforts on the verification of participation, documentation of affected status, and blood sample of the identified family member before we recontact the proband for a blood sample and request ophthalmic records from the clinical practice. This minimizes the workload of the medical practice office staff by focusing their efforts on only those individuals who will be part of complete families for genetics studies.

One advantage of this practice-based survey is that one begins with a reported diagnosis and available documentation of the proband before attempting to ascertain an entire family. Potential subjects are often unsure of their own condition which would discourage them from self-referral to a research study. Given that documentation of ARM cases is a major component of the ascertainment effort, it is highly beneficial to have a known source of documentation for each proband.

RESPONSE RATE TO THE SURVEY AND PROFILES OF THE RESPONDERS The percentage of the eligible subjects who responded to the survey was 38.7%, which is relatively low. In a previous survey of eight general ophthalmology practices in the Pittsburgh area, the response rate was 47% (1393) from 2965 individuals surveyed. Of those who responded, 23 (17%) were deceased as indicated by cards returned on behalf of the individual, and 318 (24%) reported having at least one additional family member (alive or deceased) with ARM. Fifteen percent of the individuals who responded indicated that there was another living family member with ARM. In a similar survey of 566 individuals from a university-based retina specialty practice, we obtained a response rate of 288/566 (50.9%) with 87/288 (30.2%) of respondents reporting positive family histories of ARM. Despite the differences among these practices (urban versus rural; comprehensive versus subspecialty; community versus university), there is consistency in the percentages of respondents who report family histories of ARM.

For an epidemiologic survey, response rates below 50% are problematic for estimates of disease prevalence. However, for a screening program to identify familial ARM families, these response rates were very gratifying. In no instances were financial incentives offered for participation. If there is a selection bias, it is likely that a higher percentage of the responders will be more willing to participate in a research study. The variations in response rates may reflect a number of factors such as the distribution of subjects in rural and urban areas, cultural differences in people's natural hesitance to respond to surveys – even when they are sent from their own physicians, and the type of ophthalmic practice (comprehensive as compared to subspecialty-based). However, there was no effect of age, sex, or severity of ocular disease on the likelihood that an individual would respond to the survey except for those patients over the age of 90. Individuals over 90 had a response rate of 27% (43/159) compared to the overall response rate of 38.7%. This difference is not large enough to warrant exclu-

sion of these individuals. Therefore, it is not effective to tailor a screening based upon age, sex, type of macular pathology, or visual acuity. There were no reported adverse responses from either patients or the participating physicians and staff. Only a small percentage (14%) of the respondents specifically requested that they not be contacted by the research group, indicating that the remaining respondents would be motivated to participate in ARM research studies.

There were no differences in age, sex, or severity of disease between the eligible cohort and the patients with a positive family history. No significant differences in the characteristics of ARM between the eligible cohort and those who reported a positive family history were observed.

We have previously hypothesized that younger individuals with ARM are more likely to have a familial form of the disease⁶ than older individuals who may have phenocopies of ARM. However, we observed no differences in the percentages of familial reports for different ages of subjects (based on the person's age at the time of the survey, not an estimated age of onset). In order for this original hypothesis to be valid, we would have to consider a counteracting ascertainment bias that causes the younger affected individuals to be less aware of other family members with ARM. This could be due to the age-dependent penetrance of the condition, and the fact that many individuals with ARM changes are relatively asymptomatic. The Beaver Dam study has shown that there is a much higher prevalence of ARM features in the younger population compared to endstage disease causing vision loss.⁷

A number of subjects (40) who responded to the survey were unsure if they had macular degeneration, even though nine of these individuals had received laser treatment for choroidal neovascular membranes. This highlights the potential problems with patient self-reporting of their own condition and those of other family members. This was alluded to in the case-control trial by Hyman et al.⁴ in 1983 in which 11.3% of siblings self-reported a history of ARM, while the eye examiners reported a sibling history of ARM in 19.9% of individuals.

ESTIMATED PREVALENCE OF FAMILIAL ARM The prevalence of familial ARM in this survey could be as high as 26% if no selection bias existed or as low as 10.1% if there were no familial cases among the nonrespondents to the survey. This prevalence is very similar to the 24% and 30.2% values that we observed in similar surveys conducted at different times and with diverse clinical practices (see above). This range of familial ARM prevalences is consistent with previous epidemiologic studies.^{2,4,8} A case-control study by Hyman et al.⁴ noted a positive family history in 21.6% of 228 individuals with documented ARM. Gass's retrospective study of 200 patients with ARM found a positive family history in 19%.² Soubrane et al.⁸ found a much lower prevalence of familial ARM, 10% of 352 individuals in their case-control study.

Individuals with nonatrophic, nonexudative ARM had the same frequency of positive family histories as individuals with either form of endstage disease. There is no reason to believe that ARM with geographic atrophy is more or less a familial condition than exudative ARM. This survey gives no indication as to whether there are overlapping genetic etiologies.

CONCLUSIONS The use of billing records to create a potential cohort of research subjects for a large-scale clinical study has proven to be a cost-effective approach that can conform to current OPRR guidelines and preserve patient confidentiality. Billing records do not provide an adequate database for estimates of disease prevalence due to errors in coding and patient mortality, but such lists can be effectively used for screening programs. There are undoubtedly many factors that contribute to the willingness of individuals to participate in clinical research, but age, disease type, and severity were not significant factors in this study. A significant percentage of ARM patients were aware of the condition in other family members, though it is clear that some patients are unaware of their own diagnosis and that of their family members. Our observed prevalence of familial ARM is consistent with previously published studies as well as other surveys that we have performed. The long-term goal of these investigations will be the identification of one or more genes that confer ARM susceptibility to the general population. These efforts complement the recent advances that have been made in the determination of specific hereditary macular dystrophies such as Sorsby's fundus dystrophy and Stargardt's disease.

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