CORRESPONDENCE

Familial Aggregation of Age-related Maculopathy

EDITOR:

THE ARTICLE, "FAMILIAL AGGREGATION OF AGE-RELATED Maculopathy," by J. M. Seddon, U. A. Ajani, and B. D. Mitchell (*Am J Ophthalmol*, 123:199–206, February 1997) on the family aggregation of age-related macular degeneration (AMD)¹ gives valuable information. We are engaged in a similar study and this prompts us to ask a few questions and to make a few remarks.

The authors refer to a new international classification system² but use the terms age-related maculopathy (ARM) and AMD as if these are similar entities within this system. In the probands, different severity grades of ARM seem to be lumped, and differences in the genetic contribution to each of the stages of ARM thus cannot be identified.

We wonder if selection bias may play a role when looking at the response figures in Table 1.¹ Did all 119 case probands give permission to approach their family members? In our study, this was not the case. Or were those who did not give permission considered to be ineligible? From what total number of persons were the 72 control probands selected? We also wonder if the response of numbers with medical records should not be 61% (177/290) and 62% (146/236).

Table 2¹ is of considerable interest in showing the sensitivity of self-reported ARM in case families vs control families to be 45% vs 18% and the specificity 90% vs 86%, respectively. We conclude, therefore, that inferences based on self-reported ARM are weak.

We wonder if one should not try to separate in Tables 3 and 4¹ siblings of probands and parents or children of probands. Most children will not yet have reached the age of onset of AMD, leading to more

misclassification among the healthy subjects and a lower relative risk.

Finally, we ask ourselves if the suggestion to screen first-degree relatives of patients with exudative ARM is cost-effective, especially when one reads in a recent conclusion in another article on AMD from the same author³ that "... treatment is not available or is ineffective for most patients ..."

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AUTHOR REPLY

AGE-RELATED MACULAR DEGENERATION IS A COMMON, complex disease that is phenotypically heterogeneous, and it seems reasonable to expect that multiple genes may influence susceptibility. We agree that efforts to identify genes (and other risk factors) influencing susceptibility to this disorder will be enhanced by recognizing the potential multifactorial nature of this disorder and to the extent possible, considering homogeneous subtypes. In our analysis, we did, in fact, detect stronger evidence of familial aggregation among relatives of exudative cases than

among relatives of dry maculopathy cases.¹ We did not, however, explore other possible sources of clinical heterogeneity, largely because standardized ophthalmic examinations were not performed on the probands' relatives. However, it will be essential to establish clinical/etiologic subtypes in order to more fully dissect out the genetic/familial contribution of this disorder.

Not all of the 119 case probands gave permission to contact all of their family members, as implied in Table 1.¹ The extent of familial aggregation could have been overestimated if the prevalence of AMD was higher in relatives of those giving permission than in relatives of those denying permission. We have no evidence either for or against this possibility although we observed no apparent clinical or demographic differences between the case probands who granted and denied permission.

The specificity of self-reported AMD compared to medical record diagnosis was high (>99% if one excludes "unknowns"), although the sensitivity of the self-reported diagnosis was poor, particularly among the relatives of the control probands. We, therefore, based our conclusions on analysis of medical record diagnosis of AMD as determined by a review of ocular records.

We believe that more rigid diagnostic criteria, obtained from standardized ophthalmic examinations and photography, are required to identify specific causal or susceptibility genes for the various forms of AMD. Funding constraints precluded our use of such measures for this study under discussion. We have developed a uniform, standardized ophthalmic examination and photography protocol that has been in use since 1991 for evaluation of all of our participating family members throughout the United States.²

It would be helpful to separate out the familial risk to parents, siblings, and offspring, although it was not

possible to obtain meaningful prevalence estimates because of the low numbers of participating living parents and age-eligible offspring in this series. As noted in our paper, however, our results were essentially unchanged after excluding relatives younger than age 55 years.

Currently, treatment is not available or is ineffective for most patients with AMD. However, behavior modification may prevent the onset or progression of the disease in some cases, in particular avoidance of smoking³ and possibly dietary intervention. Also, early identification of the exudative form of the disease could improve the outcome of laser treatment. Because the cost-benefit issues of screening have yet to be evaluated, we stated that "it is premature at this point to recommend general screening measures . . .".¹ However, at this time, based on available evidence, it is reasonable to suggest that "first-degree relatives of patients with the exudative form of age-related maculopathy, particularly those over age 65 years, be examined for evidence of age-related maculopathy."¹

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